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**Clinical Study Report Synopsis**

Drug Substance	Rosuvastatin calcium
Study Code	4522IL/0096 D3562C00096
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**A study to evaluate the Use of Rosuvastatin in subjects On Regular haemodialysis: an Assessment of survival and cardiovascular events (AURORA)**

**A double blind, randomised, multicentre, phase IIIb, parallel-group study to compare the effects of rosuvastatin (10 mg oral) with placebo on assessment of survival and cardiovascular events when given to subjects with end-stage renal failure on chronic haemodialysis treatment**

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<b>Study dates:</b>	First patient enrolled: 16 January 2003 Last patient last visit: 06 October 2008
<b>Phase of development:</b>	Therapeutic confirmatory (III)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

## Study centres

The study patients were randomised at 280 centres in 25 countries.

## Publications

Fellström B, Holdaas H, Jardine AG, Rose H, Schmieder R, Wilpshaar W, et al. Effect of Rosuvastatin on Outcomes in Chronic Haemodialysis Patients: Baseline Data from the AURORA Study. *Kidney Blood Press Res* 2007;30:314-22.

Fellström BC, Jardine AG, Schmieder RE, Holdass H, Bannister, K, Beutler J, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med* 2009;360:1395-407.

Fellström B, Zannad F, Schmieder R, Holdaas H, Jardine A, Rose H, et al. Effect of rosuvastatin on outcomes in chronic haemodialysis patients - design and rationale of the AURORA study. *Curr Control Trials Cardiovasc Med.* 2005;6,1-9.

## Objectives and criteria for evaluation

**Table S1 Primary and secondary objectives and outcome variables**

Objectives	Outcome variables	Type
<b>Primary</b>	<b>Primary</b>	
To determine the effects of treatment with rosuvastatin compared to placebo, by assessing time to major cardiovascular event (combined endpoint of non-fatal stroke, non-fatal myocardial infarction or cardiovascular death).	Time from randomisation to major cardiovascular event (time from randomisation until the earliest occurrence of non-fatal stroke, non-fatal myocardial infarction or cardiovascular death).	Efficacy
<b>Secondary</b>	<b>Secondary</b>	
To determine the effect of treatment with rosuvastatin compared to placebo by assessment of the time to death from any cause in each treatment group.	Time from randomisation to death from any cause	Efficacy
To determine the effects of treatment with rosuvastatin compared to placebo on major cardiovascular event free survival, by assessment of the time to the first major cardiovascular event (combined endpoint of non-fatal stroke, non-fatal myocardial infarction or cardiovascular death) or death from any other cause in each treatment group.	Major cardiovascular event free survival (time from randomisation until the earliest occurrence of non-fatal stroke, non-fatal myocardial infarction, cardiovascular death or death from any other cause)	Efficacy
To determine the effects of treatment with rosuvastatin compared to placebo on the components of time to death, in each treatment group, by assessing:	Time from randomisation to cardiovascular death. Time from randomisation to non-cardiovascular death.	Efficacy
a) time to cardiovascular death		
b) time to non-cardiovascular death		
To determine the effect of treatment with rosuvastatin compared to placebo by assessment of the time to first atherosclerotic cardiac event (combined endpoint of coronary heart disease death and non-fatal myocardial infarction)	Time from randomisation until the earliest occurrence of an atherosclerotic cardiac event (non-fatal myocardial infarction or coronary heart disease death)	Efficacy

**Table S1 Primary and secondary objectives and outcome variables**

Objectives	Outcome variables	Type
To determine the effects of treatment with rosuvastatin compared to placebo on the time to first procedure as a result of stenosis or thrombosis of the vascular access (AV fistula and grafts only) for haemodialysis in each treatment group	Time from randomisation to the first procedure as a result of stenosis or thrombosis of the vascular access (AV fistulas and grafts only) for haemodialysis.	Efficacy
To determine the effects of treatment with rosuvastatin compared to placebo on the incidence of coronary or peripheral revascularisations (including above ankle limb amputations) in each treatment group.	The incidence of coronary or peripheral revascularisations (including above ankle limb amputations). Time to the first coronary or peripheral revascularisation (including above ankle limb amputations).	Efficacy
To assess the safety of treatment with rosuvastatin compared to placebo.	The incidence of adverse events and laboratory data during long term treatment in each group	Safety
To determine the cost due to hospitalisation (expressed as cost per life year saved) on treatment with rosuvastatin compared to placebo.	Costs per life year saved.	HEOR
<b>Tertiary</b>	<b>Tertiary</b>	
To determine the effect of treatment with rosuvastatin compared to placebo on the percentage changes in TC, LDL-C, HDL-C, non HDL-C (TC minus HDL-C), TC/HDL-C, LDL-C/HDL-C, ApoB, ApoA1, ApoB/ApoA1, oxidised LDL, TG and CRP, from baseline to 3 and 12 months post randomisation. Additionally the percentage changes in TC, LDL-C, HDL-C, non HDL-C (TC minus HDL-C), TC/HDL-C, LDL-C/HDL-C and TG at 24, 36 months (yearly if required) and final visit.	The percentage changes in TC, LDL-C, HDL-C, non HDL-C (TC minus HDL-C), TC/HDL-C, LDL-C/HDL-C, apoB, apoA1, apoB/apoA1, oxidised LDL, TG and hsCRP, from baseline to 3 and 12 months post randomisation. The percentage changes in TC, LDL-C, HDL-C, non HDL-C (TC minus HDL-C), TC/HDL-C, LDL-C/HDL-C and TG at 24, 36 months (yearly if required) and final visit.	Efficacy

ApoA1 Apolipoprotein A-1; ApoB Apolipoprotein B; CRP C-reactive protein; HDL-C High density lipoprotein cholesterol; HEOR Health economics and outcomes research; LDL-C Low density lipoprotein cholesterol; TC Total cholesterol; TG Triglycerides. Note that CRP was measured with the high sensitivity assay and is hereafter referred to as hsCRP.

## Study design

This was a Phase IIIb, multicentre, placebo-controlled, randomised, double-blind, parallel-group study to investigate the effects of treatment with rosuvastatin (10 mg) on the prevention of major cardiovascular events (cardiovascular death, non-fatal stroke or non-fatal myocardial infarction), when given to patients with end-stage renal failure undergoing chronic haemodialysis treatment (including haemofiltration and haemodialfiltration).

## Target healthy volunteer population and sample size

The study recruited male or female patients with end-stage renal failure, aged 50 to 80 years, who had received regular chronic haemodialysis treatment (including haemofiltration and haemodialfiltration) for at least 3 months. The patients should not have had any underlying haematological, neoplastic, metabolic (excluding diabetes), gastrointestinal or infectious conditions that were expected to limit survival to less than 1 year and were also unrelated to end stage renal disease.

Approximately 2700 patients were to be randomised at approximately 300 sites from Australia, Canada, Europe, South Korea, Mexico and Brazil. The sample size calculation was based on the single primary endpoint of time from randomisation to major cardiovascular event (5% p-value spend on this single endpoint). A final significance level of 4.719% was used to adjust for the interim analysis performed by the Data and Safety Monitoring Board using the stopping rule of 0.0026.

The major cardiovascular event rate per year was estimated to be 9.756% per year for rosuvastatin patients. This equated to a hazard rate of 0.008554423 per month and a hazard ratio for rosuvastatin compared to placebo (rosuvastatin/placebo) of 0.803. In order to detect a hazard ratio of  $\leq 0.803$  (or  $\geq 1.245$ ) for rosuvastatin compared to placebo at a 2-sided significance level of 4.719% (5% level adjusted for the interim analysis using the stopping rule of 0.0026), major cardiovascular events for 805 patients would give 87% power. At study closure, 804 patients had had a major cardiovascular event.

### **Investigational product and comparator: dosage, mode of administration and batch numbers'**

Table S2 presents the details of treatment used in the AURORA study. Individual batch numbers and further information are presented in the Clinical Study Report.

**Table S2** Details of investigational product and any other study treatments

<b>Investigational product or test drug</b>	<b>Dosage form, strength, dosing schedule, and route of administration</b>	<b>Manufacturer</b>	<b>Formulation number</b>
Rosuvastatin tablets	10 mg oral tablets daily	AstraZeneca	F12672
Matching tablets	Placebo oral tablets daily	AstraZeneca	F12831

### **Duration of treatment**

After a 2-week run-in period, subjects meeting the study inclusion criteria and having none of the exclusion criteria were allocated to receive either rosuvastatin 10 mg/day or matching placebo. The study was to be stopped when 805 primary endpoints had occurred.

### **Statistical methods**

Analysis of primary and secondary time to first event variables were based on Cox proportional hazards models and the score test was used to calculate p-values. Only randomised treatment was used as a covariate and the exact method was used for ties.

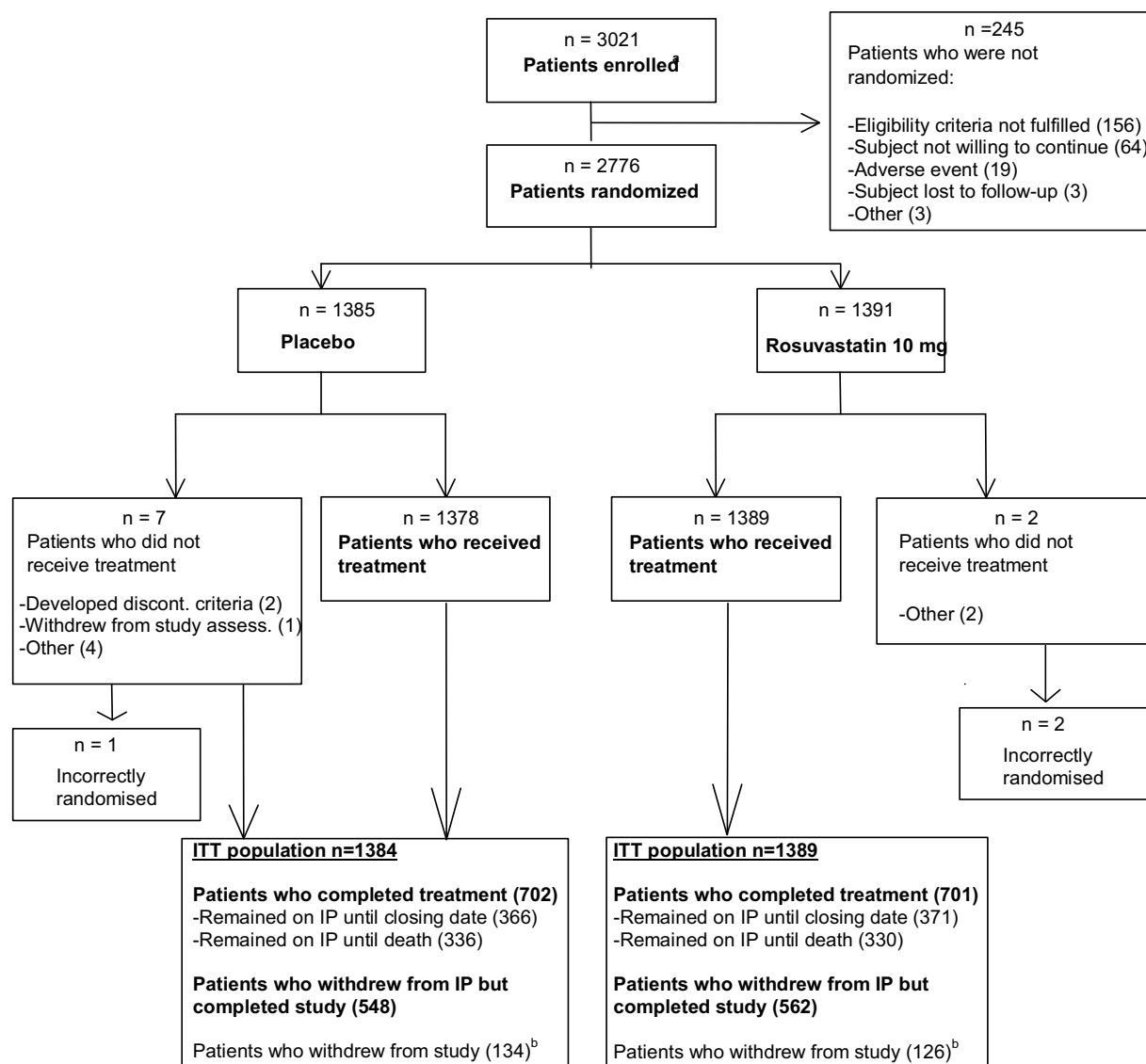
Analysis results are presented as a hazard ratio with the corresponding confidence interval and p-value. A 95.281% confidence interval was produced for time from randomisation to major cardiovascular event (95% level adjusted to account for the interim analysis).

Curves showing the proportion of patients with endpoints over time were estimated for each treatment group using the Kaplan-Meier method.

## Subject population

Figure S1 shows the disposition of study patients in the AURORA trial. The study population was 62% male and 38% female with an average age at randomisation of 64 years. The majority of the population was Caucasian (85%). Demographics and baseline characteristics were similar among treatment groups.

**Figure S1 Patient disposition**



a Informed consent received.

b Vital status was obtained for all randomised patients at the end of the study, including patients that withdrew from the study.

## Summary of efficacy results

The estimated hazard ratios and 95% confidence intervals for all adjudicated primary and secondary time to first event endpoints in the AURORA trial are presented in [Table S3](#). Rosuvastatin did not significantly affect the primary endpoint (time to first major cardiovascular event) when compared to placebo. Analyses of individual components of the primary endpoint, of secondary endpoints, and of subgroups were consistent with the main findings.

**Table S3 Primary and secondary time to event endpoints. Estimated Hazard ratio and 95% Confidence Interval (ITT population).**

Endpoint	Number of events		HR	95% CI		p-value
	Placebo n= 1384	Rosuvastatin n= 1389		Lower	Upper	
Primary event	408	396	0.963	0.839	1.106	0.5946
Death from any cause	660	636	0.964	0.864	1.075	0.5068
Major cardiovascular event or death	645	614	0.943	0.845	1.053	0.2999
cardiovascular death	324	324	0.997	0.855	1.163	0.9715
Non cardiovascular death	268	248	0.920	0.774	1.093	0.3433
Atherosclerotic cardiac event	266	258	0.960	0.809	1.139	0.6388
Vascular access procedure	360	390	1.102	0.955	1.271	0.1855
Revascularisations	152	148	0.983	0.784	1.233	0.8840

CI Confidence interval; HR Hazard ratio; ITT Intention-to-treat

As expected, rosuvastatin significantly lowered LDL-C compared to placebo. Other lipid/lipoprotein values were generally lower in the rosuvastatin group than the placebo group during the treatment phase of the study, with the exception of HDL-C and ApoA1 which were slightly higher in the rosuvastatin group. Rosuvastatin also significantly lowered hsCRP when compared to placebo.

## Summary of safety results

[Table S4](#) summarizes the adverse events (AEs) occurring during the AURORA trial by category. The number of patients with treatment-emergent AEs, serious AEs (SAE), and permanent or temporary discontinuations of IP due to AEs, were similar for both treatment groups. Mean exposure was approximately 2.4 years in both treatment groups. The most common AEs with rosuvastatin were consistent with prior knowledge and current labelling.

**Table S4 Treatment emergent adverse events. Number (%) of patients who had at least one adverse event in any category (safety population)**

AE category	Number (%) of patients	
	Placebo n= 1378	Rosuvastatin n= 1389
Any AE	1290 (93.6)	1312 (94.5)
Any SAE	1003 (72.8)	1017 (73.2)
Any AE leading to death	452 (32.8)	439 (31.6)
Any AE leading to permanent discontinuation of IP	519 (37.7)	486 (35.0)
Any AE leading to temporary discontinuation of IP	272 (19.7)	284 (20.4)

Includes adverse events that started during the treatment phase, or were ongoing from the screening period and worsened during the treatment phase, up to 30 days of permanently stopping study medication.