AstraZeneca

Drug product:	CRESTOR 10- and 20-mg tablet	**SYNOPSIS**	
Drug substance(s):	Rosuvastatin calcium		
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Report on the Randomized Treatment Phase

An Open-label, Randomized, Multi-center, Phase IIIb, Parallel Group Switching Study to Compare the Efficacy and Safety of Lipid Lowering Agents Atorvastatin and Simvastatin with Rosuvastatin in High Risk Subjects with Type IIa and IIb Hypercholesterolemia (MERCURY II)

International co-ordinating investigator

Trial center(s)

This trial was conducted at 152 centers that actually randomized subjects: US (117 centers), Canada (19 centers), Argentina (4 centers), Brazil (6 centers), and Mexico (6 centers).

Publications

None at the time of writing this report.

Trial dates		**Phase of development**
First subject enrolled	28 November 2001	Therapeutic confirmatory (IIIb)
Last subject completed	24 October 2003 (Randomized phase)	

Objectives

The primary objective of the trial was to compare the efficacy of rosuvastatin with the efficacy of atorvastatin and simvastatin in bringing subjects at high risk for coronary heart disease (CHD) to their National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) low-density lipoprotein cholesterol (LDL-C) target goal at Week 16. Subjects were treated with atorvastatin or simvastatin for 16 weeks, or with rosuvastatin for 8 weeks following 8 weeks of comparator treatment.

The secondary objectives in the randomized treatment phase of the trial were:

1. To compare the efficacy of rosuvastatin with the efficacy of atorvastatin and simvastatin in bringing subjects to their European Atherosclerosis Society (EAS) LDL-C target goal at Week 16; subjects either had switched to rosuvastatin at Week 8 or had remained on original comparator treatment.

2. To compare the efficacy of rosuvastatin with the efficacy of atorvastatin and simvastatin in bringing subjects to both their EAS LDL-C and total cholesterol (TC) target goals at Week 16; subjects either had switched to rosuvastatin at Week 8 or had remained on original comparator treatment.

3. To compare the efficacy of rosuvastatin with the efficacy of atorvastatin and simvastatin in bringing subjects to their Canadian Medical Association LDL-C target goal at Week 16; subjects either had switched to rosuvastatin at Week 8 or had remained on original comparator treatment.

4. To compare the efficacy of rosuvastatin with the efficacy of atorvastatin and simvastatin in bringing subjects to their NCEP ATP III LDL-C target goal at Week 8.

5. To compare the efficacy of rosuvastatin with the efficacy of atorvastatin and simvastatin in bringing subjects to their EAS LDL-C target goal at Week 8 and to their Canadian LDL-C target goal at Week 8.

6. To compare the efficacy of rosuvastatin with the efficacy of atorvastatin and simvastatin in bringing subjects with high triglyceride (TG) levels ($\geq$ 200 mg/dL [2.26 mmol/L]) to their non-high-density lipoprotein cholesterol (HDL-C) target goal at Week 16 based on NCEP ATP III criteria; subjects either had switched to rosuvastatin at Week 8 or had remained on original comparator treatment.

7. To compare the efficacy of rosuvastatin with the efficacy of atorvastatin and simvastatin in modifying lipids and lipoproteins at Week 16; subjects either had switched to rosuvastatin at Week 8 or had remained on original comparator treatment.

8. To compare the efficacy of rosuvastatin with the efficacy of atorvastatin and simvastatin in modifying lipid and lipoprotein at Week 8.

9. To compare rosuvastatin with atorvastatin and simvastatin at 8 and 16 weeks of treatment with respect to the incidence and severity of adverse events (AEs) and abnormal laboratory values.

10. To assess whether there is a relationship between systemic exposure to rosuvastatin and calculated creatinine clearance (CrCl) and/or creatine kinase (CK).

In addition to the primary and secondary objectives described in the study protocol, additional efficacy analyses were undertaken on the data from the randomized phase of this trial.

The secondary objective in the extension phase of the trial was to assess the safety of extended treatment with rosuvastatin.

Trial design

This randomized, open-label, parallel-group, multi-center, trial in subjects at high risk for CHD was designed primarily to determine whether switching subjects treated initially with atorvastatin or simvastatin to rosuvastatin is more effective than continued treatment with the comparator statins in bringing additional subjects to goals.

Subjects underwent a 6-week dietary lead-in period to stabilize baseline LDL-C values off lipid lowering therapy.

At the end of the 6-week dietary lead-in period, eligible subjects were randomly assigned to 1 of 5 treatments for 8 weeks (Period 1): 1) rosuvastatin 20 mg, 2) atorvastatin 10 mg, 3) atorvastatin 20 mg, 4) simvastatin 20 mg, or 5) simvastatin 40 mg.

At the end of Period 1, all subjects were randomly assigned within each treatment arm to an additional 8 weeks of treatment (Period 2) with either the original comparator treatment or rosuvastatin:

Rosuvastatin 20 mg → rosuvastatin 20 mg.

Atorvastatin 10 mg → atorvastatin 10 mg or rosuvastatin 10 mg.

Atorvastatin 20 mg → atorvastatin 20 mg or rosuvastatin 20 mg.

Simvastatin 20 mg → simvastatin 20 mg or rosuvastatin 10 mg.

Simvastatin 40 mg → simvastatin 40 mg or rosuvastatin 20 mg.

In both Period 1 and Period 2, the results of lipid analyses remained blinded to both investigators and trial subjects.

After successful completion of the randomized treatment phase, eligible subjects could elect to participate in an open-label extension phase examining the safety of rosuvastatin. This Clinical Study Report (CSR) reports on the randomized treatment phase of the trial.

Target subject population and sample size

Male and non-pregnant female subjects (aged 18 years or older) with primary hypercholesterolemia, types IIa or IIb were recruited. Subjects had fasting LDL-C concentrations ≥130 mg/dL (3.36 mmol/L) but <250 mg/dL (6.46 mmol/L) and a history of CHD or other atherosclerotic disease, diabetes, and fasting TG concentrations <400 mg/dL (4.52 mmol/L).

Sample sizes were calculated as follows. A clinically meaningful difference between rosuvastatin and each comparator in terms of the primary endpoint would be a difference of 15% in the percentage of subjects reaching NCEP ATP III LDL-C goal at 16 weeks of treatment. The desired power for this trial was 80%. The two-sided significance level was 5% (0.05) for each pairwise comparison in each arm. The atorvastatin 10 mg, atorvastatin 20 mg, simvastatin 20 mg, and simvastatin 40 mg arms required 174 evaluable subjects in each of the two Period 2 treatment arms; that is, each of these 4 treatment arms required at least 348 evaluable subjects in Period 1. To allow for a dropout rate of approximately 10% during treatment, it was planned that 390 subjects would be randomized to the atorvastatin 10 mg, atorvastatin 20 mg, simvastatin 20 mg, and simvastatin 40 mg (Period 1 treatment) arms. Because of the Week 8 comparison, 390 subjects also were to be randomized to the rosuvastatin 20 mg arm for comparability. Hence, in total, 1950 subjects were to be randomized into the trial. To allow for a withdrawal rate of up to approximately 60% during the dietary lead-in period, it was planned that approximately 4875 subjects would be entered into the dietary lead-in period.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Investigational product: Rosuvastatin 10 mg or rosuvastatin 20 mg once daily in oral tablet form. The batch numbers for rosuvastatin 10 mg were: 2000026097, 2000030229, 2000030930, 2000031949, 2000034767, 80526J01, 84370A01, 90325E02. The batch numbers for rosuvastatin 20 mg were: 2000026931, 2000021421, 2000025904, 2000030461, 2000030933, 2000031293, 2000033770, 2000034769, 80579C01, 82995F01.

Comparator: Atorvastatin 10 mg (batch numbers: 2000026176, 2000043369, 84383J01), 20 mg (batch numbers: 2000026178, 2000043370, 84386A01), simvastatin 20 mg (batch numbers: 2000025853, 84384G01), 40 mg (batch numbers: 200025904, 84385D01), once daily in commercially available tablets.

Duration of treatment

After a 6-week dietary lead-in period, eligible subjects were randomized to rosuvastatin, atorvastatin, or simvastatin, once daily for 8 weeks (Period 1). This was followed by another 8 weeks of treatment (Period 2) with subjects randomized to either the same comparator at the

same dose given in Period 1, or rosuvastatin. After successful completion of the randomized treatment phase, eligible subjects could elect to participate in the open-label extension phase. This CSR reports on the randomized treatment phase.

Criteria for evaluation (main variables)

Efficacy

The following efficacy variables were studied in the randomized treatment phase.

Primary variable: Percentage of subjects achieving the NCEP ATP III LDL-C goal at Week 16 of treatment with rosuvastatin, atorvastatin, and simvastatin; subjects either had switched to rosuvastatin at Week 8 or had continued original comparator treatment.

Secondary variables:

1. Percentage of subjects achieving the EAS LDL-C goal at Week 16 of treatment with rosuvastatin, atorvastatin and simvastatin; subjects either had switched to rosuvastatin at Week 8 or had continued original comparator treatment.

2. Percentage of subjects achieving both the EAS LDL-C and TC goals at Week 16 of treatment with rosuvastatin, atorvastatin and simvastatin; subjects either had switched to rosuvastatin at Week 8 or had continued original comparator treatment.

3. Percentage of subjects achieving the Canadian Medical Association LDL-C goal at Week 16 of treatment with rosuvastatin, atorvastatin and simvastatin; subjects either had switched to rosuvastatin at Week 8 or had continued original comparator treatment.

4. Percentage of subjects achieving the NCEP ATP III LDL-C goal at Week 8 of treatment with rosuvastatin, atorvastatin and simvastatin.

5. Percentage of subjects achieving the EAS LDL-C goal at Week 8, and percentage of subjects achieving the Canadian LDL-C goal at Week 8 of treatment with rosuvastatin, atorvastatin and simvastatin.

6. Percentage of subjects who with high TG levels (≥200 mg/dL [2.26 mmol/L]) who have achieved their LDL-C and non-HDL-C goals at Week 16 of treatment, based on NCEP ATP III criteria, with rosuvastatin, atorvastatin and simvastatin; subjects either had switched to rosuvastatin at Week 8 or had continued original comparator treatment.

7. Percent change from baseline in TC, LDL-C, high-density lipoprotein cholesterol (HDL-C), TG, non-HDL-C, TC/HDL-C, LDL-C/HDL-C, non-HDL-C/HDL-C, Apolipoprotein B (ApoB), Apolipoprotein A-I (ApoA-I), ApoB/ApoA-I at Week 16 of treatment with rosuvastatin, atorvastatin and simvastatin; subjects either had switched to rosuvastatin at Week 8 or had continued original treatment.

8. Percent change from baseline in TC, LDL-C, HDL-C, TG, non-HDL-C, TC/HDL-C, LDL-C/HDL-C, non-HDL-C/HDL-C, ApoB, ApoA-I, ApoB/ApoA-I at Week 8 of treatment with rosuvastatin, atorvastatin and simvastatin.

Additional efficacy variables

- Percentages of subjects who achieved NCEP ATP III LDL-C, EAS LDL-C, EAS LDL-C and TC, and Canadian Medical Association LDL-C goals at 16 weeks of continuous treatment with rosuvastatin, atorvastatin, or simvastatin (ie, without switching treatments)
- Percent change from baseline in TC, LDL-C, HDL-C, TG, non-HDL-C, TC/HDL-C, LDL-C/HDL-C, non-HDL-C/HDL-C, ApoB, ApoA-I, ApoB/ApoA-I at 16 weeks of continuous treatment with rosuvastatin, atorvastatin or simvastatin (ie, without switching treatments)
- Percentage of subjects achieving LDL-C target < 100 mg/dL and Apolipoprotein B target of < 90 mg/dL at Week 16, subjects having switched to rosuvastatin at Week 8 or having continued on their original treatment
- Percent changes from Week 8 to Week 16 in TC, LDL-C, HDL-C, TG, non-HDL-C, TC/HDL-C, LDL-C/HDL-C, non-HDL-C/HDL-C, ApoB, ApoA-I, and ApoB/ApoA-I, subjects having switched to rosuvastatin at Week 8 or having continued their original treatment
- Analyses with EAS LDL-C were also conducted with EAS-3 LDL-C

Safety

The following secondary safety variables were studied in the randomized treatment phase:

1. Safety evaluation of rosuvastatin, atorvastatin and simvastatin therapy as determined by AEs and laboratory data at Weeks 8 and 16. Laboratory data included hematology, clinical chemistry (hepatic biochemistry and CK), urinalysis, vital signs and weight, physical examination, and systemic exposure to rosuvastatin.

2. Determination of whether there is a relationship between systemic exposure to rosuvastatin and calculated CrCl and/or CK. The relationship between rosuvastatin plasma concentration and calculated CrCl and CK were assessed at Week 8 and Week 16; subjects switched to rosuvastatin at Week 8 had rosuvastatin plasma concentration determination and CrCl and CK analyzed on 1 occasion (Week 16) only.

Statistical Methods

Efficacy

Efficacy analyses were performed on the intention-to-treat (ITT) population (using both last-observation carried forward [LOCF] and observed data) and the per protocol

(PP) population (using observed data). The Friedewald value was the primary efficacy measure for LDL-C, except at those visits where TG >400 mg/dL (4.52 mmol/L), when the β quantification measurement of LDL-C was used.

The current trial was designed primarily to evaluate the efficacy of rosuvastatin, compared with the other statins, in bringing additional subjects to goals. For the primary endpoint, there were 4 separate analyses for each of the secondary endpoints 1, 2, 3, and 6. *(The rosuvastatin 20-mg arm, involving no switch of treatment at Week 8, was not subject to these analyses of comparative efficacy at 16 weeks.*) For each of these analyses, the numbers of subjects reaching and not reaching goal on rosuvastatin and comparator at Week 16 were compared using a logistic regression analysis. Treatment and center were fitted as factors and baseline LDL-C included as a covariate. In each treatment arm, there was only 1 treatment comparison: rosuvastatin 10 mg versus comparator (atorvastatin 10 mg or simvastatin 20 mg) or rosuvastatin 20 mg versus comparator (atorvastatin 20 mg or simvastatin 40 mg).

Secondary endpoints 4 and 5 were analyzed in the same way; a single analysis was conducted for each endpoint to compare response across all 5 (Period 1) treatment arms at Week 8. The numbers of subjects reaching and not reaching goal at Week 8 were compared across all 5 (Period 1) treatment arms using a logistic regression analysis. Factors were fitted for treatment (rosuvastatin 20 mg, atorvastatin 10 mg and 20 mg, simvastatin 20 mg and 40 mg) and center, with baseline LDL-C included as a covariate. To allow for the 4 treatment comparisons in these analyses, a Bonferroni correction was applied and a significance level of 0.0125 used for each comparison.

During the course of the trial, the EAS guidelines were revised. These revised guidelines, hereafter referred to as EAS-3, were based on the Third Joint Task Force of European and other societies (Joint European Societies) on cardiovascular disease prevention in clinical practice. Subjects are assigned a risk group based on atherosclerotic disease, diabetes, total cholesterol, LDL-C, blood pressure, and 10-year risk of fatal cardiovascular disease. Analyses also were performed using these new EAS-3 guidelines in addition to the EAS guidelines that were published at the start of the study.

Secondary endpoint 7 was analyzed using analysis of variance (ANOVA) models. A separate ANOVA model was used for each lipid parameter within each set of Period 2 treatment arms (each arising from a single Period 1 treatment arm). The results were presented in terms of least squares means (LS means) and the difference between the LS means, with p-values and associated 95% confidence intervals for the 4 sets of (Period 2) treatment arms.

Secondary endpoint 8 used one ANOVA model for each lipid parameter to compare the percentage change from baseline at Week 8 across all 5 (Period 1) treatment arms. These results were presented in terms of LS means and differences between LS means for the comparisons of interest, with associated 98.75% confidence intervals and p-values for each comparison.

Subgroup analysis

Numbers and percentages of subjects reaching NCEP ATP III LDL-C goal at Week 16 (the primary efficacy analysis) were presented for relevant pre-specified subgroups defined according to age, sex, race, baseline renal function, and EAS risk group in the ITT population (LOCF data). Contingency tables (2x2) for the numbers and percentages reaching goal at Week 16 (EAS LDL-C, NCEP ATP III LDL-C, EAS LDL-C and TC) by Week 8 response (at goal/not at goal) were produced for the ITT population (LOCF data).

Additional efficacy analyses

An additional analysis directly compared all subjects (ITT population, LOCF data) from the rosuvastatin 20-mg arm and a subset of subjects from each of the other treatment arms, consisting of subjects who *did not switch treatment at 8 weeks*. The numbers of subjects reaching and not reaching goal (NCEP ATP III, EAS, EAS-3 and Canadian) at Week 16 were compared across the 5 treatment arms using a logistic regression analysis. A single analysis was conducted to compare response across these treatment arms at Week 16. An ANOVA model for each lipid parameter was used to compare the percentage change from baseline at Week 16 across the 5 treatment arms.

Additional analyses were also performed on the ITT population to compare treatment groups with respect to the percentage change from Week 8 LOCF to Week 16 in lipid parameters and the percentage of subjects reaching LDL-C target < 100 mg/dL and Apolipoprotein B target of < 90 mg/dL. These analyses were performed as described above using ANOVA and logistic regression analysis, respectively.

An exploratory logistic regression analysis was performed to assess the impact of pre-specified demographic and baseline variables on the numbers of subjects reaching NCEP ATP III LDL-C goal at 16 weeks in the ITT population (LOCF). These variables were age, sex, race, body mass index, baseline renal function (CrCl), baseline HDL-C, and baseline TG.

Safety

Subjects who received at least 1 dose of trial medication were included in the safety analysis. During the randomized treatment phase, AEs were classified either as reported during the dietary lead-in phase or as treatment-emergent during the randomized treatment phase (ie, either starting during the randomized treatment phase or ongoing from the dietary lead-in phase and subsequently worsening during the randomized treatment phase). The incidence of AEs was tabulated by treatment received according to the body system and preferred term. Hematology, clinical chemistry, and urinalysis data were listed for each subject and summarized for each treatment group. Hematology and clinical chemistry values outside the laboratory reference ranges were highlighted. Safety at 16 weeks was reported when all subjects completed the randomized treatment periods.

Plots were prepared to depict the relationship between rosuvastatin plasma concentrations and baseline creatinine clearance (CrCl), creatine kinase (CK), and the change from baseline in CK for the subset of subjects receiving rosuvastatin in Periods 1 and/or 2. Plots also were prepared to depict the relationship between CK and baseline CrCl as well as the change in rosuvastatin plasma concentrations from Week 8 to Week 16 and baseline CrCl.

Subject population

Of the 1993 subjects randomized to treatment with rosuvastatin, atorvastatin, or simvastatin:

- 1983 were analyzed for safety.
- At Week 8, 1933 subjects were analyzed for efficacy in an ITT population and 1586 in a PP population.
- At Week 16, 1827 subjects were analyzed for efficacy in an ITT population and 1384 in a PP population.

Overall, the treatment groups were comparable for demographic and baseline characteristics (age, sex, weight, BMI, renal impairment, and CHD risk factors). The age and sex balance in the trial population are common in subjects presenting with primary hypercholesterolemia in clinical practice, with 41% 65 years of age or greater and 56% male, overall. The majority of patients were white (80%, overall). Most subjects had normal (51%, overall) or mildly impaired (40%, overall; CrCl 50 to ≤80 mL/min) renal function.

More than sufficient subjects were recruited to give the trial the desired statistical power (80%). The trial population was adequately representative of the target population for statins, and their baseline characteristics resembled those in the target population. The use of concomitant medications was reasonable in the clinical context given the subject population under study.

Subject population and disposition are presented in Table S1.

Table S1 Study populations for Period 1 and Period 2 by randomized treatment groups, number of subjects (randomized subjects)

	Period 1					
	R20	**A10**	**A20**	**S20**	**S40**	**Total**
Randomized[a]	392	403	395	402	401	1993
Safety[b]	391	400	392	400	400	1983
Efficacy: Intention-to-treat Week 8[c]	383	389	383	387	391	1933
Efficacy: Intention-to-treat Week 16[d]	362	369	366	364	366	1827

	Period 2								
Period 2 treatment	**R20/R20**	**A10/R10**	**A10/A10**	**A20/R20**	**A20/A20**	**S20/R10**	**S20/S20**	**S40/R20**	**S40/S40**
Randomized[b]	367	191	185	186	186	183	190	189	191
Safety[c]	365	190	184	185	183	182	187	187	187
Efficacy: Intention-to-treat Week 8[d]	366	191	184	186	185	183	190	188	190
Efficacy: Intention-to-treat Week 16[e]	362	189	180	184	182	179	185	183	183

[a] All subjects randomized to receive trial therapy.

[b] The numbers of subjects who received treatment (ie, the safety population) presented in this table are based on actual treatment. One misrandomized subject who did not receive 1 of the randomized treatment assignments for Period 1 is not included.

[c] All subjects who received trial therapy in Period 1 and had a baseline reading and at least 1 postbaseline (Week 0) reading in Period 1 for 1 or more lipid variables.

[d] All subjects who received trial therapy in Periods 1 and 2 and had a baseline reading and at least 1 postbaseline (Week 0) reading in Periods 1 and 2 for 1 or more lipid variables.

[e] The numbers of subjects who received treatment (ie, the safety population) presented in this table are based on actual treatment. Misrandomized subjects (n=6) who did not receive 1 of the randomized treatment assignments are not included in this table but are included in other tabulations of safety.

A10 or A20, Atorvastatin 10 or 20 mg; R10 or R20, Rosuvastatin 10 or 20 mg; S20 or S40, Simvastatin 20 or 40 mg. (For example, S20/R10 represents simvastatin 20 mg in Period 1 followed by rosuvastatin 10 mg in Period 2).

Efficacy results

The current trial was designed primarily to evaluate the efficacy of switching from comparator statins to rosuvastatin, in bringing additional subjects with primary hypercholesterolemia and at high risk for coronary heart disease to LDL-C goals.

Compared to continuing on Period 1 treatment, switching to rosuvastatin at Week 8 brought significantly ($p<0.001$) more subjects to NCEP ATP III LDL-C goal (Table S2).

Table S2 Percentage of subjects reaching NCEP ATP III LDL-C goal at Week 16 (LOCF on ITT population)

Statistic		Treatment Period 1/Period 2[a]							
		A10/R10 (n=189)	**A10/A10 (n=180)**	**A20/R20 (n=184)**	**A20/A20 (n=182)**	**S20/R10 (n=179)**	**S20/S20 (n=185)**	**S40/R20 (n=183)**	**S40/S40 (n=183)**
Baseline LDL-C: mean (SD)	mg/dL	171.7 (27.68)	167.0 (27.23)	168.6 (25.78)	166.8 (26.66)	168.1 (24.55)	171.0 (26.47)	169.7 (26.92)	167.1 (28.79)
Week 16 LDL-C: mean (SD)	mg/dL	93.2 (26.93)	107.3 (24.97)	83.0 (26.08)	95.4 (26.99)	91.3 (25.29)	115.8 (29.35)	80.1 (26.21)	102.1 (30.69)
Reaching target: n/N[b]		124/189	75/180	145/184	116/182	131/179	58/184	153/183	102/182
Proportion reaching target		0.66	0.42	0.79	0.64	0.73	0.32	0.84	0.56
Difference: Rosuvastatin minus Comparator		0.24		0.15		0.42		0.28	
p-value[c]		<0.001		<0.001		<0.001		<0.001	

[a] Subjects who did not receive medication in Period 2 were not included in the analyses.
[b] n/N represents the number of subjects reaching target / the number with recorded data.
[c] p-value obtained from a logistic regression analysis. p-values <0.05 are statistically significant.
A10 or A20, Atorvastatin 10 or 20 mg; R10 or R20, Rosuvastatin 10 or 20 mg; S20 or S40, Simvastatin 20 or 40 mg; SD, Standard deviation; SE, Standard error.

Switching to rosuvastatin 10 mg significantly increased the percentage of subjects who achieved NCEP ATP III LDL-C goal at Week 16 compared to those who continued treatment with atorvastatin 10 mg (66% vs 42%) and simvastatin 20 mg (73% vs 32%). Switching to rosuvastatin 20 mg significantly increased the percentage of subjects who achieved NCEP ATP III LDL-C goal at Week 16 compared to those who continued treatment with atorvastatin 20 mg (79% vs 64%), and simvastatin 40 mg (84% vs 56%). The differences between rosuvastatin and comparator in the percentage of subjects who achieved NCEP ATP III LDL-C goal at Week 16 were all equal to or greater than the 15% used to size this trial and are considered to reflect a clinically meaningful benefit to switching to rosuvastatin.

Results for the secondary variables supported those for the primary variable. Compared with subjects who continued treatment with other statins, switching to rosuvastatin at Week 8 brought a significantly greater percentage of subjects to EAS LDL-C, EAS-3 LDL-C, Canadian Medical Association LDL-C, EAS LDL-C or EAS-3 LDL-C plus TC, and LDL-C plus ApoB goals at Week 16. Additionally, compared with subjects who continued treatment on other statins, switching to rosuvastatin at Week 8 brought a significantly greater percentage of subjects with high TG (≥200 mg/dL) to their LDL-C and non-HDL-C goals at Week 16.

Switching to rosuvastatin at Week 8 also significantly improved lipid profiles (eg, LDL-C, [Table S3] TC, non-HDL-C, LDL-C/HDL-C ratio, TC/HDL-C ratio, non-HDL-C/HDL-C ratio, ApoB, and ApoB/ApoA-I ratio) at Week 16. In addition, the analyses of the Week 8 data and data for continuous treatment for 16 weeks supported the clinical benefit of rosuvastatin 20 mg. The favorable effect of switching to rosuvastatin compared with continuing treatment with atorvastatin or simvastatin was consistent across age, sex, and renal function subgroups.

Table S3 Percentage change from baseline to Week 16 in LDL-C levels (LOCF on ITT population)

Statistic	Treatment Period 1/Period 2[a]							
	A10/R10 (n=189)	**A10/A10 (n=180)**	**A20/R20 (n=184)**	**A20/A20 (n=182)**	**S20/R10 (n=179)**	**S20/S20 (n=185)**	**S40/R20 (n=183)**	**S40/S40 (n=183)**
N	189	180	184	182	179	184	183	182
LS mean of % change (SE)	-46.6 (1.09)	-36.2 (1.08)	-50.8 (1.18)	-43.4 (1.19)	-45.5 (1.10)	-32.1 (1.11)	-53.7 (1.10)	-39.6 (1.08)
Difference Rosuvastatin minus comparator (SE)	-10.3 (1.42)		-7.5 (1.55)		-13.4 (1.47)		-14.2 (1.45)	
95% CI[b]	-13.1 to –7.5		-10.5 to –4.4		-16.3 to –10.5		-17.0 to –11.3	
p-value[c]	p<0.001		p<0.001		p<0.001		p<0.001	

[a]Subjects who did not receive medication in Period 2 were not included in the analyses.
[b]Lower and upper confidence interval limits for difference in LS means.
[c]p-values were based on 4 separate pairwise analyses. p-values<0.05 are statistically significant.
A10 or A20 Atorvastatin 10 or 20 mg; CI Confidence interval; LS mean least squares mean; R10 or R20 Rosuvastatin 10 or 20 mg; S20 or S40 Simvastatin 20 or 40 mg; SE Standard error.

Safety results

The numbers and percentages of subjects with treatment-emergent AEs during Periods 1 and 2 are summarized in Table S4 and Table S5, respectively.

Table S4 Number (%) of subjects who had at least 1 treatment-emergent adverse event in any category in Period 1 (safety population)

Category of adverse events[a]	Period 1 treatment – number of subjects (%)				
	R20 (n=391)	**A10 (n=400)**	**A20 (n=392)**	**S20 (n=400)**	**S40 (n=400)**
Subjects with any adverse event, n (%)	150 (38.4)	144 (36.0)	126 (32.1)	126 (31.5)	152 (38.0)
Subjects who died, n (%)	1 (0.3)	0	0	0	0
Subjects discontinued due to adverse events, n (%)b	15 (3.8)	12 (3.0)	7 (1.8)	16 (4.0)	9 (2.3)
Subjects with serious adverse events, n (%)	6 (1.5)	11 (2.8)	8 (2.0)	8 (2.0)	4 (1.0)
Subjects with other significant adverse events n (%)	0	0	0	0	0

[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.

[b] The discontinuations due to AEs for Period 1 include 5 subjects (134/0014, 0140/0064, 0149/0055, 0149/0064, 0623/0013) who were randomized into Period 2, did not receive drug in Period 2, and subsequently discontinued due to AE. The table also includes 3 subjects (0154/0032, 0209/0034, 0215/0061) whose AE started during Period 1, continued into Period 2 on the same treatment, and subsequently lead to discontinuation.

A10 or A20 Atorvastatin 10 or 20 mg; R20 Rosuvastatin 20 mg; S20 or S40 Simvastatin 20 or 40 mg.

n values represent the number of subjects in the safety population who actually received that treatment in Period 1.

Note: One subject (0183/0008) did not receive 1 of the 5 randomized treatments; the data for this subject, who did not have any AEs, are not accounted for here but are included in the listings of safety data in Appendix 12.2.

Table S5 Number (%) of subjects who had at least 1 treatment-emergent adverse event in any category in Period 2 (safety population)

	Period 2 treatment – number of subjects (%)					
Category of adverse events [a]	**R10 (n=372)**	**R20 (n=740)**	**A10 (n=185)**	**A20 (n=185)**	**S20 (n=188)**	**S40 (n=188)**
Subjects with any adverse event, n (%)	130 (34.9)	278 (37.6)	60 (32.4)	72 (38.9)	58 (30.9)	51 (27.1)
Subjects who died, n (%)	1 (0.3)	0	0	0	1 (0.5)	0
Subjects discontinued due to adverse events, n (%)	9 (2.4)	7 (0.9)	1 (0.5)	4 (2.2)	1 (0.5)	1 (0.5)
Subjects with serious adverse events, n (%)	5 (1.3)	12 (1.6)	4 (2.2)	3 (1.6)	5 (2.7)	3 (1.6)
Subjects with other significant adverse events n (%)	0	0	0	0	0	0

[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.

A10 or A20 Atorvastatin 10 or 20 mg; R10 or R20 Rosuvastatin 10 or 20 mg; S20 or S40 Simvastatin 20 or 40 mg;

n values represent the number of subjects in the safety population who actually received that treatment in Period 2.

Note: Subjects may appear in more than 1 treatment group.

In general, the adverse event profile was similar to what is expected during treatment with statins. There were no adverse events indicative of hepatic dysfunction, which has been reported previously with other statins. Myalgia was reported by 2.7% of subjects in Period 1 and 1.5% of subjects in Period 2. Only 1 muscle adverse event (leg cramps, COSTART term of hypertonia, in 1 subject) was associated with a clinically important elevation in CK (>10 times the upper limit of normal [ULN]); this subject was treated with rosuvastatin 20 mg and recovered following discontinuation. There were no cases of rhabdomyolysis.

Changes in clinical laboratory results were generally small and showed no treatment-related trends. Of the 1983 subjects in the safety population, only 1 (0.05%) subject had a clinically important elevation in alanine aminotransferase (ALT) (>3 times the ULN on 2 consecutive visits) and 5 (0.25%) had a clinically important elevation in CK (>10 times the ULN on at least 1 occasion). These individually clinically important abnormalities are consistent with the known effects of statins on skeletal muscle, did not suggest a difference among the treatment groups, and do not raise any particular safety concerns regarding treatment with rosuvastatin. A >30% increase from baseline in serum creatinine was reported by 23 subjects (1.2%). No subject had a clinically important elevation (ie, doubling) of creatinine. The creatinine increases occurred with all treatments and in both treatment periods and did not appear to reflect renal impairment. There were no cases of renal failure.

Shifts in urine protein (from none/trace to ≥++) were low in frequency and similar among the treatment groups. These shifts appeared to be neither persistent nor associated with other signs of renal injury such as hematuria or elevated creatinine.

Over the ranges examined, neither increased rosuvastatin plasma concentration nor decreased CrCl appear to be associated with elevated CK.

Changes in vital signs and physical findings were small and showed no safety concerns.

Date of the report

17 November 2004