Drug product:	Rosuvastatin tablets 10 mg and 20 mg	**SYNOPSIS**	
Drug substance(s):	Rosuvastatin calcium		
Document No.:	001		
Edition No.:	001		
Study code:	D3560C00069		
Date:	15 December 2004		

A 12-week, randomised, double-blind, force-titration, parallel group, multicentre, phase IIIB study to compare the efficacy of rosuvastatin with atorvastatin and placebo in the treatment of non-diabetic, non-atherosclerotic, metabolic syndrome patients with raised LDL-C and a 10-year risk for CHD of >10%

Publications

Stalenhoef et al, 2003 (Design abstract presented at the International Diabetes Federation Congress, Paris, August 2003.)

Study dates		**Phase of development**
First patient enrolled	16 May 2002	Therapeutic confirmatory (IIIb)
Last patient completed	30 September 2003	

Objectives

The primary objective of this study was to compare the effect of rosuvastatin 10 mg with atorvastatin 10 mg in the percentage reduction of low-density lipoprotein cholesterol (LDL-C) in patients with metabolic syndrome after 6 weeks of treatment.

The secondary objectives were:

1. To compare the effects of rosuvastatin 10 mg with atorvastatin 10 mg and placebo after 6 weeks of treatment in patients with metabolic syndrome, on:

- bringing patients to an optimal LDL-C target goal of <100 mg/dL (2.59 mmol/L)[1]
- bringing patients to their established European Atherosclerosis Society /National Cholesterol Education Program (EAS/NCEP-ATP III) LDL-C target goals
- bringing patients with high triglycerides (TG) [≥200 mg/dL (2.26 mmol/L) at baseline] to their non-high-density lipoprotein (nonHDL-C) target goal (based on NCEP-Adult Treatment Panel [ATP] III criteria)
- bringing patients who have achieved their NCEP ATP-III LDL-C target goal at 6 weeks, but remain with elevated TG ≥200 mg/dL (2.26 mmol/L), to their nonHDL-C target goal (based on NCEP-ATP III criteria)
- modifying other lipids and lipoproteins
- modifying glucose metabolism
- modifying insulin resistance
- modifying inflammatory markers
- safety.

2. To compare the effects of combined rosuvastatin 10/20 mg and placebo/rosuvastatin 20 mg with atorvastatin 10/20 mg after 12 weeks of treatment in patients with metabolic syndrome, on:

- percentage reduction of LDL-C
- bringing patients to an optimal LDL-C target goal of <100 mg/dL (2.59 mmol/L)
- bringing patients to their established EAS/NCEP LDL-C target goals

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[1] The optimal target LDL-C target goal of <100 mg/dL (2.59 mmol/L) was incorrectly expressed in the protocol as ≤100 mg/dL (2.59 mmol/L)

- modifying other lipids and lipoproteins
- bringing patients with high TG [≥200 mg/dL (2.26 mmol/L) at baseline] to their nonHDL-C target goal (based on NCEP-ATP III criteria)
- bringing patients who have achieved their NCEP-ATP III LDL-C target goal at 12 weeks, but remain with elevated TG ≥ 200 mg/dL (2.26 mmol/L), to their nonHDL-C target goal (based on NCEP-ATP III criteria)
- modifying glucose metabolism
- modifying insulin resistance
- modifying inflammatory markers.

3. To compare the effects of rosuvastatin 10/20 mg with atorvastatin 10/20 mg and placebo/rosuvastatin 20 mg after 12 weeks of treatment in patients with metabolic syndrome, on:

- safety.

4. To explore the effect of rosuvastatin in modifying glucose metabolism and insulin resistance in patients with metabolic syndrome, after extended treatment with rosuvastatin.

5. To assess the safety of extended treatment with rosuvastatin.

Study design

This was a multicentre study conducted in non-diabetic, non-atherosclerotic patients with metabolic syndrome, elevated LDL-C and a 10-year risk for coronary heart disease (CHD) of >10% comprising: a 12-week, 3-arm, parallel group, double-blind, double-dummy, randomised, force-titration period comparing the efficacy and safety of rosuvastatin with atorvastatin and placebo; plus an open-label extension.

Patients underwent a 4-week dietary lead-in period when they were asked to follow the NCEP-ATP III Therapeutic Lifestyle Change (TLC) diet (Appendix I).

At the end of the 4 weeks, eligible patients who elected to continue to follow the diet were randomised at Visit 3 (the first visit of the randomised treatment period) to 1 of 3 treatment groups: rosuvastatin 10 mg, atorvastatin 10 mg or placebo for 6 weeks of treatment. This was Period 1 of the randomised treatment period. Patients were then force-titrated to receive rosuvastatin 20 mg (if they initially received rosuvastatin 10 mg or placebo) or atorvastatin 20 mg (if they initially received atorvastatin 10 mg), for a further 6 weeks. This was Period 2 of the randomised treatment period.

After successful completion of the initial 12 weeks of randomised treatment, patients were to be allowed to participate in an open-label extension period with rosuvastatin, during which

patients could titrate up from rosuvastatin 20 mg to 40 mg, if necessary, in order to meet their ATP III LDL-C and nonHDL-C target goal. Patients whose LDL-C fell below 50 mg/dL (1.30 mmol/L) could back-titrate from 20 or 40 mg to 10 or 20 mg.

This clinical study report presents results for the dietary lead-in and randomised force-titration period; results of the extension period will be reported separately.

Target patient population and sample size

Male and female patients, aged 18 years or older, with metabolic syndrome (as defined by the NCEP-ATP III guidelines), plus a raised LDL-C [≥130 mg/dL (3.36 mmol/L)]. Patients had multiple risk factors that conferred a 10-year risk score >10% for CHD, without CHD or other atherosclerotic disease (as defined by NCEP-ATP III). Diabetic patients were excluded and all patients were statin-naïve.

A total of 133 evaluable patients per active treatment group were required for 90% power of detecting a difference of 6% at the 5% two-sided level on LDL-C at Week 6 with an assumed standard deviation of 15%. Assuming a dropout of 10% during the randomised treatment period, approximately 150 patients were to have been recruited to each active treatment group. Furthermore, 75 patients in the placebo group were considered to be sufficient to detect differences between rosuvastatin 10 mg and placebo in ApoCIII, ApoCIII:B and other lipid and lipoprotein endpoints. In order to obtain the required number of randomised patients, it was expected that approximately 940 patients needed to be screened, based on a screening failure rate of 60%.

The additional response in LDL-C reduction resulting from doubling the dose of statins is typically around 6%. Therefore, an additional 6% reduction of LDL-C was considered to be clinically relevant.

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

Rosuvastatin (ZD4522, Crestor™) 10 mg and 20 mg tablets, and atorvastatin (Lipitor™) 10 mg and 20 mg capsules. Batch numbers were: rosuvastatin 10 mg TS11008, TS11015, rosuvastatin 20 mg PCA04V, PCA05V and PCA07V; and atorvastatin 10 mg ST73060-001-FB05, ST73060-001-FB08, and atorvastatin 20 mg ST74018-001-FA04, ST74018-001-FA06.

Period 1: Arm 1 - active rosuvastatin 10 mg + placebo to match atorvastatin 10 mg

Arm 2 - active atorvastatin 10 mg + placebo to match rosuvastatin 10 mg

Arm 3 - placebo to match rosuvastatin 10 mg + placebo to match atorvastatin 10 mg

Period 2: Arm 1 - active rosuvastatin 20 mg + placebo to match atorvastatin 20 mg

Arm 2 - active atorvastatin 20 mg + placebo to match rosuvastatin 20 mg

Arm 3 - active rosuvastatin 20 mg + placebo to match atorvastatin 20 mg

Extension:Rosuvastatin 10 mg, 20 mg or 40 mg.

All treatments were to be taken once daily in oral tablet/capsule form.

Duration of treatment

The study consisted of a 4-week dietary lead-in period, followed by two 6-week treatment periods (Periods 1 and 2). Patients could then elect to enter the open-label extension period of treatment with rosuvastatin. Patients were to continue in the extension until rosuvastatin was launched in their country.

Criteria for evaluation (main variables)

Efficacy

Note: for efficacy analysis at Week 12 the rosuvastatin 10/20 mg and placebo/rosuvastatin 20 mg arms were combined.

- Primary variable:
  - Percent change from baseline in LDL-C at Week 6 (rosuvastatin 10 mg and atorvastatin 10 mg only).
- Secondary variables:
  - Percent change from baseline in LDL-C at Week 6 (rosuvastatin 10 mg and placebo only)
  - Percent change from baseline in LDL-C at Week 12
  - Number and percentage of patients reaching an optimal LDL-C target goal of <100 mg/dL (2.59 mmol/L) at Weeks 6 and 12
  - Number and percentage of patients reaching their NCEP LDL-C target goals and the number and percentage of patients reaching their EAS LDL-C target goal at Week 6 and 12
  - Number and percentage of patients who achieve their NCEP nonHDL-C target goal at Weeks 6 and 12 [patients with baseline TG ≥200 mg/dL (2.26 mmol/L) only]
  - Number and percentage of patients who achieve their NCEP nonHDL-C target goal at Weeks 6 and 12 [whose TG remain ≥200 mg/dL (2.26 mmol/L) at Weeks 6 and 12]

- Percent change from baseline in total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), TG, NonHDL-C (TC-HDL-C), TC/HDL-C, LDL-C/HDL-C, NonHDL-C/HDL-C, LDL-C subfractions, small HDL, large HDL, very low-density lipoprotein-TG (VLDL-TG), VLDL-apolipoprotein B (VLDL-ApoB), LDL-ApoB, total ApoCII, total ApoCIII, ApoB, ApoA-I, ApoB/ApoA-I, ApoCIII-B, ApoA-II at Weeks 6 and 12

- Percent change from baseline in fasting plasma glucose at Weeks 6 and 12

- Percent change from baseline in insulin resistance using homeostasis model assessment (HOMA) at Weeks 6 and 12

- Percent change from baseline in C-reactive protein (hsCRP), e-selectin and interleukin-6 at Weeks 6 and 12.

In addition, the effect of age, sex, body mass index (BMI), waist circumference and baseline lipids on LDL-C was investigated at Week 6.

Safety

Safety evaluation was determined by the incidence of adverse events and abnormal laboratory data, and vital signs. Weight and waist circumference were also assessed.

Safety during the second 6 weeks of treatment was assessed separately for each of the 3 treatment groups (rosuvastatin 10/20 mg, atorvastatin 10/20 mg and placebo/rosuvastatin 20 mg).

Statistical methods

Efficacy

The study populations for efficacy analyses were as follows:

- The intention-to-treat (ITT) population comprised all patients who had at least 1 dose of study medication, a baseline reading and at least one post-baseline reading for 1 or more lipid variables in the randomised treatment period. A misunderstanding by some investigators led to misrandomisation of 42 patients. Instead of receiving the next available randomisation number and designated treatment according to the protocol methodology, these patients were allocated a blinded bottle of treatment medication. This was a genuine error with no intention to bias the study; therefore, these patients were allowed to continue in the study. Thus the ITT population was split into 2 presentations for analysis (both presentations comprising all ITT patients):

  - ITT population by ‘randomised’ treatment: analysed according to the treatment group to which the patients should have been assigned according to the randomisation schedule

  - ITT population by ‘as allocated’ treatment: analysed according to the treatment group to which the patients were actually assigned.

- PP population (subset of the ITT population) excluded patients who were major clinical study protocol violators or major clinical study protocol deviators. A major violation resulted in total exclusion of the patient from the PP analysis. A major deviation resulted in exclusion of the patient from the point where the deviation occurred (ie, at the affected visit and all subsequent visits). All misrandomised patients were excluded from the PP population.

Efficacy analyses were performed on ITT population by ‘randomised’ and by ‘as allocated’ treatment using last observation carried forward (LOCF) – the primary focus – and observed data. Analyses on the PP population used observed data only. In addition to the ITT and PP populations was the randomised population, which was comprised of all randomised patients: this was presented by ‘as allocated’ treatment group. The randomisation population by ‘as allocated’ treatment was used for patient disposition, populations and baseline information.

The primary result for the primary efficacy variable (using LOCF) was on the ITT population by 'randomised' treatment, as specified in the statistical analysis plan (SAP). However, the ITT population by 'as allocated' treatment is the focus in this report, since it uses the ITT approach but does not introduce any bias as the misrandomisations occurred whilst blind to treatment and is deemed the more clinically relevant, since it is likely to be more reflective of treatment effects. Therefore, results are presented for the primary endpoint for the ITT population by 'randomised' treatment and by 'as allocated' treatment. Thereafter, results are presented for all efficacy variables for the ITT population by ‘as allocated’ treatment. The PP analysis was performed as a robustness check of the ITT population analyses.

Patients were grouped (both ‘randomised’ and ‘as allocated’) according to treatment (rosuvastatin, atorvastatin, placebo). At Week 6, comparisons were made for rosuvastatin versus atorvastatin and rosuvastatin versus placebo. At Week 12, a comparison was made between all patients receiving rosuvastatin, grouped and analysed in a combined group (rosuvastatin 10/20 mg plus placebo/rosuvastatin 20 mg, ‘rosuvastatin combined’) and patients receiving atorvastatin 10/20 mg.

The primary analysis was analysis of variance (ANOVA) on the Week 6 percent change from baseline in LDL-C, comparing the rosuvastatin arm with the atorvastatin arm. The model included terms for treatment and centre. Results were presented as an estimate of the difference between treatments along with the 95% confidence intervals (CIs). The p-value was presented for the test of hypothesis that there was no difference between treatments (European Agency for the Evaluation of Medicinal Products, 2000).

All other endpoints were either supportive or exploratory, and so no adjustment of the significance level was necessary. Analysis of the secondary lipids, lipoproteins and the analysis of the HOMA data were to be conducted as for the primary efficacy variable, using ANOVA. For some parameters, ANOVA was inappropriate and analysis was performed using either analysis of covariance (ANCOVA) on post-baseline values, comparing treatment

groups including baseline value as a covariate or using a non-parametric Kruskal-Wallis test. The effects of age, sex, BMI, waist circumference, race and baseline lipids on LDL-C response were investigated by ANCOVA with each term being added to the model individually.

The numbers and percentages of patients reaching NCEP-ATP III, optimal NCEP (ie, LDL < 100 mg/dL) and Joint European targets were analysed by logistic regression. Results were reported as odds ratios and their 95% CI, together with p-values and summary statistics of the proportions of subjects reaching targets. The p-values were from likelihood ratio χ 2 tests, and the CIs were profile likelihood intervals.

Summary statistics were produced for numbers and percentages of patients reaching their NCEP-ATP III nonHDL-C target. These data were presented for all subjects, and for only those subjects who reached their LDL-C targets. No formal statistical analysis was performed on the NCEP-ATP III nonHDL-C target.

Analysis of inflammatory marker endpoints was performed using the non-parametric Kruskal-Wallis test as planned in the SAP.

Assessment of lipid fractions

NMR methodology was used to assess the effects of treatment on lipoprotein subfractions. The results were analysed by a method (Lipoprofile I) that reported the results in terms of lipoprotein cholesterol levels. Following database lock, the data were further analysed by an improved method (Lipoprofile II), which reported the results in terms of concentrations of lipoprotein particles. The improved Lipoprofile II analysis method was not available at the time of the database lock and therefore not specified in either the protocol or statistical analysis plan.

Safety

Two populations were defined for the analysis of safety: a safety analysis set which comprised all patients who entered the dietary lead-in period (Visit 1 onwards), and a safety population which comprised all patients who were randomised and started study medication (ie, had at least 1 dose of study medication). The safety population was based on actual treatment received; the safety analysis set was based on actual treatment received in the randomised phase.

Patient population

In total, 1338 individual patients were screened, of whom 401 were randomised to the 3 treatment groups. Failure to meet inclusion/exclusion criteria was the most common reason for withdrawal from the dietary lead-in period. Following randomisation, 8 (4.8%) patients in the rosuvastatin 10/20 mg group, 8 (5.1%) patients in the atorvastatin 10/20 mg group and 4 (5.1%) patients in the placebo/rosuvastatin 20 mg group withdrew. At baseline, 29 (17.6%) patients in the rosuvastatin 10/20 mg group, 38 (24.2%) patients in the atorvastatin 10/20 mg

group and 16 (20.3%) patients in the placebo/rosuvastatin 20 mg group were protocol violators or deviators.

Forty-two (10.5%) patients were misrandomised due to a misunderstanding by some of the investigators. Thus, the ITT population was presented and analysed by 'as allocated' and by 'as randomised' treatment. The randomised population by 'as allocated' treatment comprised 165 patients in the rosuvastatin 10/20 mg group, 157 in the atorvastatin 10/20 mg group and 79 in the placebo/rosuvastatin 20 mg group. Both the ITT population by 'randomised' treatment and the ITT population by 'as allocated' treatment comprised 164 patients in the rosuvastatin 10/20 mg group, 155 in the atorvastatin 10/20 mg group and 78 in the placebo/rosuvastatin 20 mg group, although the 2 presentations did not contain an identical set of patients. The PP population, which excluded major protocol violators and deviators (including misrandomised patients), comprised 136 patients in the rosuvastatin 10/20 mg group, 119 in the atorvastatin 10/20 mg group and 63 in the placebo/rosuvastatin 20 mg group. Five patients received treatment other than that to which they were allocated (due to dispensing errors): for the safety analysis, these patients were classified 'Other'.

Patients were between 31 and 82 years of age and 97.8% were Caucasian. Demographic characteristics and medical history of the randomised patients were generally representative of the target population for the investigational product and were reasonably well matched between treatment groups. Overall, approximately two-thirds of the population were male.

The treatment groups were well balanced with respect to NCEP-ATP III risk category. With a mean overall weight of 91.4 kg, patients were generally overweight but this was to be expected in this population. All but 4 patients (1 in the rosuvastatin 10/20 mg group and 3 in the atorvastatin 10/20 mg group) met at least 3 criteria for metabolic syndrome. Although the mean BMI values were similar in each treatment group, more patients had a BMI $\geq$30 kg/m^2 in the atorvastatin 10/20 mg group than in the rosuvastatin 10/20 mg or placebo/rosuvastatin 20 mg groups. Almost all patients had hypertension or were being treated with hypertensive medication (97.3%), abdominal obesity (92.3%) and triglycerides $\geq$150 mg/dL (85.3%); the treatment groups were well balanced with respect to these parameters. Less than half the patients had low HDL (45.6%) and few patients had elevated blood glucose. The treatment groups were generally well balanced with respect to risk factors.

The number of patients who were more than 80% compliant with taking study medication was high. One patient took concomitant medication disallowed by the protocol.

Efficacy results

Results of the analysis of the percent change from baseline in LDL-C after 6 weeks of treatment (at Week 6), for rosuvastatin and atorvastatin, are shown in Table S1. Results are presented for the ITT population by 'randomised' treatment (the primary result) and by 'as allocated' treatment (the focus for efficacy variables), as previously described in the statistical methods efficacy section.

Table S1 Analysis of percent change from baseline in LDL-C after 6 weeks of treatment with rosuvastatin 10 mg or atorvastatin 10 mg (LOCF on ITT population)

	ITT population by 'randomised' treatment		ITT population by 'as allocated' treatment	
	Rosuvastatin 10 mg	**Atorvastatin 10 mg**	**Rosuvastatin 10 mg**	**Atorvastatin 10 mg**
Statistic				
	N=164	**N=155**	**N=164**	**N=155**
LDL-C value				
Baseline[a]				
n	164	153	164	153
mg/dL, mean (SD)	168.3 (24.95)	170.1 (25.74)	169.7 (25.45)	168.0 (25.22)
mmol/L, mean (SD)	4.360 (0.6463)	4.405 (0.6666)	4.396 (0.6591)	4.351 (0.6529)
Week 6 (LOCF)				
n	162	151	162	151
mg/dL, mean (SD)	96.7 (27.03)	108.1 (25.76)	96.0 (25.22)	105.3 (25.28)
mmol/L, mean (SD)	2.505 (0.7002)	2.799 (0.6669)	2.486 (0.6532)	2.727 (0.6547)
Analysis[b]				
Number in analysis	162	150	162	150
LS mean percent change at Week 6 (SE)	–41.7 (1.23)	–35.7 (1.30)	–42.7 (1.07)	–36.6 (1.12)
	Rosuvastatin 10 mg versus atorvastatin 10 mg		**Rosuvastatin 10 mg versus atorvastatin 10 mg**	
Difference[c] (SE)	–6.1 (1.73)		–6.1 (1.50)	
95% CI	–9.5 to –2.7		–9.1 to –3.2	
p value[d]	0.0005		<0.0001	

[a] The means at baseline and Week 6 are presented for all patients with a baseline value or Week 6 value and not for patients with both a baseline and Week 6 value.

[b] Analysis of variance (ANOVA) at Week 6 (last observation carried forward [LOCF]).

[c] Difference in least squares (LS) mean percent change (rosuvastatin 10 mg minus atorvastatin 10 mg).

[d] p-value for treatment effect from ANOVA model with terms for treatment and country; $p<0.05$ is statistically significant.

N = number of patients in the intention to treat (ITT) population; n = number of patients with recorded data;
SD = standard deviation; SE = standard error; CI = confidence interval.

Primary variable

A greater reduction in LDL-C was observed after 6 weeks in patients in the rosuvastatin 10 mg group compared with patients in the atorvastatin 10 mg group and this difference was statistically significant (–41.7% versus –35.7% respectively, p=0.0005 for the ITT population by 'randomised' treatment; –42.7% versus –36.6%, respectively, p<0.0001 for the ITT population by 'as allocated' treatment).

Secondary LDL-C variables and lipid target goals

A statistically significant greater reduction in LDL-C was observed after 12 weeks in patients in the 'rosuvastatin combined' group compared with patients in the atorvastatin 10/20 mg group.

A statistically significant greater percentage of patients reached the optimal LDL-C target goal of <100 mg/dL in the rosuvastatin 10 mg group compared with patients in the atorvastatin 10 mg group at Week 6, as did patients in the 'rosuvastatin combined' group compared with patients in the atorvastatin 10/20 mg group at Week 12.

A statistically significant greater percentage of patients reached their NCEP-ATP III LDL-C target goal in the rosuvastatin 10 mg group compared with patients in the atorvastatin 10 mg group at Week 6, as did patients in the 'rosuvastatin combined' group compared with patients in the atorvastatin 10/20 mg group at Week 12. Similarly, a statistically significant greater percentage of patients reached their EAS LDL-C target goal in the rosuvastatin 10 mg group compared with patients in the atorvastatin 10 mg group at Week 6, as did patients in the 'rosuvastatin combined' group compared with patients in the atorvastatin 10/20 mg group at Week 12.

At Week 6, a statistically significant greater reduction in LDL-C was observed and more patients achieved their LDL-C target goals (ie, optimal goal of <100 mg/dL, NCEP and EAS) in the rosuvastatin 10 mg group compared with patients in the placebo group.

For the patients with baseline TG ≥200 mg/dL and for those patients whose TG remained ≥200 mg/dL, the proportion of patients achieving both the NCEP-ATP III LDL-C and nonHDL-C target goals was higher in the rosuvastatin 10 mg group than in the atorvastatin 10 mg group at Week 6, and was higher in the 'rosuvastatin combined' group than in the atorvastatin 10/20 mg group at Week 12. As specified in the statistical analysis plan, no formal statistical analysis was performed for this variable.

Other lipids and apolipoproteins

Treatment with rosuvastatin resulted in a lipid and lipoprotein profile that was generally more favourable than that seen in patients treated with atorvastatin. Results for the main lipids, apolipoproteins of interest are summarised below.

At Week 6, in both rosuvastatin 10 mg and atorvastatin 10 mg groups there was an increase in HDL-C and large reductions in serum TC, nonHDL-C, TG and lipid ratios (TC/HDL-C, nonHDL-C/HDL-C and LDL-C/HDL-C). The increase in HDL-C and decrease in TC, nonHDL-C and lipid ratios was greater (statistically significant difference in mean percentage change between treatment groups) in patients in the rosuvastatin 10 mg group compared with patients in the atorvastatin 10 mg group. At Week 12, in both the 'rosuvastatin combined' and atorvastatin 10/20 mg groups there was an increase in HDL-C and large reductions in TC, nonHDL-C, TG and lipid ratios. The mean increase in HDL-C and mean decrease in TC, nonHDL-C and lipid ratios were greater (statistically significant difference between treatment groups) in patients in the 'rosuvastatin combined' group compared with patients in the atorvastatin 10/20 mg group.

At Week 6 there was an increase in ApoA-I and large reductions in ApoB and the ratio ApoB/ApoA-I in both rosuvastatin 10 mg and atorvastatin 10 mg groups. There was a statistically significant greater increase in ApoA-I and statististically significant greater decrease in ApoB and ApoB/ApoA-I in patients in the rosuvastatin 10 mg group compared with patients in the atorvastatin 10 mg group. At Week 12 there was an increase in ApoA-I and large reductions in ApoB and the ratio ApoB/ApoA-I in both 'rosuvastatin combined' and atorvastatin 10/20 mg groups. There was a statistically significant greater increase in ApoA-I and a statistically significant greater decrease in ApoB and ApoB/ApoA-I in patients in the patients in the 'rosuvastatin combined' group compared with patients in the atorvastatin 10/20 mg group.

Lipoprofile I and II analysis of lipid subfractions

The key findings were as follows:

At Week 6 there was a large percentage increase in intermediate HDL-C (using Lipoprofile I) and large percentage increase in large HDL-C (Lipoprofile I) / large HDL (Lipoprofile II) and little change in small HDL-C (Lipoprofile I) / small HDL (Lipoprofile II) in both rosuvastatin 10 mg and atorvastatin 10 mg groups. There was a statistically significant greater increase in large HDL-C (Lipoprofile I) / large HDL (Lipoprofile II) in patients in the rosuvastatin 10 mg group compared with patients in the atorvastatin 10 mg and placebo groups (as indicated by analysis of mean percentage change using Lipoprofile I and analysis of median percentage change using Lipoprofile II). At Week 12, there was a large percentage increase in intermediate HDL-C (using Lipoprofile I) and large HDL-C (Lipoprofile I) / large HDL (Lipoprofile II) and little change in small HDL-C (Lipoprofile I) / small HDL (Lipoprofile II) in both 'rosuvastatin combined' and atorvastatin 10/20 mg groups. There was a statistically significant greater increase in large HDL-C (Lipoprofile I) / large HDL (Lipoprofile II) in patients in the 'rosuvastatin combined' group compared with patients in the atorvastatin 10/20 mg group.

At Week 6, patients in the rosuvastatin 10 mg and atorvastatin 10 mg groups showed decreases from baseline in large LDL-C (Lipoprofile I) / large LDL (Lipoprofile II), small LDL-C (Lipoprofile I) / small LDL (Lipoprofile II) and intermediate LDL-C (Lipoprofile I). Using Lipoprofile I there was no statistically significant difference in the comparison of the

rosuvastatin 10 mg and atorvastatin 10 mg groups for change in any LDL-C subfraction. However, Lipoprofile II analysis indicated a statistically significant greater percentage reduction in small LDL in patients in the rosuvastatin 10 mg group compared with patients in the atorvastatin 10 mg group. At Week 12, patients in the 'rosuvastatin combined' and atorvastatin 10/20 mg groups showed decreases from baseline in concentrations of large LDL-C (Lipoprofile I) / large LDL (Lipoprofile II , intermediate LDL-C (Lipoprofile I) and small LDL-C (Lipoprofile I) / small LDL (Lipoprofile II). There was no statistically significant difference in the comparison of the 'rosuvastatin combined' and atorvastatin 10/20 mg groups for change in any LDL-C / LDL subfraction.

HOMA and blood glucose

There was little change from baseline in fasting blood glucose and no statistically significant difference between the treatment groups at Week 6 or Week 12. There was no real change in HOMA in any treatment group and no statistically significant differences between the treatment groups.

Inflammatory markers

Median hsCRP concentrations decreased in all 3 treatment groups at Week 6 and further decreased at Week 12. There were no statistically significant differences between the treatment groups.

Changes from baseline in e-selectin and interleukin 6 at Weeks 6 and 12 were small in all treatment groups and there were no statistically significant differences between rosuvastatin and atorvastatin.

Safety results

Adverse events (AEs) by category and the number (percentage) of patients with treatment-emergent AEs during the first 6 weeks (Period 1) and second 6 weeks (Period 2) of randomised treatment are summarised in Table S2.

Table S2 Number (percentage) of patients with treatment-emergent AEs and total number of AEs by category during the first 6 and second 6 weeks of randomised treatment[a]

Category of adverse event	Number (percentage) of patients who had a treatment emergent adverse event in each category[b]							
	Period 1				Period 2			
	Rosuvastatin 10 mg	Atorvastatin 10 mg	Placebo	Other	Rosuvastatin 10/20 mg	Atorvastatin 10/20 mg	Placebo/ Rosuvastatin 20 mg	Other
	N=163	N=154	N=79	N=5	N=158	N=150	N=75	N=4
Any adverse events	41 (25.2)	39 (25.3)	14 (17.7)	0	35 (22.2)	31 (20.7)	18 (24.0)	2 (50)
Serious adverse events	0	3 (1.9)	0	0	1 (0.6)	1 (0.7)	0	0
Serious adverse events leading to death	0	1 (0.6)	0	0	0	1 (0.7)	0	0
Serious adverse events not leading to death	0	2 (1.3)	0	0	1 (0.6)	0	0	0
Discontinuations of study treatment due to adverse events	2 (1.2)	3 (1.9)	3 (3.8)	0	2 (1.3)	1 (0.7)	0	0
	Total number of adverse events[b]							
Adverse events	53	62	27	0	53	52	29	2
Serious adverse events	1	3	0	0	1	1	0	0
Adverse events leading to discontinuation	2	3	5	0	2	1	0	0

[a] Safety population by actual treatment received.

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

N = number of patients in the safety population.

Both rosuvastatin 10/20 mg and atorvastatin 10/20 mg were generally well tolerated. A similar incidence of treatment-emergent AEs was experienced in both treatment groups with the majority of AEs being of mild to moderate intensity. Two patients (1.3%) in the atorvastatin 10/20 mg group died from cardiovascular causes: 1 patient during Period 1 and 1 during Period 2. Three patients experienced non-fatal SAEs during the randomised period: 1 in the rosuvastatin 10/20 mg group during Period 2; 2 in the atorvastatin 10/20 mg group during Period 1. No serious adverse events (SAEs) occurred in the placebo/rosuvastatin 20 mg group. During Period 1, 2 (1.2%) patients in the rosuvastatin 10 mg group, 3 (1.9%) patients in the atorvastatin 10 mg group and 3 (3.8%) patients in the placebo group experienced AEs leading to study drug discontinuation (DAEs). During Period 2, 2 (1.3%) patients in the rosuvastatin 10/20 mg group, 1 (0.7%) patient in the atorvastatin 10/20 mg group and 0 patients in the placebo/rosuvastatin 20 mg group experienced DAEs.

Concerning muscle symptoms, during Period 1, 9 (5.5%) patients experienced 10 AEs in the rosuvastatin 10 mg group, 13 (8.4%) patients experienced 17 AEs in the atorvastatin 10 mg group and 4 (5.1%) patients experienced 5 AEs in the placebo group (for completeness, counts include AEs in this category that were serious and DAEs). During Period 2, 8 (5.1%) patients experienced 11 AEs in the rosuvastatin 10/20 mg group, 4 (2.7%) patients experienced 5 AEs in the atorvastatin 10/20 mg group and 7 (9.3%) patients experienced 7 AEs in the placebo/rosuvastatin 20 mg group (for completeness, counts include AEs in this category that were serious and DAEs). Treatment-emergent myalgia occurred with low frequency in all treatment groups in both period: during Period 1 in 3 (1.8%), 2 (1.3%) and 2 (2.5%) patients in the rosuvastatin 10 mg, atorvastatin 10 mg and placebo groups respectively; during Period 2 in 4 (2.5%), 3 (4.0%) and 1 (0.7%) patients the rosuvastatin 10/20 mg, placebo/rosuvastatin 20 mg and atorvastatin 10/20 mg groups, respectively. Myalgia was associated with increased serum CK in 1 patient, from the rosuvastatin 10/20 mg group, in whom CK was elevated to >10 times ULN, which is consistent with a diagnosis of myopathy. CK levels were elevated to >10 times ULN in 1 further patient in the atorvastatin 10/20 mg group who had asymptomatic, exercise-induced elevation in CK.

Concerning hepatic symptomatology there was no suggestion of clinically important hepatic dysfunction in any treatment group. ALT elevations >3 times ULN occurred in 1 (0.6%) patient in the rosuvastatin 10/20 mg group. Other hepatic data were generally unremarkable and there were no clinically important differences between treatments. Changes in the other laboratory data (haematology, renal, other biochemistry) were generally small and there were no clinically important differences between treatments.

Vital signs and physical examination data, urinalysis and renal chemistry data (including serum creatinine) were generally unremarkable and there were no clinically important differences between treatments.