Drug product:	Rosuvastatin tablets 10, 20 and 40 mg	**SYNOPSIS**	
Drug substance(s):	Rosuvastatin		
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A 24-week, Randomised, Open-label, Parallel-group, Multicentre Study which Compares the Efficacy and Safety of Rosuvastatin 10, 20 and 40 mg with Atorvastatin 10, 20, 40 and 80 mg when Force-titrated in the Treatment of Patients with Primary Hypercholesterolemia and Either a History of Coronary Heart Disease (CHD) or Clinical Evidence of Atherosclerosis or a CHD Risk Equivalent (10-year Risk Score >20%)

ECLIPSE - An **E**valuation to **C**ompare **L**ipid-lowering effects of rosuvastatin and atorvastatin **I**n force-titrated patients: a **P**rospective **S**tudy of **E**fficacy and tolerability

International co-ordinating investigator

Study centres

This study was conducted at 118 centres from 10 countries: Germany (22 centres), Italy (20), Finland (15), France (13), Canada (12), Sweden (12), Greece (8), Portugal (7), Denmark (5), and Turkey (4).

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	12 January 2004	Therapeutic confirmatory (IIIb)
Last patient completed	26 September 2005	

Objectives

The primary objective of the study was to compare the efficacy of rosuvastatin with atorvastatin in bringing patients to their established National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) low-density lipoprotein cholesterol (LDL-C) target goal (<100 mg/dL) at Week 24, in patients with hypercholesterolaemia and either a history of CHD, or clinical evidence of atherosclerosis, or a CHD risk equivalent (10-year risk score of >20%).

Secondary objectives of the study were:

- To compare the efficacy of rosuvastatin with atorvastatin in bringing patients to their established NCEP ATP III LDL-C target goal (<100 mg/dL) at Weeks 6, 12, and 18
- To compare the efficacy of rosuvastatin with atorvastatin in bringing patients to their established European (2003) LDL-C target goal (<2.5 or <3.0 mmol/L, depending on risk category) at Weeks 6, 12, 18, and 24
- To compare the efficacy of rosuvastatin with atorvastatin in bringing patients to an LDL-C goal of <75 mg/dL (1.94 mmol/L) at Weeks 6, 12, 18, and 24
- To compare the efficacy of rosuvastatin with atorvastatin in bringing patients to their established European (2003) combined LDL-C and total cholesterol (TC) target goal (<2.5 or <3.0 mmol/L and <4.5 or <5.0 mmol/L, respectively, depending on risk category) at Weeks 6, 12, 18, and 24
- To compare the efficacy of rosuvastatin with atorvastatin in bringing patients to their established NCEP ATP III non high-density lipoprotein cholesterol (nonHDL-C) target goal at Weeks 6, 12, 18, and 24 (ie, combined nonHDL-C [<130 mg/dL] and LDL-C [<100 mg/dL] target goal, where baseline triglycerides [TG] ≥200 mg/dL)
- To compare the efficacy of rosuvastatin with atorvastatin in modifying lipids and lipoproteins (LDL-C, TC, HDL-C, TG, nonHDL-C, LDL-C/HDL-C, TC/HDL-C, nonHDL-C/HDL-C, lipoprotein (a) [Lp(a)], apolipoprotein (Apo) B, ApoA-I, and ApoB/ApoA-I) at Weeks 6, 12, 18, and 24
- To compare the laboratory data and the frequency and severity of adverse events (AEs) with rosuvastatin and atorvastatin.

In addition, there were tertiary objectives comparing rosuvastatin and atorvastatin in terms of bringing patients to national LDL-C target goal, direct medical costs, number of titrations, and cost-effectiveness; the results of these analyses will be reported separately from this clinical study report.

Study design

This was a 24-week, randomised, open-label, parallel-group, multinational study to compare the efficacy and safety of rosuvastatin and atorvastatin. Patients were to enter a 6-week dietary lead-in period, after which eligible patients entered a 24-week, randomised, forced-titration, treatment period (when they were to receive 6-weeks of each of rosuvastatin 10/20/40 mg [the 40 mg dose was for 12 weeks] or atorvastatin 10/20/40/80 mg). If deemed necessary, the dose of study medication could be back-titrated for safety reasons.

Target patient population and sample size

Male and female patients, 18 years of age or older, with hypercholesterolaemia and a history of CHD, or clinical evidence of atherosclerosis, or a CHD risk equivalent (10-year risk score of >20% for CHD, as described in the NCEP ATP III guidelines).

A total of 460 randomised and fully evaluable patients with hypercholesterolaemia were required per treatment arm (derived from an estimated 1020 randomised patients, recruited from approximately 3400 screened patients) for 80% power of detecting an 8% difference between groups in bringing patients to their NCEP ATP III LDL-C target goal (<100 mg/dL).

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

Rosuvastatin (ZD4522, CRESTOR™) 10 mg, 20 mg, and 40 mg, or atorvastatin 10 mg, 20 mg, 40 mg, and 80 mg. Doses were administered orally, once daily, as 1 tablet (except for atorvastatin 80 mg at Turkish centres, where 1 dose consisted of two 40 mg tablets).

The batch numbers supplied are listed in Table S1.

Table S1 Batch numbers

Product	Batch numbers
Rosuvastatin Tablets 10 mg	2000055635, 2000055641, 2000055651, 2000055658, 2000055663, 2000055676, 2000055685, 2000055693, 2000055707, 2000056347, 2000056879, 2000056883, 2000058574, 2000058873, 2000059038, 2000060203, 2000060804, 2000062891, 2000062959, 2000062994, 2000063019, 2000064807, 2000065177, 2000065688, 2000067886, 2000067920, 2000070254, 2000070352, 2000072793, 2000073018, 2000073965, 2000074139, 2000075478, 2000075514, 2000075516, 2000075536, 2000075737, 2000075774, 2000076008
Rosuvastatin Tablets 20 mg	2000055636, 2000055642, 2000055653, 2000055659, 2000055665, 2000055679, 2000055687, 2000055695, 2000055709, 2000056348, 2000056886, 2000058578, 2000058875, 2000059643, 2000060199, 2000062893, 2000062965, 2000062996, 2000063028, 2000065188, 2000065656, 2000066576, 2000066779, 2000066893, 2000066947, 2000067890, 2000067927, 2000072798, 2000073315, 2000074136, 2000075512, 2000075520, 2000075772, 2000076015, 2000076112
Rosuvastatin Tablets 40 mg	2000059641, 2000059662, 2000059818, 2000059820, 2000059821, 2000059833, 2000059835, 2000060030, 2000060050, 2000061461, 2000062895, 2000063030, 2000066887, 2000066889, 2000066891, 2000067929, 2000070710, 2000073334, 2000073349, 2000074724, 2000075510, 2000075522, 2000075739, 2000076017, 2000076765, 2000078997, 2000079150, 2000079178
Atorvastatin Tablets 10 mg	2000055638, 2000055644, 2000055655, 2000055660, 2000055672, 2000055681, 2000055689, 2000055697, 2000055711, 2000056843, 2000056845, 2000058580, 2000058630, 2000059040, 2000060205, 2000060807, 2000062910, 2000062999, 2000063021, 2000063072, 2000064809, 2000065179, 2000067892, 2000070256, 2000070357, 2000072800, 2000073961, 2000074156, 2000075492, 2000075528, 2000075848, 2000076352, 2000076561, 2000077074, 2000077669 and for Turkish centres: 0330024R
Atorvastatin Tablets 20 mg	2000055640, 2000055646, 2000055657, 2000055661, 2000055674, 2000055683, 2000055691, 2000055699, 2000055713, 2000056855, 2000056872, 2000058582, 2000058633, 2000059042, 2000059645, 2000060207, 2000062915, 2000063003, 2000063032, 2000063074, 2000066578, 2000067894, 2000072802, 2000074148, 2000074150, 2000074154, 2000075524, 2000075828, 2000076310, 2000077114, 2000077263 and for

Table S1 Batch numbers

Product	Batch numbers
Atorvastatin Tablets 40 mg	Turkish centres: 0132064 2000058600, 2000058602, 2000058606, 2000058608, 2000058610, 2000058612, 2000058636, 2000059795, 2000061287, 2000062917, 2000063064, 2000066774, 2000067897, 2000073337, 2000073536, 2000074144, 2000075484, 2000075531, 2000075850, 2000076024, 2000078613, 2000078977, 2000082961 and for Turkish centres: 0184094 and 0532064
Atorvastatin Tablets 80 mg	2000058641, 2000058644, 2000058647, 2000058877, 2000058880, 2000058883, 2000059799, 2000060765, 2000061467, 2000062922, 2000063066, 2000066776, 2000073340, 2000073539, 2000075533, 2000075852, 2000076026, 2000076299, 2000078617, 2000079008

Duration of treatment

A 6-week dietary lead-in period, followed by a 24-week randomised treatment period.

Criteria for evaluation (main variables)

Efficacy

- Primary variable:
  - Whether NCEP ATP III LDL-C target goal (<100 mg/dL) had been reached at Week 24
- Secondary variables:
  - Whether NCEP ATP III LDL-C target goal (<100 mg/dL) had been reached at Weeks 6, 12, and 18
  - Whether European (2003) LDL-C target goal (<2.5 or <3.0 mmol/L, depending on risk category) had been reached at Weeks 6, 12, 18, and 24
  - Whether an LDL-C goal of <75 mg/dL (1.94 mmol/L) had been reached at Weeks 6, 12, 18, and 24
  - Whether European (2003) combined LDL-C and TC target goal (<2.5 or <3.0 mmol/L and <4.5 or <5.0 mmol/L, respectively, depending on risk category) had been reached at Weeks 6, 12, 18, and 24
  - Whether NCEP ATP III nonHDL-C target goal had been reached at Weeks 6, 12, 18, and 24 (ie, combined nonHDL-C [<130 mg/dL] and LDL-C [<100 mg/dL] target goal, where baseline TG ≥200 mg/dL)
  - Percentage change from baseline in lipids and lipoproteins at Weeks 6, 12, 18, and 24

Safety

- Secondary variable:
  - Safety evaluation as determined by the frequency and severity of AEs and abnormal laboratory values (haematology, clinical chemistry, and urinalysis)

Statistical methods

Efficacy variables were analysed by randomised treatment based on the intention-to-treat (ITT) population. Efficacy analyses used the 'last observation carried forward' (LOCF) approach to deal with missing data; observations were only carried forward within the associated 6-week treatment period, so that data from a lower dose were not carried forward to a higher dose. A logistic regression analysis was used to analyse the primary variable and the secondary variables relating to bringing patients to the various target goals; the model included terms for baseline lipid associated with the target, region (country), treatment, and European target for relevant variables. For the secondary variables involving changes in lipids and lipoproteins, an analysis of variance (ANOVA) model was used, with terms included for region and treatment. Supplementary efficacy analyses were also performed. Summaries of the safety data were primarily based on the randomised safety population (by actual treatment received), but some were also produced for all patients who entered the dietary lead-in period; safety data were not subject to formal statistical analysis.

Patient population

In total 2696 patients entered the dietary lead-in period (of the planned 3400) and 1036 patients (compared to the planned 1020) were randomised to treatment (522 to rosuvastatin 10/20/40 mg and 514 to atorvastatin 10/20/40/80 mg). A total of 1015 were analysed for efficacy in an ITT population (505 rosuvastatin vs 510 atorvastatin); all 1036 were included in the randomised safety population (523 rosuvastatin vs 513 atorvastatin, according to actual treatment received). The majority of patients entering the randomised treatment period were Caucasian (98.5% vs 99.2% for rosuvastatin vs. atorvastatin, respectively) and almost half were ≥65 years of age (44.1% vs 44.2%). Males and females were well balanced between both treatment groups, although slightly more patients were male (57.9% males / 42.1% females vs 60.7% males/ 39.3% females). Overall, both treatment groups were comparable for demographic characteristics, key baseline characteristics and risk categories, and baseline lipids and lipoproteins. The total percentage of patients discontinuing was similar between the treatments. A total of 117 patients discontinued the study (64 [12.3%] vs 53 [10.3%]); the most common reason for discontinuation was AEs (7.9% vs 7.0%).

Efficacy results

The results of the analysis of the percentage of patients achieving NCEP ATP III LDL-C target goal (<100 mg/dL) at Week 24 (the primary variable of this study) are summarised in Table S2.

Table S2 Percentage of patients achieving NCEP ATP III LDL-C target goal at Week 24 (LOCF analysis of the ITT population)

Statistic	Treatment group Rosuvastatin 40 mg (n=505)	 Atorvastatin 80 mg (n=510)
LDL-C (mg/dL) at baseline, Mean (SD)	189.2 (21.0)	188.3 (20.4)
Achieving NCEP ATP III LDL-C target (<100 mg/dL); n/N[a]	388/464	355/476
Percentage achieving target	83.6	74.6
95% confidence interval	79.9 to 86.9	70.4 to 78.4
Difference in percentages	9.0	NA
Analysis		
p-value[b]	<0.001	NA

a n/N represents the number of patients achieving target / the number of patients with recorded data.
b p-value obtained from logistic regression analysis (factors included in the model for treatment and region, with baseline LDL-C included as a covariate); values <0.05 are statistically significant.
ATP Adult Treatment Panel; ITT Intention-to-treat; LDL-C Low-density lipoprotein cholesterol; LOCF Last observation carried forward; NA Not applicable; NCEP National Cholesterol Education Program; SD Standard deviation.

Rosuvastatin (10 to 40 mg) was more effective than atorvastatin (10 to 80 mg) for getting patients to their LDL-C goals after 6, 12, 18, and 24 weeks (including the NCEP ATP III goal [<100 mg/dL; the primary efficacy variable of the study], 83.6% vs 74.6% after 24 weeks; the European [2003] goal [<2.5 or <3.0 mmol/L, depending on risk category], 82.8% vs 73.3% after 24 weeks; and an LDL-C goal of <75 mg/dL, 45.9% vs 28.8% after 24 weeks; p<0.001 in all cases), as well as to other treatment target goals (eg, NCEP ATP III nonHDL-C [the combined nonHDL-C {<130 mg/dL} and LDL-C {<100 mg/dL}goal, where baseline TG ≥200 mg/dL] and European [2003] combined LDL-C and TC[<2.5 or <3.0 mmol/L and <4.5 or <5.0 mmol/L, respectively, depending on risk category]).

In terms of changes in lipids and lipoproteins, rosuvastatin (10 to 40 mg) produced a greater overall improvement in the atherogenic lipid profile compared with atorvastatin (10 to 80 mg), including statistically greater reductions in LDL-C (-57.3% vs –52.2% after 24 weeks, p<0.001) and greater increases in HDL-C (8.4% vs 1.8% after 24 weeks, p<0.001). The efficacy results from this study were consistent with findings from other clinical studies in the rosuvastatin clinical development programme.

Results from supplementary analyses performed supported those from the main analyses; rosuvastatin (10 to 40 mg) was more effective than atorvastatin (10 to 80 mg) for getting patients to their updated NCEP ATP III (2004) LDL-C goal (<100 mg/dL if High-risk, <70 mg/dL if Very high-risk) (45.5% vs 33.8% after 24 weeks; p<0.001) and updated combined nonHDL-C (<130 mg/dL or <100 mg/dL) and LDL-C goal (<100 mg/dL or <70 mg/dL), where baseline TG ≥200 mg/dL (42.9% vs 27.9% after 24 weeks; p<0.001).

Safety results

Treatment-emergent adverse events, by category, are summarised in Table S3.

The most commonly reported treatment-emergent AEs (≥2% in either group) were myalgia (8.4% for rosuvastatin vs 8.6% for atorvastatin), angina pectoris (3.0% vs 2.1%), nasopharyngitis (2.7% vs 3.5%), bronchitis (2.5 vs 1.9%), headache (2.1% vs 2.5%), and ALT increased (1.7% vs 2.9%).

Table S3 Number (%) of patients who had a treatment-emergent adverse event in any category (randomised safety population)

Category of AE	Number (%) of patients who had a treatment-emergent AE in each category[a]								
	R10 (n=522)	R20 (n=492)	R40 (n=480)	Total R (n=525)	A10 (n=514)	A20 (n=503)	A40 (n=484)	A80 (n=453)	Total A (n=514)
Any AE	126 (24.1)	110 (22.4)	150 (31.3)	282 (53.7)	109 (21.2)	100 (19.9)	92 (19.0)	105 (23.2)	270 (52.5)
SAE	12 (2.3)	9 (1.8)	16 (3.3)	33 (6.3)	9 (1.8)	13 (2.6)	5 (1.0)	10 (2.2)	30 (5.8)
AE leading to death	3 (0.6)	1 (0.2)	0 (0)	4 (0.8)	0 (0)	1 (0.2)	0 (0)	0 (0)	1 (0.2)
AE leading to premature discontinuation[b]	15 (2.9)	11 (2.2)	14 (2.9)	39 (7.4)	7 (1.4)	9 (1.8)	11 (2.3)	8 (1.8)	35 (6.8)
Drug-related AE	17 (3.3)	19 (3.9)	34 (7.1)	66 (12.6)	15 (2.9)	13 (2.6)	24 (5.0)	31 (6.8)	74 (14.4)
Drug-related SAE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.2)	1 (0.2)	2 (0.4)

a 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. Patients can appear in more than 1 dose group. Treatment groups represent treatment received at the onset/worsening of the adverse event.

b 3 other patients (2 rosuvastatin and 1 atorvastatin) were recorded as having discontinued due to an AE; however, no AEs leading to premature discontinuation were reported (E0304007 [rosuvastatin] and E0304028 [atorvastatin] had no AE form completed for an AE leading to discontinuation; E0514009 [rosuvastatin] had a post treatment AE, which began >30 days after the last dose, but was indicated as discontinuing due to the AE.

AE Adverse event; A10, A20, A40, and A80 Atorvastatin 10 mg, 20 mg, 40 mg, and 80 mg; R10, R20, and R40 Rosuvastatin 10 mg, 20 mg, and 40 mg; SAE Serious adverse event; Total R Total rosuvastatin and Total A Total atorvastatin.

Rosuvastatin was well tolerated across the dose range (10 to 40 mg), with a safety profile similar to atorvastatin (10 to 80 mg). The frequency of treatment-emergent AEs associated with both treatments was generally similar; the frequency of deaths, SAEs, and discontinuations due to AEs was low, and were generally similar.

There were 6 deaths, 5 in the randomised treatment period (4 in patients receiving rosuvastatin [peripheral ischaemia, sudden death, myocardial infarction, cardiac arrest] and 1 in a patient receiving atorvastatin [malignant neoplasm]) and 1 which occurred >30 days after the last dose (cerebrovascular accident in a patient who had received rosuvastatin). All deaths were attributed to events that could be expected in this study population and none was considered related to study treatment.

The AEs that were reported in this study were consistent with the age and underlying medical conditions of the patient population and the known safety profile of statins. The frequency of liver and renal AEs was low in both groups. None of the cases of myalgia was associated with a clinically important elevation in CK (>10 x ULN). Myalgia was reported by 8.4% of patients receiving rosuvastatin and 8.6% of patients receiving atorvastatin); there was 1 case of myopathy (on atorvastatin 40 mg); there were no cases of myositis or rhabdomyolysis. The pattern of other significant AEs did not reveal any unexpected findings or new treatment-related patterns for rosuvastatin (10 to 40 mg). Changes in clinical laboratory results were generally small and similar between the groups. There were few clinically important elevations in ALT (>3 x ULN on 2 consecutive occasions at least 48 hours apart), none of which was symptomatic (6 patients overall: 2 on rosuvastatin [0.4%] and 4 on atorvastatin [0.8%]). No patients in either group had a clinically important elevation in CK (>10 x ULN). The frequency of creatinine values >30% increased from baseline was low and similar for both groups and there were no increases from baseline in serum creatinine which were >100%. Dipstick urinalysis results showed low frequencies of patients with increases in urinary protein (proteinuria), both alone and when combined with blood (haematuria), in both the rosuvastatin and atorvastatin groups (proteinuria alone [increase from none/trace at baseline to ++ or greater at the last visit] 1.8% vs 0.4%; haematuria alone [increase from none/trace at baseline to + or greater at the last visit] 4.0% vs 2.1%; combined proteinuria and haematuria at the last visit 0.0% vs 0.2%). Most cases of proteinuria were transient in nature, with only 2 cases where proteinuria persisted (1 in each group), and were not associated with other signs of renal injury such as haematuria or elevated creatinine. Changes in vital signs were small and showed no treatment-related effects.

Date of the report

3 February 2006