Drug product:	Rosuvastatin tablets 40 mg	**SYNOPSIS**	
Drug substance(s):	Rosuvastatin		
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A 6-week, Open-label, Randomised, Multicentre, Phase IIIb, Parallel-group Study to Compare the Safety and Efficacy of Rosuvastatin 40 mg and Rosuvastatin 40 mg in Combination with Ezetimibe 10 mg in Subjects with Hypercholesterolaemia and Coronary Heart Disease (CHD) or Atherosclerosis or a CHD Risk Equivalent (10-year Risk Score of >20%)

EXPLORER - EXamination of **P**otential **L**ipid-modifying effects **O**f **R**osuvastatin in combination with **E**zetimibe versus **R**osuvastatin alone

International co-ordinating investigator

Study centres

This study was conducted at 58 centres from 5 countries: the United States (30 centres), Germany (18), Austria (5), Switzerland (4), and South Africa (1).

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	04 June 2004	Therapeutic confirmatory (IIIb)
Last patient completed	23 June 2005	

Objectives

The primary objective of the study was to compare the efficacy of rosuvastatin 40 mg monotherapy with rosuvastatin 40 mg/ezetimibe 10 mg combination 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 6.

Secondary objectives of the study were:

- To compare the efficacy of rosuvastatin monotherapy with the combination of rosuvastatin and ezetimibe in bringing patients to their established European (2003) LDL-C target goal (<2.5 or <3.0 mmol/L, depending on risk category) at Week 6

- To compare the efficacy of rosuvastatin monotherapy with the combination of rosuvastatin and ezetimibe 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 Week 6

- To compare the efficacy of rosuvastatin monotherapy with the combination of rosuvastatin and ezetimibe in bringing patients to their established NCEP ATP III non-high-density lipoprotein cholesterol (nonHDL-C) target goal at Week 6 (ie, combined nonHDL-C [<130 mg/dL] and LDL-C [<100 mg/dL] target goal, where baseline triglycerides (TG) ≥200 mg/dL)

- To establish the efficacy of the combination of rosuvastatin and ezetimibe compared with rosuvastatin monotherapy on 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 Week 6

- To assess the change in high sensitivity C-reactive protein (hs-CRP) with rosuvastatin monotherapy and with the combination of rosuvastatin and ezetimibe at Week 6

- To compare the laboratory data and the frequency and severity of adverse events (AEs) with rosuvastatin monotherapy with the combination of rosuvastatin and ezetimibe

There were also exploratory objectives relating to the collection of biomarker samples (for sitosterol, lanosterol, and C4) from patients in this study; the results from these will be reported separately. These objectives were designed to increase knowledge of the mechanisms involved in cholesterol homeostasis by exploring the 3 principal pathways involved, namely cholesterol absorption (sitosterol), cholesterol synthesis (lanosterol), and bile acid secretion (C4).

Study design

This was a 6-week, randomised, open-label, parallel-group, multinational study to compare the efficacy and safety of rosuvastatin 40 mg monotherapy and the combination of rosuvastatin 40 mg and ezetimibe 10 mg. Patients were to enter a 6-week dietary lead-in period, after which eligible patients entered a 6-week randomised treatment period.

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 190 randomised and fully evaluable patients with hypercholesterolaemia were required per treatment arm (derived from an estimated 420 randomised patients, recruited from approximately 1235 screened patients) for 95% power of detecting a 12% 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™) 40 mg or rosuvastatin 40 mg plus ezetimibe 10 mg. Doses were administered orally, once daily, as 1 or 2 tablets. The batch numbers for rosuvastatin 40 mg were 2000034334, 2000063488, 2000059828, 2000069442, 2000075504, and 2000077291, and for ezetimibe 10 mg were 2000059007, 2000072098, 2000076128, 2000059699, and 2000075503.

Duration of treatment

A 6-week dietary lead-in period, followed by a 6-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 6
- Secondary variables:
  - Whether European (2003) LDL-C target goal (<2.5 or <3.0 mmol/L, depending on risk category) had been reached at Week 6
  - 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 Week 6
  - Whether NCEP ATP III nonHDL-C target goal had been reached at Week 6 (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 Week 6
  - Percentage change from baseline in hs-CRP at Week 6 (median baseline)

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. 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. Analysis of hs-CRP was performed using the non-parametric Wilcoxon Rank Sum test and the robust regression technique of the MM Estimation. Supplementary efficacy analyses were also performed. Summaries of the safety data were primarily based on the randomised safety population (by actual treatments 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 1197 patients entered the dietary lead-in period (of the planned 1235) and 469 patients (compared to the planned 420) were randomised to treatment (230 to rosuvastatin monotherapy vs 239 to rosuvastatin/ezetimibe combination). A total of 465 were analysed for efficacy in an ITT population (230 vs 235); 468 were included in the randomised safety population (230 vs 238). The majority of patients entering the randomised treatment period were Caucasian (91.7% in the rosuvastatin monotherapy group vs 93.3% in the rosuvastatin/ezetimibe combination group) and almost half were ≥65 years of age (47.0% vs 46.4%). Males and females were well balanced between both treatment groups, although slightly more patients were male (55.7% males / 44.3% females vs 58.6% males/ 41.4% females). Overall, both treatment groups were comparable for demographic characteristics, key baseline characteristics and risk categories, and baseline lipids and lipoproteins. Mean LDL-C levels were consistent with the inclusion criteria; this represents a high-risk population presenting with hypercholesterolaemia and CHD or atherosclerosis. A total of 12 patients discontinued the study (4 [1.7%] vs 8 [3.3%]); the most common reason for discontinuation was AEs (1.3% vs 2.5%).

Efficacy results

The results of the analysis of the percentage of patients achieving the NCEP ATP III LDL-C target goal (<100 mg/dL) at Week 6 (the primary variable of this study) are summarised in Table S1.

Table S1 Percentage of patients achieving NCEP ATP III LDL-C target goal at Week 6 (LOCF analysis of the ITT population)

Statistic	Treatment group	
	Rosuvastatin 40 mg	Rosuvastatin 40 mg + ezetimibe 10 mg
	(n=230)	(n=235)
LDL-C (mg/dL) at baseline, Mean (SD)	190.8 (22.6)	189.2 (22.4)
Achieving NCEP ATP III LDL-C target (<100 mg/dL); n/N[a]	182/230	221/235
Percentage achieving target	79.1	94.0
95% confidence interval	73.3 to 84.2	90.2 to 96.7
Difference in percentages	NA	14.9
Analysis		
p-value[b]	NA	<0.001

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 40 mg/ezetimibe 10 mg combination was more effective than rosuvastatin 40 mg monotherapy for getting patients to their LDL-C goals after 6 weeks (94.0% vs 79.1% to NCEP ATP III goal [<100 mg/dL; the primary efficacy variable of the study] and 93.6% vs 74.3% to European [2003] goal [<2.5 or <3.0 mmol/L, depending on risk category]; p<0.001 in both cases), as well as to other treatment target goals (eg, NCEP ATP III nonHDL-C goal [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 goal [<2.5 or <3.0 mmol/L and <4.5 or <5.0 mmol/L, respectively, depending on risk category]).

Furthermore, rosuvastatin 40 mg/ezetimibe 10 mg combination was more effective at reducing LDL-C than rosuvastatin 40 mg monotherapy, producing a statistically significantly greater reduction in LDL-C after 6 weeks (-69.8% vs –57.1%, p<0.001). In terms of changes in other lipids and lipoproteins, rosuvastatin 40 mg/ezetimibe 10 mg combination provided greater reductions in TC, TG, nonHDL-C, ApoB, LDL-C/HDL-C, TC/HDL-C, nonHDL-C/HDL-C, and ApoB/ApoA-I, as well as hs-CRP, than rosuvastatin 40 mg monotherapy, with similar effects being observed on HDL-C (10.8% vs 8.5%) and ApoA-I raising. Rosuvastatin 40 mg, alone and in combination with ezetimibe 10 mg, produced an overall improvement in the atherogenic lipid profile.

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 40 mg/ezetimibe 10 mg combination was more effective than rosuvastatin 40 mg monotherapy 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) (82.1% vs 42.2%; 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 (79.5% vs 27.5%; p<0.001).

Safety results

Treatment-emergent adverse events, by category, are summarised in Table S2.

Table S2 Number (%) of patients who had a treatment-emergent adverse event in any category (randomised safety population)

Category of AE	Number (%) of patients who had an AE in each category[a]			
	Rosuvastatin 40 mg (n=230)		Rosuvastatin 40 mg + ezetimibe 10 mg (n=238)	
Any AE	77	(33.5)	75	(31.5)
SAE[b]	4	(1.7)	5	(2.1)
AE leading to death	0	(0)	1[d]	(0.4)
AE leading to premature discontinuation	3	(1.3)	6	(2.5)
Rosuvastatin-related AE only[c]	21	(9.1)	2	(0.8)
Rosuvastatin- and ezetimibe-related AE	NA	NA	16	(6.7)

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.
b No SAEs were considered related to rosuvastatin or ezetimibe.
c No events were considered related only to ezetimibe.
d Patient died following an acute myocardial infarction.
AE Adverse event; NA Not applicable; SAE Serious adverse event.

The most commonly reported treatment-emergent AEs (≥2% in either group) were myalgia (2.9% for rosuvastatin 40 mg/ezetimibe 10 mg combination vs 3.0% for rosuvastatin 40 mg monotherapy), angina pectoris (0.4% vs 2.6%), nausea (2.5% vs 2.2%), and ALT increased (2.5% vs 0.4%).

Rosuvastatin 40 mg, alone and in combination with ezetimibe 10 mg, was well tolerated. The frequency of treatment-emergent AEs associated with both treatment groups was generally similar; the frequency of deaths, SAEs, and discontinuations due to AEs was low, and were generally similar. 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 lipid-lowering medication.

The frequency of liver, muscle, 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). There were no cases of myopathy, myositis, or rhabdomyolysis. The pattern of other significant AEs did not reveal any unexpected findings or new treatment-related patterns for rosuvastatin 40 mg.

Changes in clinical laboratory results were generally small and overall similar between the groups. No patients in either group had an ALT value >3 x ULN on 2 consecutive occasions at least 48 hours apart, or any clinically important treatment-emergent elevation in CK (>10 x ULN on at least 1 occasion). The frequency of creatinine values >30% increased from baseline was low for both groups and there were no increases from baseline in serum creatinine which were >100%; there was no clinically meaningful change in the mean creatinine value for either group. Changes in urinalysis (based on a single on-treatment dipstick test) showed low frequencies of urinary protein and blood in both groups. Changes in vital signs were small and showed no treatment-related effects.

Date of the report

06 January 2006