Drug product:	Rosuvastatin 20 mg tablets	**SYNOPSIS**	
Drug substance(s):	Rosuvastatin		
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A 26-week, Double-blind, Randomised, Multicentre, Phase IIIb, Parallel-group Study to Compare the Efficacy and Safety of Rosuvastatin (40 mg) with Atorvastatin (80 mg) in Subjects with Hypercholesterolaemia and Coronary Heart Disease (CHD) or CHD Risk Equivalents

POLARIS - Prospective Optimisation of Lipids by Atorvastatin or Rosuvastatin Investigated in high-risk Subjects with hypercholesterolaemia

International co-ordinating investigator

Study centres

This study was conducted at 145 centres from 6 countries: United States (75 centres), Belgium (20), Germany (14), United Kingdom (13), Canada (12), and Spain (11).

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	30 April 2003	Therapeutic confirmatory (IIIb)
Last patient completed	15 September 2004	

Objectives

The primary objective of the study was to compare the efficacy of rosuvastatin with atorvastatin by assessing the percentage change from baseline to Week 8 in low-density lipoprotein cholesterol (LDL-C) concentration in patients with hypercholesterolaemia and CHD or CHD risk equivalents.

Secondary objectives of the study were:

- To compare the efficacy of rosuvastatin with atorvastatin in modifying other lipids and lipoproteins at Week 8 (total cholesterol [TC], high-density lipoprotein cholesterol [HDL-C], triglycerides [TG], nonHDL-C, LDL-C/HDL-C, TC/HDL-C, nonHDL-C/HDL-C, apolipoprotein [Apo] B, ApoA-I, and ApoB/ApoA-I)
- To compare the efficacy of rosuvastatin with atorvastatin in modifying all lipids and lipoproteins at Week 26
- To compare the efficacy of rosuvastatin and atorvastatin in bringing patients to their established National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) LDL-C target goal at Weeks 8 and 26
- To compare the efficacy of rosuvastatin and atorvastatin in bringing patients to their established European Atherosclerosis Society (EAS) LDL-C target goal at Weeks 8 and 26
- To compare the efficacy of rosuvastatin and atorvastatin in bringing patients to their established NCEP ATP III nonHDL-C target goal at Weeks 8 and 26
- To compare the efficacy of rosuvastatin and atorvastatin in bringing patients to their established EAS combined LDL-C and TC target goal at Weeks 8 and 26
- To compare the laboratory data and the frequency and severity of adverse events (AEs) with rosuvastatin and atorvastatin

Study design

This was a 26-week, randomised, double-blind, parallel-group, multinational study to compare the efficacy and safety of rosuvastatin and atorvastatin in patients with hypercholesterolaemia and CHD or CHD risk equivalents.

Patients were to enter a 6-week dietary lead-in period, after which eligible patients entered a 26-week randomised treatment period (an initial 2-week period when they were to receive rosuvastatin 20 mg or atorvastatin 40 mg, followed by a forced-titration to rosuvastatin 40 mg or atorvastatin 80 mg). If deemed necessary after 8 weeks, the dose of study medication could be reduced (to the lower initial dose) or additional lipid-lowering medication prescribed (except for statins or fibrates).

Target patient population and sample size

Male and female patients, 45 to 80 years of age, with hypercholesterolaemia and a history of CHD or clinical evidence of atherosclerosis (diabetic or non-diabetic) or multiple risk factors that conferred a 10-year risk score of >20% for CHD (as described in the NCEP ATP III guidelines).

A total of 360 randomised and fully evaluable patients with hypercholesterolaemia, derived from an estimated 800 recruited patients, were required per treatment arm for 85% power of detecting a 3% difference (standard deviation 13.3%) between groups in the mean percentage change from baseline in LDL-C.

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

Rosuvastatin (ZD4522, CRESTOR™) 20 mg or atorvastatin 40 mg. Doses were administered orally, once daily, as a 1 or 2 encapsulated tablets. The batch numbers for rosuvastatin 20 mg were ST73066-001-FB12 and ST73066-001-FB13, and for atorvastatin 40 mg were ST74019-001-FA07 and ST74019-001-FA08.

Duration of treatment

A 6-week dietary lead-in period, followed by a 26-week randomised treatment period.

Criteria for evaluation (main variables)

Efficacy

- Primary variable:
  - Percentage change from baseline in LDL-C concentration at Week 8
- Secondary variables:
  - Percentage change from baseline in other lipids and lipoproteins at Week 8
  - Percentage change from baseline in all lipids and lipoproteins at Week 26
  - Whether NCEP ATP III LDL-C target goal had been reached at Weeks 8 and 26
  - Whether EAS LDL-C target goal had been reached at Weeks 8 and 26
  - Whether NCEP ATP III nonHDL-C target goal had been reached at Weeks 8 and 26
  - Whether EAS combined LDL-C and TC target goal had been reached at Weeks 8 and 26

Safety

- Secondary variables:
  - Safety evaluation as determined by comparison of laboratory data (haematology, clinical chemistry, and urinalysis) and the frequency and severity of adverse events

Statistical methods

Efficacy variables were analysed based on the intention-to-treat (ITT) population, by treatment randomly allocated. The primary analysis used the 'last observation carried forward' (LOCF) approach. An analysis of variance (ANOVA) model was used for the primary variable, and for the secondary variables involving lipids and lipoproteins. The percentages reaching their target goals after 8 weeks were compared using logistic regression analysis. In addition, an early analysis of the lipid data was performed when all patients had completed their lipid assessments after 8 weeks; this was performed by an independent external team in order to preserve the study blinding. Summaries of the safety data were based on the 2 safety populations: the dietary lead-in safety population and the randomised safety population (by treatments actually received); safety data were not subject to formal statistical analysis.

Patient population

The type and disposition of patients and their baseline characteristics and risk categories are summarised in Tables S1 and S2.

Table S1 Demographic characteristics (full data set)

Demographic characteristic		**Number (%) of patients**					
		Dietary lead-in period (non-randomised)		**Randomised treatment period**			
				Total Rosuvastatin		**Total Atorvastatin**	
		(n=1979)		**(n=432)**		**(n=439)**	
Sex (n [%])	Male	1284	(64.9)	281	(65.0)	248	(56.5)
	Female	695	(35.1)	151	(35.0)	191	(43.5)
Age (years)	Mean (SD)	61.3	(8.9)	62.6	(8.5)	61.6	(8.8)
	Range	33 to 84		39 to 80		39 to 80	
18 to 64	n (%)	1251	(63.2)	254	(58.8)	266	(60.6)
≥65	n (%)	727	(36.7)	178	(41.2)	173	(39.4)
Not calculated	n (%)	1	(0.1)	0		0	
Race (n [%])	Caucasian	1786	(90.2)	397	(91.9)	403	(91.8)
	Black	111	(5.6)	28	(6.5)	27	(6.2)
	Asian	17	(0.9)	3	(0.7)	0	
	Hispanic	45	(2.3)	1	(0.2)	6	(1.4)
	Other	20	(1.0)	3	(0.7)	3	(0.7)
	Not recorded	20	(1.0)	0		0	

Table S1 Demographic characteristics (full data set)

Demographic characteristic		Number (%) of patients					
		Dietary lead-in period (non-randomised)		Randomised treatment period			
				Total Rosuvastatin		Total Atorvastatin	
		(n=1979)		(n=432)		(n=439)	
Disposition							
N (%) of patients:	Completed	871	(30.6)	393	(91.0)	399	(90.9)
	Discontinued	1979	(69.4)	39	(9.0)	40	(9.1)
N analysed for safety[a]		1979		432		439	
N analysed for efficacy[b] (ITT)		Not applicable		428		432	

a Two safety populations were used: dietary lead-in safety population - all patients who entered the dietary lead-in period, including safety assessments in the period up to randomisation; randomised safety population – all patients who were randomised and took at least 1 dose of study medication.
b Number of patients who took at least 1 dose of study medication, had a baseline lipid measurement, and at least 1 post-baseline lipid measurement for at least 1 lipid variable.
ITT Intention-to-treat; N Number; SD Standard deviation.

Table S2 Key baseline characteristics and risk categories (randomised population)

Baseline characteristic			Treatment group			
			Total Rosuvastatin (n=432)		Total Atorvastatin (n=439)	
Weight	Mean (SD)	kg	85.9	(16.9)	85.2	(18.1)
	Range		47 to 158		39 to 159	
<50 kg	n (%)		1	(0.2)	2	(0.5)
50 to 90 kg	n (%)		277	(64.1)	292	(66.5)
>90 kg	n (%)		154	(35.6)	144	(32.8)
Not recorded	n (%)		0		1	(0.2)
Body mass index	Mean (SD)	kg/m^2	29.80	(5.08)	30.11	(6.05)
	Range		18.6 to 52.8		16.0 to 67.1	
<20 kg/m^2		n (%)	1	(0.2)	4	(0.9)
20 to <25 kg/m^2		n (%)	58	(13.4)	66	(15.0)
25 to <30 kg/m^2		n (%)	194	(44.9)	175	(39.9)
≥30 kg/m^2		n (%)	179	(41.4)	193	(44.0)

Table S2 Key baseline characteristics and risk categories (randomised population)

Baseline characteristic		Treatment group			
		Total Rosuvastatin (n=432)		Total Atorvastatin (n=439)	
Not calculated	n (%)	0		1	(0.2)
Waist circumference					
Males: ≤102 cm	n (%)	132	(47.0)	123	(49.6)
Males: >102 cm	n (%)	142	(50.5)	120	(48.4)
Males: Not recorded	n (%)	7	(2.5)	5	(2.0)
Females: ≤88 cm	n (%)	41	(27.2)	53	(27.7)
Females: >88 cm	n (%)	106	(70.2)	136	(71.2)
Females: Not recorded	n (%)	4	(2.6)	2	(1.0)
Renal function (creatinine clearance)					
Normal (>80 mL/min)	n (%)	233	(53.9)	237	(54.0)
Mild impairment (50 to ≤80 mL/min)	n (%)	173	(40.0)	173	(39.4)
Moderate impairment (30 to <50 mL/min)	n (%)	25	(5.8)	23	(5.2)
Severe impairment (<30 mL/min)	n (%)	1	(0.2)	1	(0.2)
Not calculated	n (%)	0		5	(1.1)
Lipid-lowering medication pre-study	n (%)	300	(69.4)	321	(73.1)
Metabolic syndrome at baseline					
Yes	n (%)	233	(53.9)	244	(55.6)
No	n (%)	198	(45.8)	191	(43.5)
Not known	n (%)	1	(0.2)	4	(0.9)
Diabetes Mellitus (Type 1 or 2)	n (%)	161	(37.3)	180	(41.0)

LDL-C Low-density lipoprotein cholesterol; SD: standard deviation.

Efficacy results

The results of the analysis of the percentage change from baseline in LDL-C concentration at Week 8 (the primary variable of this study) are summarised in Table S3.

Table S3 Percentage change from baseline in LDL-C concentration at Week 8 (Last Observation Carried Forward analysis of the ITT population)

Statistic			Treatment group			
			Rosuvastatin 40 mg (n=428)		Atorvastatin 80 mg (n=432)	
Baseline LDL-C[a]	Mean (SD)	mmol/L	4.894	(0.548)	4.886	(0.573)
		mg/dL	189.3	(21.2)	189.0	(22.1)
Week 8 LDL-C	Mean (SD)	mmol/L	2.157	(0.791)	2.332	(0.676)
		mg/dL	83.4	(30.6)	90.2	(26.2)
Mean percentage change from baseline in LDL-C (SD)			-55.88	(15.43)	-52.18	(13.39)
Analysis						
Lsmean percentage change (standard error)			-55.89	(0.68)	-52.18	(0.68)
Difference in lsmeans (standard error)			-3.71 (0.97)			
95% confidence interval			-5.61 to –1.82			
p-value[b]			<0.001			

a Baseline value calculated as the mean of the available values at the last 3 consecutive visits, including any scheduled repeated visits, among Weeks –2, -1, and 0.
b p-value obtained from ANCOVA model; values <0.05 are statistically significant.
ANCOVA Analysis of covariance; ITT Intention-to-treat; LDL-C Low-density lipoprotein cholesterol; Lsmean Least squares mean; SD Standard deviation.

Rosuvastatin 40 mg was more effective at reducing LDL-C than atorvastatin 80 mg, producing a statistically significantly greater reduction in LDL-C after 8 weeks (-55.9% vs –52.2%, p<0.001).

Results for the secondary variables supported those for the primary variable. In terms of other lipids and lipoproteins, rosuvastatin 40 mg produced an overall improvement in the atherogenic lipid profile compared with atorvastatin 80 mg after 8 weeks, including a greater increase in HDL-C (9.6% vs 4.4%, p<0.001). In addition, rosuvastatin 40 mg was more effective than atorvastatin 80 mg for getting patients to their LDL-C goals (80.1% vs 71.6% to NCEP ATP III <100 mg/dL goal, 36.1% vs 18.1% to NCEP ATP III<70 mg/dL goal, and 78.9% vs 69.1% to EAS goal; p=0.003, p<0.001, and p<0.001 respectively), as well as to other treatment target goals (NCEP ATP III nonHDL-C and EAS combined LDL-C and TC). The effects seen after 26 weeks were consistent with those seen after 8 weeks, both with regard to producing an overall improvement in the atherogenic lipid profile (including a greater reduction in LDL-C [-57.0% vs –52.5%] and a greater increase in HDL-C [11.0% vs 6.2%]) and in getting patients to their LDL-C and other treatment target goals. The benefits of rosuvastatin compared with atorvastatin were also seen in those with metabolic syndrome (no formal statistical analysis performed). The efficacy results from this study were consistent with findings from other clinical studies in the rosuvastatin clinical development programme.

Safety results

Treatment-emergent adverse events, by category and most commonly reported, are summarised in Tables S4 and S5.

Table S4 Number (%) of patients who had a treatment-emergent adverse event in any category and total number of adverse events (randomised safety population)

Category of AE	Number (%) of patients who had an AE in each category[a]							
	R20 (n=432)	**R40 (n=424)**	**R40+LLM (n=14)**	**Total R (n=432)**	**A 40 (n=439)**	**A80 (n=428)**	**A80+LLM (n=26)**	**Total A (n=439)**
Any AE	98 (22.7)	274 (64.6)	10 (71.4)	307 (71.1)	96 (21.9)	275 (64.3)	12 (46.2)	312 (71.1)
SAE	0	28 (6.6)	0	28 (6.5)	3 (0.7)	22 (5.1)	0	25 (5.7)
AE leading to death	0	1 (0.2)	0	1 (0.2)	0	0	0	0
AE leading to premature discontinuation	6 (1.4)	16 (3.8)	0	22 (5.1)	8 (1.8)	21 (4.9)	0	27 (6.2)
Drug-related AE	18 (4.2)	49 (11.6)	0	64 (14.8)	25 (5.7)	58 (13.6)	1 (3.8)	78 (17.8)
Drug-related SAE	0	2 (0.5)	0	2 (0.5)	0	1 (0.2)	0	1 (0.2)
Drug-related AE leading to death	0	0	0	0	0	0	0	0
Drug-related AE leading to premature discontinuation	3 (0.7)	8 (1.9)	0	11 (2.5)	7 (1.6)	16 (3.7)	0	21 (4.8)
Other significant AEs[b]	10 (2.3)	46 (10.8)	0	52 (12.0)	11 (2.5)	44 (10.3)	0	52 (11.8)
	Total number of AEs							
Any AE	145	639	16	800	144	618	17	779
SAE	0	36	0	36	3	23	0	26
AE leading to death	0	1	0	1	0	0	0	0
AE leading to premature discontinuation	10	22	0	32	11	37	0	48
Drug-related AE	28	59	0	87	34	91	1	126
Drug-related SAE	0	4	0	4	0	1	0	1
Drug-related AE leading to death	0	0	0	0	0	0	0	0
Drug-related AE leading to premature discontinuation	5	10	0	15	10	29	0	39
Other significant AEs[b]	13	60	0	73	11	57	0	68

a Patient 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 treatment group. Treatment groups represent treatment received at the onset/worsening of the adverse event.

b Other significant AEs were identified by the Study Team Physician during the evaluation of the safety data, and are those that were considered of particular clinical importance; they include conditions commonly associated with marked haematological and other laboratory abnormalities, and reported side-effects of statins (eg, AEs suggestive of liver disturbance, muscle conditions, and renal disturbance). Since other significant AEs may also be serious and/or lead to discontinuation, there may be some overlap between the different categories of AEs.

AE Adverse event; A40 or A80 Atorvastatin 40 or 80 mg; R20 or R40 Rosuvastatin 20 or 40 mg; SAE Serious adverse event; Total A or R Total atorvastatin or rosuvastatin; +LLM Plus additional lipid-lowering medication.

Table S5 Number (%) of patients with the most commonly reported treatment-emergent adverse events (randomised safety population)

Preferred term[a]	Number (%) of patients with the most commonly reported[b] treatment-emergent AEs							
	R20 (n=432)	R40 (n=424)	R40+LLM (n=14)	Total R (n=432)	A 40 (n=439)	A80 (n=428)	A80+LLM (n=26)	Total A (n=439)
Nasopharyngitis	8 (1.9)	19 (4.5)	1 (7.1)	27 (6.3)	3 (0.7)	12 (2.8)	2 (7.7)	17 (3.9)
Arthralgia	4 (0.9)	21 (5.0)	0	25 (5.8)	4 (0.9)	13 (3.0)	1 (3.8)	18 (4.1)
Myalgia	4 (0.9)	18 (4.2)	0	22 (5.1)	3 (0.7)	25 (5.8)	0	26 (5.9)
Upper respiratory tract infection	2 (0.5)	16 (3.8)	3 (21.4)	20 (4.6)	1 (0.2)	16 (3.7)	0	17 (3.9)
Back pain	2 (0.5)	16 (3.8)	0	18 (4.2)	6 (1.4)	15 (3.5)	0	21 (4.8)
Sinusitis	0	17 (4.0)	0	17 (3.9)	1 (0.2)	7 (1.6)	0	8 (1.8)
Urinary tract infection	5 (1.2)	12 (2.8)	1 (7.1)	15 (3.5)	5 (1.1)	20 (4.7)	0	25 (5.7)
Diarrhoea	6 (1.4)	9 (2.1)	0	15 (3.5)	6 (1.4)	10 (2.3)	0	16 (3.6)
Headache	3 (0.7)	11 (2.6)	0	14 (3.2)	4 (0.9)	10 (2.3)	0	14 (3.2)
Fatigue	4 (0.9)	9 (2.1)	0	13 (3.0)	3 (0.7)	8 (1.9)	0	11 (2.5)
Dizziness	1 (0.2)	12 (2.8)	0	13 (3.0)	3 (0.7)	7 (1.6)	0	10 (2.3)
Constipation	5 (1.2)	8 (1.9)	0	13 (3.0)	4 (0.9)	4 (0.9)	0	8 (1.8)
Bronchitis	3 (0.7)	9 (2.1)	0	12 (2.8)	3 (0.7)	20 (4.7)	0	23 (5.2)
Pain in extremity	3 (0.7)	10 (2.4)	0	12 (2.8)	3 (0.7)	11 (2.6)	0	14 (3.2)
Depression	3 (0.7)	10 (2.4)	0	12 (2.8)	0	9 (2.1)	0	9 (2.1)
Cough	1 (0.2)	10 (2.4)	0	11 (2.5)	1 (0.2)	10 (2.3)	0	11 (2.5)
Nausea	2 (0.5)	7 (1.7)	0	9 (2.1)	6 (1.4)	6 (1.4)	0	12 (2.7)
Flatulence	4 (0.9)	5 (1.2)	0	9 (2.1)	4 (0.9)	5 (1.2)	1 (3.8)	10 (2.3)
Hypertension	1 (0.2)	8 (1.9)	0	9 (2.1)	0	8 (1.9)	0	8 (1.8)

a Patient 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 This table uses a cut-off of ≥2% in either the Total R or Total A group . Patients can appear in more than 1 treatment group. Treatment groups represent treatment received at the onset/worsening of the adverse event.

AE Adverse event; A40 or A80 Atorvastatin 40 or 80 mg; R20 or R40 Rosuvastatin 20 or 40 mg; Total A or R Total atorvastatin or rosuvastatin; +LLM Plus additional lipid-lowering medication.

Rosuvastatin 40 mg was well tolerated, with an AE profile generally similar to atorvastatin 80 mg. The frequency of treatment-emergent AEs associated with the treatments was generally similar, the frequency of deaths, SAEs, and discontinuations due to AEs was low, and there was no evidence of any treatment-related differences. The AEs that occurred 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. Myalgia was reported by 5.1% of patients receiving rosuvastatin and 5.9% of patients receiving atorvastatin (4.2% and 5.8% of those receiving rosuvastatin 40 mg and atorvastatin 80 mg, respectively); importantly, none of these cases was associated with a clinically important elevation in CK (>10 x ULN; in fact, none was >3 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 showed no treatment-related trends. There were few clinically important elevations in ALT (>3 x ULN on 2 consecutive occasions) or CK (>10 x ULN): 4 patients had elevated ALT (all in the atorvastatin 80 mg group) and 1 patient had elevated CK (in the atorvastatin 40 mg group). The frequency of creatinine values >30% increased from baseline was higher for rosuvastatin than atorvastatin (7.2% vs 3.0%); 2 patients had increases from baseline which were >100% (both on rosuvastatin 40 mg, 1 <ULN and 1 >ULN at the maximum creatinine value). Urinalysis results showed low frequencies of urinary protein (proteinuria), both alone and when combined with blood (haematuria), in both the rosuvastatin and atorvastatin groups (proteinuria alone 4.1% vs 1.0%; combined proteinuria and haematuria 1.8% and 0.3%); most cases of proteinuria were transient in nature, with only 1 case persisting (in a patient receiving rosuvastatin 40 mg). Changes in vital signs were small and showed no treatment-related effects.

Date of the report

17 February 2005