Drug product:	Rosuvastatin tablets: 10 mg	**SYNOPSIS**	
Drug substance(s):	Rosuvastatin		
Document No.:			
Edition No.:			
Study code:	4522IL/0102 (D3569C00001)		
Date:	31 January 2005		

A 6-week Open-label, Randomised, Multicentre, Phase IIIb, Parallel-group Study to Compare the Efficacy and Safety of Rosuvastatin (10 mg) with Atorvastatin (20 mg) in Subjects with Hypercholesterolaemia and Either a History of Coronary Heart Disease (CHD) or Clinical Evidence of Atherosclerosis or a CHD Risk Equivalent (10-year Risk Score of >20%)

PULSAR – A **P**rospective study to evaluate the **U**tility of **L**ow doses of the **S**tatins **A**torvastatin and **R**osuvastatin.

International co-ordinating investigator

Study centres

This study was conducted at 121 centres from 7 countries: United States (US) [41 centres], France (36 centres), Italy (12 centres), Finland (9 centres), Mexico (9 centres), the Netherlands (8 centres), and Australia (6 centres).

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First patient enrolled	10 November 2003	Therapeutic confirmatory (IIIb)
Last patient completed	26 August 2004	

Objectives

The primary objective of this study was to compare the efficacy of rosuvastatin with atorvastatin by assessing the percentage change from baseline to Week 6 in low-density lipoprotein cholesterol (LDL-C) concentrations in patients with hypercholesterolaemia and either a history of coronary heart disease (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 modifying other lipids and lipoproteins at Week 6 (total cholesterol [TC], high-density lipoprotein cholesterol [HDL-C], triglycerides [TG], nonHDL-C, LDL-C/HDL-C, TC/HDL-C, nonHDL-C/HDL-C, lipoprotein [Lp] (a), apolipoprotein [Apo] B, ApoA-I, and ApoB/ApoA-I)
- To compare the efficacy of rosuvastatin with atorvastatin in bringing patients to their established National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III LDL-C target goal at Week 6
- To compare the efficacy of rosuvastatin with atorvastatin in bringing patients to their established European Atherosclerosis Society (EAS) LDL-C target goal at Week 6
- To compare the efficacy of rosuvastatin with atorvastatin in bringing patients to their established NCEP ATP III nonHDL-C target goal at Week 6
- To compare the efficacy of rosuvastatin with atorvastatin in bringing patients to their established EAS combined LDL-C and TC target goal at Week 6
- To compare the cost-effectiveness of rosuvastatin and atorvastatin
- To compare the laboratory data and the frequency and severity of adverse events (AEs) with rosuvastatin and atorvastatin

Study design

This was a randomised, open-label, parallel-group, multinational, multicentre study to compare the efficacy and safety of rosuvastatin 10 mg with atorvastatin 20 mg over 6 weeks when given to patients with hypercholesterolaemia and either a history of CHD or clinical evidence of atherosclerosis or a CHD risk equivalent (10-year risk score >20% for CHD as described in NCEP ATP III guidelines).

Patients were to enter a 6-week dietary lead-in period, after which eligible patients were to receive 6 weeks of treatment with either rosuvastatin (10 mg) or atorvastatin (20 mg).

Target patient population and sample size

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

A total of 460 randomised and fully evaluable patients with hypercholesterolaemia, derived from an estimated 500 recruited patients, were required per treatment arm for 90% power of detecting a 3% difference (standard deviation 14%) 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™)[1] 10 mg or atorvastatin 20 mg. Doses were administered orally, once daily, as a single tablet. The batch numbers for rosuvastatin 10 mg were 2000053537 (US centres only), 2000053413, 2000053415, 2000053418, 2000053421, 2000053423, and 2000053425, and for atorvastatin 20 mg were 2000051672 (US centres only), 2000053427, 2000053429, 2000053431, 2000053433, 2000053435, and 2000053438.

Duration of treatment

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

Criteria for evaluation (main variables)

Efficacy

- Primary variable:
  - Percentage change from baseline in LDL-C concentration in the rosuvastatin treatment group (10 mg) and the atorvastatin treatment group (20 mg) at Week 6
- Secondary variables:
  - Percentage change from baseline in other lipids and lipoproteins at Week 6
  - Percentage of patients reaching NCEP ATP III LDL-C target goal at Week 6
  - Percentage of patients reaching EAS LDL-C target goal at Week 6
  - Percentage of patients reaching NCEP ATP III nonHDL-C target goal at Week 6

[1] CRESTOR is a trademark of the AstraZeneca group of companies.

- Percentage of patients reaching EAS combined LDL-C and TC target goals at Week 6

- Cost-effectiveness of rosuvastatin and atorvastatin, using analysis of cost per LDL-C lowering and cost per patient to treatment goal, following 6 weeks of treatment

Safety

- Secondary variable

  - Safety evaluation as determined by comparison of laboratory data and the frequency and severity of AEs with rosuvastatin and atorvastatin at Week 6

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 variable relating to the percentage change in other lipids and lipoproteins. The percentages of patients reaching their target goals were compared using logistic regression analysis. For the health economics variable, the cost-effectiveness of rosuvastatin 10 mg versus atorvastatin 20 mg was assessed using Incremental Cost-Effectiveness Ratios (ICERs). Summaries of the safety data were based on the 2 safety populations: the dietary lead-in safety population and the randomised safety population; safety data were not subject to formal statistical analysis.

Patient population

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

Table S1 Patient population and disposition (full data set)

Demographic characteristic		**Number (%) of patients**					
		Dietary lead-in period		**Randomised treatment period**			
				Rosuvastatin 10 mg		**Atorvastatin 20 mg**	
		(n=1901)		**(n=504)**		**(n=492)**	
Demographic characteristics (all patients)							
Sex (n [%])	Male	1051	(55.3)	273	(54.2)	285	(57.9)
	Female	850	(44.7)	231	(45.8)	207	(42.1)
Age (years)	Mean (SD)	59.6	(11.4)	60.2	(10.4)	60.7	(10.6)
	Range	22 to 91		24 to 87		21 to 84	
18 to 64	n (%)	1229	(64.7)	315	(62.5)	312	(63.4)
≥65	n (%)	672	(35.3)	189	(37.5)	180	(36.6)

Table S1 Patient population and disposition (full data set)

Demographic characteristic		Number (%) of patients					
		Dietary lead-in period		Randomised treatment period			
				Rosuvastatin 10 mg		Atorvastatin 20 mg	
		(n=1901)		(n=504)		(n=492)	
Race (n [%])	Caucasian	1337	(70.3)	376	(74.6)	380	(77.2)
	Black	74	(3.9)	23	(4.6)	17	(3.5)
	Asian	16	(0.8)	6	(1.2)	3	(0.6)
	Hispanic	463	(24.4)	98	(19.4)	90	(18.3)
	Other	10	(0.5)	1	(0.2)	2	(0.4)
	Not recorded	1	(0.1)	0		0	
Disposition							
N (%) of patients	Completed	996	(34.4)	483	(95.8)	471	(95.7)
	Discontinued	1901	(65.6)	21	(4.2)	21	(4.3)
N analysed for safety[a]		1901		504		492	
N analysed for efficacy (ITT)		Not applicable		493		481	

[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, took at least 1 dose of study treatment and had at least 1 safety assessment.

ITT Intention-to-treat; N Number; SD Standard deviation.

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

Baseline characteristic			Treatment group			
			Rosuvastatin 10 mg (n=504)		Atorvastatin 20 mg (n=492)	
Weight	Mean (SD)	kg	82.9	(17.9)	83.2	(18.4)
	Range		44 to 158		42 to 177	
<50 kg	n (%)		6	(1.2)	4	(0.8)
50 to 90 kg	n (%)		355	(70.4)	338	(68.7)
>90 kg	n (%)		143	(28.4)	150	(30.5)
Body mass index	Mean (SD)	kg/m^2	29.71	(5.58)	29.74	(5.89)
	Range		18.9 to 49.9		18.0 to 66.6	
<20 kg/m^2		n (%)	2	(0.4)	5	(1.0)
20 to <25 kg/m^2		n (%)	91	(18.1)	89	(18.1)
25 to <30 kg/m^2		n (%)	203	(40.3)	196	(39.8)
≥30 kg/m^2		n (%)	208	(41.3)	202	(41.1)

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

Baseline characteristic			Treatment group			
			Rosuvastatin 10 mg (n=504)		Atorvastatin 20 mg (n=492)	
LDL-C	Mean (SD)	mmol/L	4.272	(0.558)	4.268	(0.564)
	Range		3.00 to 5.80		2.40 to 5.90	
	Mean (SD)	mg/dL	165.1	(21.5)	164.9	(21.8)
	Range		115 to 222		93 to 229	
Renal function (creatinine clearance)						
Normal (>80 mL/min)		n (%)	292	(57.9)	271	(55.1)
Mild impairment (50 to ≤80 mL/min)		n (%)	177	(35.1)	190	(38.6)
Moderate impairment (30 to <50 mL/min)		n (%)	35	(6.9)	29	(5.9)
Not calculated		n (%)	0		2	(0.4)
Lipid-lowering medication pre-study[a]		n (%)	274	(54.3)	276	(56.2)
Metabolic syndrome at baseline						
Yes		n (%)	254	(50.4)	237	(48.2)
No		n (%)	249	(49.4)	253	(51.4)
Not known		n (%)	1	(0.2)	2	(0.4)
Diabetes Mellitus (Type 1 or 2)		n (%)	256	(50.8)	250	(50.8)

LDL-C Low-density lipoprotein cholesterol; SD Standard deviation.

[a] Based on actual treatment received during study (rosuvastatin = 505, atorvastatin = 491; 1 patient randomised to atorvastatin 20 mg received rosuvastatin 10 mg).

The groups were comparable in terms of baseline characteristics. The most common reason for discontinuation from treatment in both groups was adverse events.

Efficacy results

The results of the analysis of the percentage change from baseline in LDL-C concentration at Week 6 (the primary variable of this study) are presented in Table S3.

Table S3 Percentage change from baseline in LDL-C concentration at Week 6 (Last Observation Carried Forward analysis of the ITT population)

Statistic			Treatment group			
			Rosuvastatin 10 mg (n=493)		Atorvastatin 20 mg (n=481)	
Baseline LDL-C[a]	Mean (SD)	mmol/L	4.272	(0.558)	4.268	(0.564)
		mg/dL	165.1	(21.5)	164.9	(21.8)
Week 6 LDL-C	Mean (SD)	mmol/L	2.363	(0.667)	2.439	(0.626)
		mg/dL	91.4	(25.8)	94.3	(24.2)
Mean percentage change from baseline in LDL-C (SD)			-44.59	(14.16)	-42.67	(13.73)
Analysis						
Lsmean percentage change (standard error)			-44.59	(0.63)	-42.68	(0.64)
Difference in lsmeans (standard error)			-1.91	(0.89)	Not applicable	
95% confidence interval			-3.66 to -0.15		Not applicable	
p-value[b]			0.0331		Not applicable	

[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 using ANOVA analyses; values <0.05 are statistically significant.

ANOVA Analysis of variance; ITT Intention-to-treat; LDL-C Low-density lipoprotein cholesterol; lsmean Least squares mean; SD Standard deviation.

Rosuvastatin 10 mg was more effective at reducing LDL-C than atorvastatin 20 mg, producing a statistically significantly greater reduction in LDL-C after 6 weeks (-44.6% vs –42.7%, p=0.033).

Results for the secondary variables supported those for the primary variable. In terms of other lipids and lipoproteins, rosuvastatin 10 mg produced an overall improvement in the atherogenic lipid profile compared with atorvastatin 20 mg after 6 weeks, including a greater increase in HDL-C (6.4% vs 3.1%, p<0.001), with similar effects being observed on TC and TG with both rosuvastatin 10 mg and atorvastatin 20 mg. In addition, rosuvastatin 10 mg was more effective than atorvastatin 20 mg for getting patients to their LDL-C goal (68.8% vs 62.5% to NCEP ATP III goal, 68.0% vs 63.3% to EAS goal; p=0.022 and 0.043 respectively), with a similar effect for the NCEP ATP III nonHDL-C and EAS combined LDL-C and TC target goals. Rosuvastatin 10 mg was also considered cost-effective compared to atorvastatin 20 mg, both in terms of incremental cost per additional percentage LDL-C reduction and incremental cost per extra patient to guideline goal. The efficacy results from this study were consistent with findings from other clinical studies in the rosuvastatin clinical development programme.

Safety results

Adverse event by category reported after Week 6 are summarised in Table S4.

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]			
	Rosuvastatin 10 mg (n=505)		Atorvastatin 20 mg (n=491)	
Any AE	139	(27.5)	128	(26.1)
SAE	7	(1.4)	6	(1.2)
AE leading to death	2	(0.4)	0	
AE leading to premature discontinuation	14	(2.8)	11	(2.2)
Drug-related AE	34	(6.7)	35	(7.1)
Drug-related SAE	0		0	
Drug-related AE leading to death	0		0	
Drug-related AE leading to premature discontinuation	12	(2.4)	10	(2.0)
Other significant AE[b]	39	(7.7)	29	(5.9)
	Total number of AEs			
Any AE	226		204	
SAE	9		7	
AE leading to death	2		0	
AE leading to premature discontinuation	27		17	
Drug-related AE	53		52	
Drug-related SAE	0		0	
Drug-related AE leading to death	0		0	
Drug-related AE leading to premature discontinuation	22		14	
Other significant AE[b]	45		32	

[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 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; SAE Serious adverse event.

Only myalgia (see below) and urinary tract infection (rosuvastain 2.6% vs atorvastatin 3.3%) were observed in ≥2% of patients in either treatment group.

Rosuvastatin at a dose of 10 mg was well tolerated, with an AE profile similar to atorvastatin 20 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 events was low in both groups. Myalgia was reported by 4.8% of patients receiving rosuvastatin 10 mg and 2.6% of patients receiving atorvastatin 20 mg; importantly, none of these cases was associated with a clinically important elevation in CK (>10 x ULN; in fact, none was >3 x ULN). The pattern of other significant AEs did not reveal any unexpected findings or new treatment-related patterns for rosuvastatin 10 mg. Changes in clinical laboratory results were generally small and showed no treatment-related trends. No patients in either group had a treatment-emergent ALT value >3 x ULN on 2 consecutive occasions or any clinically important 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%. Changes in urinalysis results showed no treatment-related trends, with 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

31 January 2005