Drug product:	CRESTOR®	**SYNOPSIS**	
Drug substance(s):	Rosuvastatin		
Edition No.:	1.0		
Study code:	D3560L00039		
Date:	28 February 2007		

CASTOR – CRESTOR vs. Atorvastatin in patients with coronary heart disease

A randomised, double-blind, parallel-group, multicentre study comparing the efficacy of rosuvastatin 10 mg (with a possible titration to 40 mg) with atorvastatin 20 mg (with a possible titration to 80 mg) when given for a period of 16 weeks to patients with coronary heart disease and a previously performed percutaneous coronary intervention

Study centre(s)

This was a multicentre study conducted in 23 cardiology clinics in Sweden.

Publications

None at the time of writing this report

Study dates		**Phase of development**
First patient enrolled	12 January 2005	Therapeutic use (IV)
Last patient completed	24 March 2006	

Objectives

Primary objective

The primary objective was to compare the efficacy of once daily treatment with rosuvastatin 10 mg (with a possible dose titration to 40 mg) with the efficacy of treatment with atorvastatin 20 mg (with a possible dose titration to 80 mg) in reducing low density lipoprotein cholesterol (LDL-C) levels following 16 weeks of treatment in patients with coronary heart disease (CHD) and a previously performed percutaneous coronary intervention (PCI).

Secondary objectives

Efficacy - Lipids

- To compare the titration schedule of rosuvastatin with that of atorvastatin.
- To compare the efficacy of treatment with rosuvastatin 10 mg (with a possible dose titration to 40 mg) with the efficacy of treatment with atorvastatin 20 mg (with a possible dose titration to 80 mg) in reducing LDL-C levels to below 2.5 mmol/L (European guidelines on cardiovascular disease prevention in clinical practice).
- To compare the efficacy of once daily treatment with rosuvastatin 10 mg with that of atorvastatin 20 mg in reducing LDL-C levels following 6 weeks of treatment.
- To compare the efficacy of once daily treatment with rosuvastatin 10 mg (with a possible dose titration to 40 mg) with that of atorvastatin 20 mg (with a possible dose titration to 80 mg) in modifying levels of total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), triglycerides (TG), nonHDL-C (TC-HDL-C), LDL-C/HDL-C, TC/HDL-C, nonHDL-C/HDL-C, apolipoprotein A-I (ApoA-I), apolipoprotein B (ApoB) and ApoB/ApoA-I following 6 and 16 weeks of treatment.

Efficacy - Platelet function

- To compare the impact of treatment with rosuvastatin to that of atorvastatin and simvastatin 40 mg on clopidogrel-initiated inhibition of platelet aggregation in a subset of patients recruited in the Stockholm region.
- To compare the impact of treatment with rosuvastatin to that of atorvastatin on clopidogrel-initiated inhibition of platelet aggregation in all patients, totally and on each dose of rosuvastatin and atorvastatin.

Safety

- To determine the safety by evaluating the incidence and severity of adverse events and abnormal laboratory values through 16 weeks of treatment.

Study design

This was a 16-week, randomised, double-blind, parallel-group, multicentre study comparing the efficacy of once daily treatment with rosuvastatin,10-40 mg, with that of atorvastatin, 20-80 mg, in patients with CHD and a previously performed PCI, defined as a percutaneous transluminal coronary angioplasty (PTCA) with or without stent. The study also compared the impact of treatment with rosuvastatin to that of atorvastatin and simvastatin on clopidogrel-initiated inhibition of platelet aggregation.

Target patient population and sample size

Male or female patients, ≥18 years of age, with CHD and previously performed PCI, ongoing statin treatment and ongoing or previous clopidogrel treatment, were enrolled in the study. Patients with fasting LDL-C >2.9 mmol/L at visit 2 were randomised to treatment.

In order to have a power of 80% to detect a difference of 6 percent in LDL-C change from baseline to 16 weeks (primary efficacy variable) and to allow for an approximate discontinuation rate of 15%, 230 rosuvastatin/atorvastatin randomised patients were required. To have a power of 80% to detect a difference in means of 15% in percent change in clopidogrel-initiated inhibition of ADP-induced platelet aggregation (secondary efficacy variable) between rosuvastatin and atorvastatin and between rosuvastatin and simvastatin, and to allow for an approximate discontinuation rate of 15%, 25 randomised patients were required in each treatment group.

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

Patients were randomised to double-blind treatment with either rosuvastatin 10 mg orally once daily or atorvastatin 20 mg orally once daily and followed for 16 weeks. Patients who had not reached the LDL-C target of below 2.5 mmol/L after 6 or 10 weeks were uptitrated to the next dose step. After 14 weeks all patients received concomitant treatment with clopidogrel 75 mg for an additional two weeks. Before and after clopidogrel treatment platelet function was tested to evaluate possible interactions between the different statin treatments and the effects of clopidogrel. Patients from the Stockholm region could also be randomised to treatment with a fixed dose of open label simvastatin 40 mg orally once daily.

Study treatment was given in tablets of the following doses (batch #): rosuvastatin 10 mg (E02726-005L01), rosuvastatin 20 mg (E02726-005L01), rosuvastatin 10 mg (E02726-010L01), rosuvastatin 20 mg ((E02726-010L01), rosuvastatin 10 mg (E02726-012L01), rosuvastatin 20 mg (E02726-012L01), atorvastatin 20 mg (E02726-005L01), atorvastatin 40 mg (E02726-005L01), atorvastatin 20 mg (E02726-010L01), atorvastatin 40 mg (E02726-010L01), atorvastatin 20 mg (E01716-012L01), atorvastatin 40 mg (E02726-012L01), simvastatin 40 mg (E02726-005L03), simvastatin 40 mg (E02726-011L01), clopidogrel 75 mg (E01716-005L02).

Duration of treatment

Patients received double-blind treatment for up to 16 weeks following an enrolment period of up to 7 days.

Criteria for evaluation (main variables)

Efficacy

- Primary variable: Percent change in LDL-C from baseline to 16 weeks.
- Secondary variables – Lipids: Proportion of patients on each of the possible titrated rosuvastatin and atorvastatin doses after 16 weeks; proportion of patients achieving LDL-C target after 6 and 16 weeks; percent change in LDL-C from baseline to 6 weeks; Percent change from baseline to 6 and 16 weeks in TC, HDL-C, TG, nonHDL-C (TC-HDL-C), LDL-C/HDL-C, TC/HDL-C, nonHDL-C/HDL-C, ApoA-I, ApoB, and ApoB/ApoA-I.
- Secondary variables – Platelet function: Percent change in clopidogrel-initiated inhibition of adenosine diphosphate (ADP)-induced platelet aggregation and ADP-induced platelet P-selectin expression before and after 2 weeks treatment with clopidogrel in combination with rosuvastatin, atorvastatin or simvastatin 40 mg (Stockholm patients); percent change in clopidogrel-initiated inhibition of ADP-induced platelet aggregation before and after 2 weeks treatment with clopidogrel in combination with rosuvastatin or atorvastatin (all patients).

Safety

Safety evaluation, as determined by adverse events, abnormal laboratory data and abnormal physical examination.

Statistical methods

The primary efficacy variable, percent change in LDL-C from baseline to 16 weeks, was analysed by Analysis of Variance (ANOVA) with percent change in LDL-C as response variable and treatment (rosuvastatin or atorvastatin) as a factor. Percent change in clopidogrel-initiated inhibition of ADP-induced platelet P-selectin expression in combination with rosuvastatin, atorvastatin or simvastatin (primary analysis for the platelet function secondary efficacy variables) was analysed by ANOVA, with treatment as a factor. Descriptive statistics were used for safety assessments.

Patient population

Patient disposition is presented in Table S1 and baseline patient characteristics in Table S2. The randomised study population comprised 265 patients, of which 84 were randomised in the Stockholm region and constituted the patient subset with more extensive platelet function testing. 120 patients were randomised to rosuvastatin treatment and 119 patients to atorvastatin treatment. 26 patients in the Stockholm region were randomised to open-label treatment with simvastatin 40 mg. Of the 265 patients assigned to treatment, 263 patients were included in the safety population, 232 patients in the Intention To Treat (ITT)1 population (lipid analysis), 229 patients in the ITT2 population (platelet function analysis) and 69 in the ITT3 population (platelet function analysis in Stockholm subset). A total of 230 randomised patients completed the study: 106 on rosuvastatin, 101 on atorvastatin and 23 on simvastatin,

respectively. The number of discontinuations were similar between the treatment groups. Overall, the treatment groups were well-matched with respect to demographic and baseline characteristics and the patients had baseline lipid levels similar to those in patients with coronary heart disease.

Table S1 Patient disposition

	Atorvastatin	Rosuvastatin	Simvastatin	Total
Number of patients enrolled				640
Number of patients randomised	119	120	26	265
Number (%) of patients who completed the study	101 (84.9)	106 (88.3)	23 (88.5)	230 (86.8)
Number (%) of patients who discontinued during the study	18 (15.1)	14 (11.7)	3 (11.5)	35 (13.2)
N analysed for safety	119	118	26	263
N analysed for efficacy (ITT1)	116	116	NA	232
N analysed for efficacy (ITT2)	100	106	23	229
N analysed for efficacy (ITT3)	22	24	23	69

Data derived from Table 11.1.1- 1, Table 11.1.2- 1, Table 11.1.2- 2, Table 11.1.2- 3, Section 11.1.

Table S2 Patient population, ITT1 analysis set

	Atorvastatin (n=116)	Rosuvastatin (n=116)	Total (n=232)
Sex: n (%)			
Male	97 (83.6)	95 (81.9)	192 (82.8)
Female	19 (16.4)	21 (18.1)	40 (17.2)
Age (years)			
Mean (SD)	61.53 (8.90)	60.29 (7.61)	60.91 (8.29)
Median	61.50	60.00	60.00
Race: n (%)			
Caucasian	115 (99.1)	115 (99.1)	230 (99.1)
Oriental	1 (0.9)	1 (0.9)	2 (0.9)
Smoking status			
Non Smoker	34 (29.3)	31 (26.7)	65 (28.0)
Ex-Smoker	50 (43.1)	55 (47.4)	105 (45.3)
Occasional Smoker	5 (4.3)	4 (3.4)	9 (3.9)
Habitual Smoker	27 (23.3)	26 (22.4)	53 (22.8)

Data derived from Table 13.

Efficacy results

Lipids

A summary of lipids and lipoprotein fractions and percent change after 16 weeks treatment is presented in Table S3.

Table S3 Lipids and lipoprotein fractions at baseline and 16 weeks and percent change from baseline to 16 weeks, ITT analysis set

					Atorvastatin[c] vs Rosuvastatin[d]		
	Atorvastatin (n=116) Baseline[a]	(n=111) Week 16[a]	Rosuvastatin (n=116) Baseline[a]	(n=113) Week 16[a]	Adj mean diff (SE)	95% conf interval	p-value
LDL-C (mmol/L)	3.58 (0.54)	2.61 (0.61)[b]	3.60 (0.58)	2.44 (0.59)	4.751 (2.19)	(0.44, 9.06)	0.0309
TC (mmol/L)	5.50 (0.72)	4.44 (0.73)	5.48 (0.78)	4.28 (0.72)	2.144 (1.72)	(-1.2, 5.53)	0.2132
HDL-C (mmol/L)	1.23 (0.25)	1.22 (0.26)	1.24 (0.29)	1.30 (0.29)	-5.66 (2.16)	(-9.9, -1.4)	0.0092
non-HDL-C (mmol/L)	4.26 (0.75)	3.22 (0.69)	4.24 (0.72)	2.98 (0.66)	4.637 (2.17)	(0.37, 8.91)	0.0334
TG (mmol/L)	1.70 (0.83)	1.51 (0.75)	1.64 (0.69)	1.47 (0.74)	-2.44 (4.27)	(-11, 5.99)	0.5691
TC-C/HDL-C (ratio)	4.64 (1.12)	3.75 (0.82)	4.63 (1.06)	3.43 (0.85)	6.344 (2.19)	(2.03, 10.7)	0.0041
LDL-C/HDL-C (ratio)	3.04 (0.85)	2.22 (0.65)	3.06 (0.83)	1.98 (0.67)	8.717 (2.64)	(3.52, 13.9)	0.0011
non-HDL-C/HDL-C (ratio)	3.64 (1.12)	2.75 (0.82)	3.63 (1.06)	2.43 (0.85)	8.507 (2.76)	(3.07, 13.9)	0.0022
ApoB (g/L)	1.35 (0.24)	1.04 (0.20)	1.34 (0.26)	1.00 (0.20)	1.98 (2.1)	(-2.2, 6.11)	0.3462
ApoA-I (g/L)	1.46 (0.20)	1.45 (0.20)	1.45 (0.22)	1.51 (0.25)	-4.4 (1.59)	(-7.5, -1.3)	0.0063
ApoB / ApoA-I (ratio)	0.94 (0.23)	0.73 (0.17)	0.94 (0.22)	0.68 (0.17)	5.07 (2.28)	(0.57, 9.57)	0.0274

[a] Mean (SD)
[b] n = 112
[c] Mean atorvastatin dose at study end 65 mg
[d] Mean rosuvastatin dose at study end 28 mg
Data derived from Table 18, Table 19, Table 22 and Table 23.

Rosuvastatin was significantly more effective than atorvastatin in reducing LDL-C levels over 16 weeks of treatment in patients with CHD and a previously performed PCI (31.1% vs. 26.3%, p=0.031). More rosuvastatin treated patients reached the LDL-C target of <2.5 mmol/L than atorvastatin treated patients (58.6% vs. 42.2%, p=0.013). Fewer patients using rosuvastatin (49.5%) than those using atorvastatin (66.1%) had to be uptitrated to the highest dose (rosuvastatin 40 mg and atorvastatin 80 mg) to reach the LDL-C target of <2.5 mmol/L. The mean dose for rosuvastatin was 28 mg vs. 65 mg for atorvastatin. After 6 weeks LDL-C levels were reduced by 20.6% in rosuvastatin patients and by 16.7% in atorvastatin patients. Rosuvastatin was significantly better than atorvastatin in lowering nonHDL-C, the ApoB/ApoA-I ratio, the other lipid ratios and in increasing HDL-C and ApoA-I. There was no significant difference between rosuvastatin and atorvastatin in levels of TC, TG or ApoB.

Platelet function

Clopidogrel-initiated inhibition of ADP-induced platelet P-selectin expression in the Stockholm patients was greater in the atorvastatin group than in the rosuvastatin group (reduction of 54.3% vs. 40.1%, p=0.0082). There was no significant difference between rosuvastatin and simvastatin treated patients (reduction of 40.1% vs. 47.1%, p=0.18). The same pattern was seen with the ADP-induced platelet aggregation measured with the aggregometry method (reduction of 40.4%, 56.8% and 50.8% for rosuvastatin, atorvastatin and simvastatin, respectively, p=0.047 for rosuvastatin vs. atorvastatin, p=0.20 for rosuvastatin vs. simvastatin). ADP-induced platelet aggregation measured with the point-of-care method in all patients was similar between the rosuvastatin group and the atorvastatin group (reduction of 24.7% vs. 24.5%, p=0.97). The point-of-care method results for the Stockholm patients also showed similar reduction between treatments, but the reduction was of greater magnitude; rosuvastatin 40.9% vs. atorvastatin 53.7% (p=0.096) and rosuvastatin 40.9% vs. simvastatin 43.1% (p=0.772). There was an inverse relationship between the platelet aggregation and the statin dose with the best function of clopidogrel at the highest statin dose.

Safety results

The number (%) of patients who had at least 1 adverse event in any category is summarised in Table S4. In general, the study treatments were safe and well tolerated at all doses tested in this study. The overall incidence of adverse events (AEs) was higher in the simvastatin group than in the rosuvastatin and atorvastatin groups. The AE pattern associated with all treatments was similar and in keeping with the pharmacological profile of statins and co-treatment with clopidogrel. None of the AEs that occurred was unexpected given the age and underlying medical conditions of the patient population. The number and type of serious adverse events (SAEs) and discontinuations due to AEs (DAEs) were similar between the treatment groups and there was no evidence of any treatment related differences. One death of unknown cause occurred during the enrolment period when no study drug was taken. The investigator considered the death to be not related to study procedures.

Table S4 Number (%) of patients who had an adverse event in any category (safety analysis set)

Category of adverse event	Rosuvastatin (n=120)	Atorvastatin (n=119)	Simvastatin (n=26)	Total (n=265)
Treatment period				
Any adverse events	57 (47.5%)	61 (51.3%)	22 (84.6%)	140 (52.8%)
Serious adverse events	12 (10%)	13 (10.9%)	2 (7.7%)	27 (10.2%)
Serious adverse events leading to death	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Serious adverse events not leading to death	12 (10%)	13 (10.9%)	2 (7.7%)	27 (10.2%)
Discontinuations of study treatment due to adverse events	5 (4.2%)	2 (1.7%)	0 (0%)	7 (2.6%)

Table S4 Number (%) of patients who had an adverse event in any category (safety analysis set)

Category of adverse event	Rosuvastatin (n=120)	Atorvastatin (n=119)	Simvastatin (n=26)	Total (n=265)
Other significant adverse events	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total number of adverse events - enrolment and treatment periods				
Any adverse events	93	113	37	243
Serious adverse events	13	16	5	34
Other significant adverse events	0	0	0	0

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The incidence of common AEs (occurring at an incidence of >1.5% in any treatment group) is summarised by randomised treatment group in Table S5. The pattern of common AEs conformed to what was anticipated based on the pharmacological profile of statins, i.e. myalgia, arthralgia, diarrhoea and nausea, and clopidogrel, i.e. epistaxis. The incidence rate was similar between rosuvastatin and atorvastatin and did not appear to be related to the dose. Angina pectoris was the most commonly reported AE in all treatment groups, along with non-cardiac chest pain reflecting the medical condition of the patient population. There were no reports of myopathy or rhabdomyolysis for either compound.

The mean changes in clinical chemistry and haematology variables, pulse and blood pressure were small and generally similar between treatment groups. There were no individual abnormal values in laboratory tests according to the predefined thresholds of clinical significance (ASAT or ALAT >3 x ULN on 2 consecutive occasions, CK increase >5 x ULN). There were no patients with clinically important vital signs values.

Table S5 Number (%) of patients with the most commonly reported[a] adverse events, sorted by decreasing order of frequency as summarised over all treatment groups (safety analysis set)

Preferred term	Rosuvastatin (N=120)	Atorvastatin (N=119)	Simvastatin (N=26)	Total (N=265)
Angina pectoris	9 (7.5%)	5 (4.2%)	4 (15.4%)	18 (6.8%)
Myalgia	4 (3.3%)	5 (4.2%)	3 (11.5%)	12 (4.5%)
Nasopharyngitis	6 (5%)	4 (3.4%)	0 (0%)	10 (3.8%)
Arthralgia	3 (2.5%)	4 (3.4%)	1 (3.8%)	8 (3%)
Non-cardiac chest pain	3 (2.5%)	4 (3.4%)	1 (3.8%)	8 (3%)
Diarrhoea	0 (0%)	5 (4.2%)	1 (3.8%)	6 (2.3%)
Nausea	2 (1.7%)	4 (3.4%)	0 (0%)	6 (2.3%)
Epistaxis	0 (0%)	3 (2.5%)	2 (7.7%)	5 (1.9%)
Fatigue	2 (1.7%)	2 (1.7%)	1 (3.8%)	5 (1.9%)

Table S5 Number (%) of patients with the most commonly reported[a] adverse events, sorted by decreasing order of frequency as summarised over all treatment groups (safety analysis set)

Preferred term	Rosuvastatin (N=120)	Atorvastatin (N=119)	Simvastatin (N=26)	Total (N=265)
Headache	2 (1.7%)	2 (1.7%)	1 (3.8%)	5 (1.9%)
Influenza	1 (0.8%)	2 (1.7%)	2 (7.7%)	5 (1.9%)
Back pain	0 (0%)	3 (2.5%)	1 (3.8%)	4 (1.5%)
Chest discomfort	1 (0.8%)	1 (0.8%)	2 (7.7%)	4 (1.5%)
Cough	2 (1.7%)	2 (1.7%)	0 (0%)	4 (1.5%)
Dizziness	1 (0.8%)	2 (1.7%)	1 (3.8%)	4 (1.5%)
Hypertension	0 (0%)	3 (2.5%)	1 (3.8%)	4 (1.5%)
Rash	0 (0%)	2 (1.7%)	2 (7.7%)	4 (1.5%)
Vertigo	3 (2.5%)	1 (0.8%)	0 (0%)	4 (1.5%)

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