Drug product:	Rosuvastatin	**SYNOPSIS**	
Drug substance(s):	Rosuvastatin		
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An open-label, randomised, multi-centre, phase IIIb/IV, parallel group study to compare the efficacy and safety of rosuvastatin and atorvastatin in subjects with type IIa and IIb hypercholesterolaemia (DISCOVERY)

Study centre(s)

Subjects were recruited from a total of 70 centres in Asia (China, 20; Hong Kong, 2; Korea, 25; Malaysia, 11; Taiwan, 10; and Thailand, 2). A total of 2159 subjects were enrolled, of whom 1482 were randomised.

Publications

None at the time of writing this report

Study dates		**Phase of development**
First subject randomised	20 June 2003	IIIb/IV
Last subject randomised	30 September 2005	
Last subject completed	31 December 2005	

Objectives

Primary:

The primary objective of the study is to compare the efficacy of rosuvastatin 10 mg with atorvastatin 10 mg by assessment of the percentage of subjects who reach the 1998 European low-density lipoprotein cholesterol (LDL-C) target goal after 12 weeks of therapy.

Secondary:

1. To compare the efficacy of rosuvastatin 10 mg with atorvastatin 10 mg by assessment of the percentage of subjects who reach the 1998 European total cholesterol (TC) treatment goal after 12 weeks of therapy.

2. Percentage change in LDL-C, TC, high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) from pre-dose (week 0) and 12 weeks will be performed separately for the switched and the naïve patients.

3. To compare rosuvastatin 10 mg with atorvastatin 10 mg after 12 weeks of treatment with respect to the incidence and severity of adverse events and abnormal laboratory values.

The primary objective of the optional extension study, which will be reported separately, is to assess the long-term safety of rosuvastatin.

Study design

This was a randomised, multi-national, multi-centre, open-label, two-arm parallel group study comparing the efficacy and safety of rosuvastatin (10 mg/day) with atorvastatin (10 mg/day) when given for 12 weeks to subjects with primary hypercholesterolaemia, who could be either statin naïve or have been receiving "start doses" of other lipid-lowering therapies that had proved ineffective ("switched" subjects). An optional extension period allowed responding subjects to continue on rosuvastatin treatment in the event that the drug had not yet become available commercially at the end of the main study period. This clinical study report describes the results of the 12-week parallel group phase of the study. The extension period of the study will be reported separately.

Target subject population and sample size

Male or female subjects, 18 years of age or older, with primary hypercholesterolaemia who were either statin naïve, with an LDL-C level > 3.5 mmol/L (135 mg/dL), or had been receiving "start doses" of other lipid-lowering therapies that had proved ineffective, with an LDL-C level > 3.1 mmol/L (120 mg/dL), and a cardiovascular (CV) risk > 20%/10 years, type 2 diabetes, or a history of coronary heart disease (CHD) or other established atherosclerotic disease. Dietary counselling for approximately six weeks was required before statin-naïve patients could enter the study. Switched subjects could enter the study directly at visit 1, with no dietary run-in period.

The size of the study population was calculated to detect a clinically meaningful difference in efficacy between rosuvastatin and atorvastatin, and was based on the primary endpoint, the percentage of subjects reaching the 1998 European LDL-C goal of < 3 mmol/L (115 mg/dL) at week 12. On the basis that subjects would be randomised to rosuvastatin or atorvastatin in the ratio 2:1, it was estimated that 918 evaluable subjects would be required to achieve 90% power for a two-sided significance level of 5% (a = 0.05). To allow for a withdrawal rate of up to 10% during the study, it was planned to randomise approximately 1,020 subjects into the

study, and allowing also for a withdrawal rate of 25% between visit 1 and subsequent randomisation at visit 2, to enrol approximately 1,362 subjects into the study.

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

Rosuvastatin, 10 mg in oral tablet form, was administered once daily.
ADM/batch numbers used were: ADM10361D03, ADM12492C03, ADM14128C03, ADM90325E02, ADM93626J02, CA639, E01811-05L02, E01811-05L05, E01811-12L01.

Atorvastatin, 10 mg in oral tablet form, was administered once daily. Commercial supplies were sourced locally. Batch numbers used were: 0101042, 0117013, 0226103, 0229023, 0229073, 0236072, 0391053, 0401093, 0413092, 0439024, 045079, 0462044, 0474023, 0480054, 0541053, 0553054, 337 003208, 3370-2312, 375044, 451034, 45837003, 536093.

Duration of treatment

Twelve weeks. During the optional extension period, reported separately, subjects could continue on rosuvastatin up to local launch time or up to 6 months from visit 1.

Criteria for evaluation (main endpoints)

Efficacy

Primary endpoint:

Percentage of subjects reaching the 1998 European LDL-C target goal at week 12. (The 1998 European LDL-C goal was < 3 mmol/L [115 mg/dL]; Wood et al, Eur Heart J 1998;19:1434-1503).

Secondary endpoints:

1. Percentage of subjects reaching the 1998 European TC target goal at week 12. (The 1998 European TC goal was < 5 mmol/L [190 mg/dL]; Wood et al, Eur Heart J 1998;19:1434-1503).

2. Percentage change in LDL-C, TC, HDL-C, and TG from pre-dose (week 0) to week 12 (performed separately for switched and naïve subjects).

3. Percentage of subjects reaching the 2003 European LDL-C and TC target goals at week 12. (Individual subject goals were assigned following calculation of the 10-year CV disease risk, as described by Conroy et al, Eur Heart J 2003;24:987-1003 and De Backer et al, Eur Heart J 2003;24:1601-1610).

Safety

Incidence and severity of adverse events and abnormal laboratory values.

Statistical methods

Efficacy evaluations were based on an intention-to-treat (ITT) analysis set comprising all randomised subjects who had received at least one dose of study medication for whom there were measurements at both baseline (week -2) and at least one post-treatment visit for one or more lipid parameters. For subjects withdrawing prior to week 12, measurements obtained at the withdrawal visit were to be carried forward as the week 12 values. Numbers and percentages of subjects on rosuvastatin and atorvastatin reaching each efficacy goal at week 12 were compared using a logistic regression model, with factors fitted for treatment, region, subject type (naïve or switched), treatment-by-subject type and treatment-by-region interactions, and the pre-dose lipid parameter fitted as a covariate. Formal treatment comparisons of percentage changes from baseline in lipid parameters at week 12 were performed separately for naïve and switched subjects using an analysis of covariance (ANCOVA) model, with factors fitted for treatment, region, and treatment-by-region interaction, and the pre-dose lipid parameter fitted as a covariate. Safety analyses were performed upon the safety analysis set, which comprised all randomised subjects who received at least one dose of study medication, according to treatment actually received.

Subject population

The subject population and disposition are presented in Table S1. A total of 2159 subjects were enrolled in the study at 70 centres in 6 countries or regions, of whom 1482 were randomised in an approximately 2:1 ratio to treatment with rosuvastatin (n = 995) or atorvastatin (n = 487). Among the 677 subjects not randomised, the most common reason for not proceeding was a failure to meet the eligibility criteria (n = 641; 94.7%). Randomised subjects in the two treatment groups were well balanced in terms of demographic and physical characteristics, and baseline levels, characteristic of the target population, were similar in naïve and switched subjects in the two groups.

Table S1 Subject population and disposition

		Rosuvastatin		Atorvastatin		Total	
Population							
N randomised (N planned)		995	(612)	487	(306)	1482	(918)
Demographic characteristics (ITT analysis set)		n = 950		n = 472		n = 1422	
Sex (n and % of subjects)	Male	496	(52.2)	235	(49.8)	731	(51.4)
	Female	454	(47.8)	237	(50.2)	691	(48.6)
Age (years)	Mean (SD)	60.3	(10.34)	60.8	(10.10)	60.5	(10.2)
	Range	33 to 93		30 to 87		30 to 93	
Race (n and % of subjects)	Caucasian	5	(0.5)	4	(0.8)	9	(0.6)
	Oriental	929	(97.8)	455	(96.4)	1384	(97.3)
	Other	16	(1.7)	13	(2.8)	29	(2.0)
Baseline characteristics (ITT analysis set)		n = 950		n = 472		n = 1422	
Height (cm)	Mean (SD)	161.7	(8.54)	161.5	(8.36)	161.6	(8.48)
	Range	135 to 188		139 to 187		135 to 188	
Weight (kg)	Mean[a] (SD)	67.4	(11.62)	66.6	(11.42)	67.1	(11.55)
	Range	36 to 116		41 to 115		36 to 116	
Body mass index (BMI) (kg/m^2)	Mean[a] (SD)	25.7	(3.67)	25.5	(3.56)	25.6	(3.63)
	Range	15.7 to 41.5		16.7 to 41.4		15.7 to 41.5	
Serum lipids (mmol/L, SD)							
Naïve subjects	LDL-C	4.32	(0.680)	4.38	(0.808)	ND	
	TC	6.47	(0.829)	6.50	(0.906)	ND	
Switched subjects	LDL-C	3.93	(0.781)	3.90	(0.754)	ND	
	TC	6.04	(0.872)	5.95	(0.853)	ND	
2003 European LDL-C goal[b] (n and % of subjects)	< 2.5 mmol/L	819	(86.2)	413	(87.5)	1232	(86.6)
	< 3.0 mmol/L	131	(13.8)	59	(12.5)	190	(13.4)

		Rosuvastatin		Atorvastatin		Total	
Disposition (All randomised subjects)		n = 995		n =487		n = 1482	
N (%) of subjects who	Completed	932	(93.7)	458	(94.0)	1390	(93.8)
	Discontinued	65	(6.5)	27	(5.5)	92	(6.2)
N analysed for safety[c]		989		484		1473	
N analysed for efficacy (ITT)		950		472		1422	

[a] For subjects in the rosuvastatin group, n = 949
[b] For details of the 2003 European LDL-C goals in relation to risk category, see Table 5, Section 5.5.3.1, in the body of this study report
[c] Number of subjects who received at least one dose of study medication
ITT=Intention to treat; N/n=Number; ND=not determined

Efficacy results

The proportions of subjects reaching 1998 European LDL-C (primary endpoint), 1998 European TC, and 2003 European LDL-C and TC (secondary endpoint) goals after 12 weeks of therapy are summarised in Table S2.

A significantly greater proportion of hypercholesterolaemic subjects receiving rosuvastatin reached the 1998 European LDL-C goal of < 3.0 mmol/L (115 mg/dL) at week 12 than did so receiving atorvastatin (79.5% vs 69.4%, p<0.0001).

A significantly greater proportion of hypercholesterolaemic subjects receiving rosuvastatin also reached the 1998 European TC goal of < 5 mmol/L (190 mg/dL) at week 12 than did so receiving atorvastatin (77.1% vs 67.5%, p<0.0001).

Similarly, significantly greater proportions of hypercholesterolaemic subjects receiving rosuvastatin reached their 2003 European LDL-C and TC goals than did so receiving atorvastatin (65.8% vs 49.5% and 64.0% vs 49.7%, p<0.0001 for each).

Table S2 Number (%) of subjects reaching 1998 and 2003 European lipid goals at week 12 (ITT analysis set)

	Rosuvastatin (n = 950)		Atorvastatin (n = 472)*	
N (%) reaching 1998 European LDL-C goal of < 3.0 mmol/L (115 mg/dL)**	755	(79.5)	327	(69.4)
	rosuvastatin vs atorvastatin p<0.0001			
N (%) reaching 1998 European TC goal of < 5 mmol/L (190 mg/dL)	732	(77.1)	318	(67.5)
	rosuvastatin vs atorvastatin p<0.0001			
N (%) reaching 2003 European LDL-C goal***	625	(65.8)	233	(49.5)
	rosuvastatin vs atorvastatin p<0.0001			
N (%) reaching 2003 European TC goal***	608	(64.0)	234	(49.7)
	rosuvastatin vs atorvastatin p<0.0001			

*One subject in the atorvastatin treatment group was excluded from calculations related to efficacy variables because week 12 lipid data were provided by a non-study laboratory. Percentage calculations are therefore based on there having been 471 subjects in the atorvastatin group. **Primary endpoint ***2003 European goals published in De Backer et al, Eur Heart J 2003;24:1601-1610

Percentage changes from baseline levels of LDL-C, TC, HDL-C, and TG in statin naïve and switched subjects are shown in Table S3.

Table S3 Changes in lipid profiles between baseline and week 12 (ITT analysis set)

		Rosuvastatin (n =950)					Atorvastatin (n = 472)*					
Lipid	Subject type	mmol/L (mean)		n	LS mean % change (SE)		mmol/L (mean)		n	LS mean % change (SE)		p-value rosuvastatin vs atorvastatin
		Week -2	Week 12				Week -2	Week 12				
LDL-C												
	Naïve	4.32	2.29	515	-47.5	(0.90)	4.38	2.64	267	-40.2	(1.18)	<0.0001
	Switched	3.93	2.52	433	-33.9	(1.51)	3.90	2.89	204	-24.0	(1.83)	<0.0001
TC												
	Naïve	6.47	4.29	516	-34.2	(0.66)	6.50	4.61	267	-29.6	(0.87)	<0.0001
	Switched	6.04	4.53	434	-23.1	(1.07)	5.95	4.89	204	-16.3	(1.29)	<0.0001
HDL-C												
	Naïve	1.31	1.33	516	0.7	(0.88)	1.33	1.32	267	-1.6	(1.15)	0.0826
	Switched	1.26	1.27	434	1.3	(1.23)	1.24	1.25	204	1.5	(1.49)	0.8477
TG												
	Naïve	1.85	1.48	516	-13.5	(1.60)	1.74	1.44	267	-11.8	(2.11)	0.5011
	Switched	1.86	1.61	434	-1.2	(2.94)	1.77	1.63	204	0.4	(3.55)	0.6684

* One subject in the atorvastatin treatment group was excluded from calculations related to efficacy variables because week 12 lipid data were provided by a non-study laboratory. Calculations of efficacy variables were therefore based on the remaining 471 subjects; n = number of subjects

Rosuvastatin was significantly more effective than atorvastatin in reducing both LDL-C and TC levels from baseline in statin naïve subjects (-47.5% vs -40.2% for LDL-C; -34.2% vs -29.6% for TC; $p<0.0001$ in each case). Similarly, rosuvastatin was significantly more effective than atorvastatin in reducing LDL-C and TC levels in switched subjects (-33.9% vs -24.0% for LDL-C; -23.1% vs -16.3% for TC; $p<0.0001$ in each case). There were minimal alterations from baseline in HDL-C levels in either naïve or switched subjects in both rosuvastatin and atorvastatin treatment groups, or in TG levels in switched subjects in both groups. There was no statistically significant difference between treatment groups in the extent of the decrease from baseline in TG levels in naïve subjects (-13.5% in the rosuvastatin group vs -11.8% in the atorvastatin group; $p = 0.5011$).

The week 12 data indicate a clinical benefit of rosuvastatin 10 mg greater than that obtained with atorvastatin 10 mg in terms of its ability to enable subjects with primary hypercholesterolaemia to reach their LDL-C and TC goals.

Safety results

Both study treatments were generally well tolerated, and the incidence of adverse events (AEs), the types of which were similar between the treatment groups, and serious adverse events (SAEs) was low (Table S4). The proportions of subjects in the two groups that discontinued study treatment because of treatment-emergent AEs were similar (rosuvastatin group, 20 subjects, 2.0%; atorvastatin group, 10 subjects, 2.1%). No new safety issues were identified, the majority of AEs leading to discontinuation among subjects in the rosuvastatin group being either listed events, such as myalgia or headache, or events not unexpected among the hypercholesterolaemic statin target population, such as acute coronary syndrome and hypertension. All SAEs, with the exception of chronic hepatitis reported by one subject receiving rosuvastatin, were judged by the investigator as having had no causal relationship with investigational product. The case report of chronic hepatitis is confounded by the finding of positive serology for hepatitis B surface antigen. “Other significant AEs” (OAEs), principally myalgia and increased circulating levels of creatine kinase (CK), were reported by approximately 2% of subjects in each treatment group. The four deaths that occurred during the study, two (0.2%) (sudden death; cerebral infarction/sepsis) in the rosuvastatin group and two (0.4%) (hypertensive heart disease; multi-organ failure) in the atorvastatin group, were considered by the investigator to have been unrelated to investigational product.

Table S4 Number (%) of subjects who had at least one treatment-emergent adverse event in any category, and total numbers of adverse events (safety analysis set)

Category of adverse event	N (%) of subjects who had an adverse event in each category[a]			
	Rosuvastatin (n = 989)		Atorvastatin (n = 484)	
Number of subjects				
Any adverse event	205	(20.7)	82	(16.9)
Serious adverse event	27	(2.7)	10	(2.1)
Serious adverse event leading to death	2	(0.2)	2	(0.4)
Serious adverse event not leading to death	26	(2.6)	9	(1.9)
Discontinuation of study treatment due to adverse event	20	(2.0)	10	(2.1)
Number of adverse events				
	Total number of adverse events			
Adverse events	302		143	
Serious adverse events	36		13	

[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.

The five most frequently reported AEs are shown in Table S5, amongst which upper respiratory tract infection, the most common, affected approximately 1.9% of subjects overall.

Table S5 Number (%) of subjects with the most commonly reported[a] treatment-emergent adverse events, sorted by decreasing order of frequency (safety analysis set)

Preferred term	N (%) of subjects who had an adverse event			
	Rosuvastatin (n = 989)		Atorvastatin (n = 484)	
	n	(%)	n	(%)
Upper respiratory tract infection	21	(2.1)	7	(1.4)
Dizziness	10	(1.0)	9	(1.9)
Headache	9	(0.9)	6	(1.2)
Nasopharyngitis	10	(1.0)	2	(0.4)
Myalgia	8	(0.8)	4	(0.8)

[a] Events with a total frequency of ≥ 0.8% across both treatment groups are included in this table.

Mean changes from baseline in circulating levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, CK, and creatinine at week 12 were small, comparable between rosuvastatin and atorvastatin treatment groups, and generally unremarkable. One (0.1%) subject in the rosuvastatin group had both ALT and AST levels at week 12 of special note (> 3 x ULN [the upper limit of normal]). (This subject is that for whom chronic hepatitis was reported as an SAE at week 12 noted previously). No week 12 ALT or AST levels were > 3 x ULN in the atorvastatin group, and no subject in either treatment group registered an increase requiring special note (> 10 x ULN) in serum levels of CK. One subject in the rosuvastatin group (none in the atorvastatin group) had a > 100% increase in serum creatinine from baseline to a level greater than the upper limit of the reference range at week 12. Vital signs, weight, and BMI were essentially unchanged in both treatment groups, although there were slight decreases in systolic and diastolic blood pressure, of the order of 2 to 5 mm Hg, in each.

Date of the report

10 February 2007