Drug Product	Crestor	**SYNOPSIS**	
Drug Substance	Rosuvastatin calcium		
Study Code	D3560L00021 (4522US/0001)		
Edition Number	1		
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A 12-Week, Randomized, Open-Label, 3-Arm, Parallel Group, Multicenter, Phase IIIb Study Comparing the Efficacy and Safety of Rosuvastatin 20 mg and 40 mg with that of Atorvastatin 80 mg in Patients with Acute Coronary Syndromes (LUNAR)

Study centers

Included in this study were 169 investigative centers in the following countries: United States (166 centers), Costa Rica (2 centers), and Panama (1 center)

Publications

Pitt B, Loscalzo J, Ycas J, Raichlen J, for the LUNAR Study Group. Acute coronary syndromes do not lower lipid levels. J Am Coll Cardiol 2006;47(4)(Suppl 1):323A (Abstract 959-186).

Pitt B, Loscalzo J, Ycas J, Raichlen J. Lipid levels after acute coronary syndromes. J Am Coll Cardiol 2008; 51:1440-45.

Study dates		**Phase of development**
First patient enrolled	14 December 2003	IIIb
Last patient completed	31 August 2007	

Objectives

The primary objective of this study was to compare the efficacy of rosuvastatin 20 mg and rosuvastatin 40 mg with that of atorvastatin 80 mg in reducing low-density lipoprotein cholesterol (LDL-C) levels in patients with acute coronary syndromes (ACS) over 6 to 12 weeks of once daily treatment.

The secondary objectives of the study were to compare the efficacy of once daily rosuvastatin 20 mg and rosuvastatin 40 mg with that of once daily atorvastatin 80 mg, and to evaluate the safety of these treatments, in patients with ACS by assessing:

1. The percent change from baseline in LDL-C levels at 2, 6, and 12 weeks of treatment

2. The percent change from baseline in total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), non-HDL-C (non-HDL-C = TC – HDL-C), apolipoprotein A-I (ApoA-I), apolipoprotein B (ApoB), LDL-C/HDL-C, TC/HDL-C, non-HDL-C/HDL-C, and ApoB/ApoA-I over 6 to 12 weeks, at 6 weeks, and at 12 weeks of treatment

3. The percent change from baseline in the level of high sensitivity C-reactive protein (hsCRP), an inflammatory marker, over 6 to 12 weeks of treatment, at 6 weeks, and at 12 weeks of treatment

4. Safety and tolerability by evaluating the incidence and severity of adverse events (AEs), abnormal physical examination findings, and abnormal laboratory values through 12 weeks of treatment

Study design

This was a 12-week, randomized, open-label, 3-arm, parallel-group, multicenter, Phase IIIb study comparing the efficacy of rosuvastatin 20 mg and 40 mg with that of atorvastatin 80 mg, and evaluating the safety of these treatments in patients with ACS. Investigators were blinded to the measurements of primary and secondary endpoint parameters in patients on study treatment. Lipid and lipoprotein assessments were made at 2, 6, and 12 weeks of treatment.

Target patient population and sample size

Adult patients (18 to 75 years of age) with evidence of coronary artery disease, who were hospitalized with recent chest pain (ischemic symptoms). Both those patients who had non-ST segment elevation ACS and those patients with ST segment elevation ACS who received optimal reperfusion therapy were eligible. At randomization, patients must have had an LDL-C level >70 mg/dL and fasting TG level <500 mg/dL.

To provide 90% power to observe superiority if the real difference between the 2 treatments was 4%, it was estimated that 621 patients (207 in each treatment arm) would be required in the intent-to-treat (ITT) population. A total of 825 patients were actually randomized to treatment.

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

The study medication was rosuvastatin 20 mg (batch numbers: PCA05V, TS12032, TX13073, E03420-048B01), rosuvastatin 40 mg (batch numbers: PDA04V, TX13074, TX14006), and

atorvastatin 80 mg (batch numbers: 04446V, 15933V, 20514V, 12786V) in oral tablet form for once daily use.

Duration of treatment

Rosuvastatin or atorvastatin was administered once daily for a 12-week treatment period.

Criteria for evaluation (main variables)

Efficacy

The primary variable was the percent change from baseline in LDL-C levels (measured as direct LDL-C, not by the Friedewald calculation) over 6 to 12 weeks, calculated as the average of the percent changes at Week 6 and at Week 12. Friedewald LDL-C values were evaluated as a sensitivity analysis.

Secondary lipid and lipoprotein efficacy variables included:

- Percent change from baseline in LDL-C levels at 2, 6, and 12 weeks of treatment
- Percent change from baseline in TC, HDL-C, TG, non-HDL-C, ApoA-I, ApoB, LDL-C/HDL-C, TC/HDL-C, non-HDL-C/HDL-C, and ApoB/ApoA-I at Week 6, Week 12, and the average of the percent changes at Week 6 and Week 12
- Percent change from baseline in the level of the inflammatory marker CRP at 6 weeks, at 12 weeks, and the average of Weeks 6 and 12

Secondary safety variables:

- Safety and tolerability were evaluated by determining the incidence and severity of AEs, abnormal physical examination findings, and abnormal laboratory values through 12 weeks of treatment

Statistical methods

The primary efficacy analysis was based on the ITT population (patients who had a baseline measurement, had at least 1 post-baseline measurement, and who had taken at least 1 dose of study medication). Analyses were performed using a last-observation-carried-forward (LOCF) method on the ITT population for all efficacy variables, which involved an average of the 6- and 12-week values. Analysis of covariance (ANCOVA) was used as the primary analysis for percent change from baseline in LDL-C levels, with a main effect for treatment and baseline level of LDL-C as a covariate.

For a given comparison, a non-inferiority hypothesis was tested first, followed by a superiority hypothesis. A margin of inferiority of 3% was used. If the upper bound of the confidence interval for the difference in percent change from baseline in LDL-C for rosuvastatin less atorvastatin was below 3%, then non-inferiority was established. Only if the rosuvastatin

40-mg dose was found to be statistically superior to atorvastatin 80 mg was the rosuvastatin 20 mg versus atorvastatin 80 mg contrast formally tested. Because this was a closed-end procedure, no correction for multiplicity was used. Secondary endpoints were tested in a similar manner as the primary endpoint, except that non-inferiority testing was not done (except for the Friedewald LDL-C as a sensitivity analysis). Treatment group comparisons for CRP were analyzed using the Wilcoxon rank sum test.

Patient population

A total of 1391 patients entered the screening period. Of these, 825 (59.3%) were randomized to study treatment (277 patients were randomized to rosuvastatin 20 mg, 270 patients were randomized to rosuvastatin 40 mg, and 278 patients were randomized to atorvastatin 80 mg). Of the 825 randomized patients, 196 (23.8%) withdrew from the randomized treatment period. The percentage of patients withdrawing during randomized treatment was similar in the 3 treatment groups. The most common reason for study discontinuation overall was AEs (51/825, 6.2%).

Of the 825 randomized patients, 799 (96.8%) received study therapy and were evaluated for safety. A total of 754 (91.4%) were included in the ITT population and 651 (78.9%) were included in the PP population for analyses of efficacy. The treatment groups were similar with respect to the percentages of patients in the analysis populations.

The majority of randomized patients were Caucasian and male. The proportions of males to females were similar between treatment groups, however. More than 87% of patients were ≤65 years of age. Baseline characteristics and medical histories were generally comparable between the 3 treatment groups. The 3 treatment groups were similar in the distribution of patients in each of the ACS categories (ST elevation myocardial infarction, non-ST elevation myocardial infarction, and unstable angina).

Efficacy results

Table S1 summarizes the average of the percent change from baseline values at Week 6 and Week 12 for the primary variable and for key secondary variables.

Table S1 **Key efficacy results – analysis of the average of the percent change from baseline at Week 6 and Week 12 in lipid parameters and inflammatory marker CRP comparing rosuvastatin and atorvastatin treatment groups (LOCF, ITT population)**

	Rosuva 20 mg (N=246)	Rosuva 40 mg (N=251)	Atorva 80 mg (N=257)	Rosuva 20 mg versus Atorva 80 mg	Rosuva 40 mg versus Atorva 80 mg
Primary - LDL-C					
n for % change	246	251	257		
LS mean (Atorva LS mean)[a]	-41.64 (43.01)	-46.55 (-42.91)		1.37	-3.63
CI of difference vs Atorva 80 mg	-1.73 to 4.46	-6.74 to -0.53		p=0.3870	p=0.0219
Secondary					
TC					
n for % change	246	251	257		
LS mean (Atorva LS mean)[a]	-28.23 (-31.25)	-31.84 (-31.25)		3.02	-0.59
CI of difference vs Atorva 80 mg	0.51 to 5.53	-3.18 to 2.00		p=0.0186	p=0.6528
HDL-C					
n for % change	246	251	257		
LS mean (Atorva LS mean)[a]	9.57 (5.66)	11.50 (5.90)		3.91	5.60
CI of difference vs Atorva 80 mg	0.99 to 6.83	2.45 to 8.74		0.0087	0.0005
TG					
n for % change	246	251	257		
LS mean (Atorva LS mean)[a]	-9.54 (-18.00)	-14.41 (-18.17)		8.45	3.76
CI of difference vs Atorva 80 mg	2.12 to 14.79	-3.41 to 10.92		p=0.0090	p=0.3036
ApoB/ApoA-I					
n for % change	223	224	231		
LS mean (Atorva LS mean)[a]	-39.28 (-38.44)	-42.67 (-38.55)		-0.84	-4.12
CI of difference vs Atorva 80 mg	-3.46 to 1.78	-6.80 to -1.44		p=0.5285	p=0.0026

Table S1 **Key efficacy results – analysis of the average of the percent change from baseline at Week 6 and Week 12 in lipid parameters and inflammatory marker CRP comparing rosuvastatin and atorvastatin treatment groups (LOCF, ITT population)**

	Rosuva 20 mg (N=246)	Rosuva 40 mg (N=251)	Atorva 80 mg (N=257)	Rosuva 20 mg versus Atorva 80 mg	Rosuva 40 mg versus Atorva 80 mg
CRP					
n for % change	238	241	249		
Median	-84.94	-83.05	-85.00	p=0.4557	p=0.2844

Note: A negative value for the LS mean difference indicates a greater percentage decrease (or a lesser percent increase), whereas a positive value indicates less of a percentage decrease (or a greater percent increase).

[a] Because the comparisons of Rosuva 20 mg vs Atorva 80 mg and Rosuva 40 mg vs Atorva 80 mg are fit with separate ANCOVA models, they yield slightly different estimates of the Atorva 80 mg LS mean for percent change.

ApoA-I Apolipoprotein A-I; ApoB Apolipoprotein B; Atorva Atorvastatin; CI Confidence interval; CRP C-reactive protein; HDL-C High-density lipoprotein cholesterol; ITT Intent-to-treat; LDL-C Low-density lipoprotein cholesterol; LOCF Last observation carried forward; LS mean Least squares mean; Rosuva Rosuvastatin; TC Total cholesterol; TG Triglycerides.

For the primary endpoint, treatment with rosuvastatin 40 mg resulted in a statistically significant greater reduction in LDL-C compared with patients receiving atorvastatin 80 mg (46.8% vs 42.7%, p=0.0219). Rosuvastatin 20 mg and atorvastatin 80 mg were essentially similar to each other in treatment effect (the average of percent changes at Week 6 and Week 12 in direct LDL-C was a decrease of 42.0% and 42.7%, respectively; CI, -1.73 to 4.46), and the superiority of neither could be established.

For the secondary efficacy variables of percent change at Weeks 2, 6, and 12, the percent change from baseline in LDL-C was numerically greater in the rosuvastatin 40 mg group compared with the atorvastatin 80 mg group at all 3 time points, but this trend was only statistically significant at Week 12. Atorvastatin 80 mg showed greater percent reductions in direct LDL-C than rosuvastatin 20 mg at Weeks 2, 6, and 12, with the results at 2 and 6 weeks (but not at 12 weeks) being statistically significant. At Week 12, the percent decrease was nearly the same in both groups (43.5% for atorvastatin 80 mg vs 42.3% for rosuvastatin 20 mg).

For the secondary efficacy analysis of other lipid parameters, the study showed that, compared with atorvastatin 80 mg, rosuvastatin 40 mg statistically significantly increased HDL-C and ApoA-I (a clinically favorable response) and statistically significantly decreased LDL-C/HDL-C, TC/HDL-C, non-HDL-C/HDL-C, ApoB/ApoA-I, and LDL-C (Friedewald). There were no statistically significant differences between rosuvastatin 40 mg and atorvastatin 80 mg in average percent change from baseline in TC, TG, non-HDL-C, or ApoB. In the

comparison of rosuvastatin 20 mg and atorvastatin 80 mg, rosuvastatin 20 mg statistically significantly increased HDL-C and ApoA-I, but atorvastatin 80 mg was statistically significantly better in decreasing TC and TG. There were no other statistically significant differences between rosuvastatin 20 mg and atorvastatin 80 mg for any other secondary lipid parameter.

Values for the inflammatory marker CRP decreased in all treatment groups. There were no statistically significant differences between rosuvastatin (either dose) and atorvastatin in average of the percent change from baseline of Weeks 6 and 12 in CRP.

The effects of rosuvastatin on lipids, lipoproteins, and their ratios were clinically significant and consistent with the known efficacy profile of this drug.

Safety results

Study treatments were well tolerated. The overall AE profile associated with each treatment dose group was similar. The majority of patients who experienced AEs had AEs that were mild to moderate in severity. Two patients in the rosuvastatin 40 mg group (arrhythmia and MI) and 1 patient (arrhythmia) in the atorvastatin 80 mg group died during the course of the study; the deaths were considered by the investigator not to be related to study treatment. There were no treatment-related (investigators' assessment) SAEs in any treatment group. The overall frequency of AEs leading to discontinuation of a patient from study treatment (DAEs) was low (3.7% for rosuvastatin 20 mg, 6.1% for rosuvastatin 40 mg, and 9.3% for atorvastatin 80 mg). None of the AEs that occurred in this study were unexpected for this study population.

Changes in clinical laboratory results were generally small and showed no treatment-related trends. Two patients (1 in the rosuvastatin 20 mg group and 1 in the atorvastatin 80 mg group) had clinically important elevations in alanine aminotransferase (ALT) (>3 × upper limit of normal [ULN] on 2 consecutive visits) that were reported as AEs and ultimately led to the withdrawal of these patients from the study. One patient (in the rosuvastatin 40 mg group) had a clinically important elevation of creatine kinase (CK) (ie, >10 × ULN), and no patients had clinically important elevations of serum creatinine (ie, increase >100% from baseline). Six patients in the rosuvastatin 40 mg group had proteinuria at the final visit (defined as a shift in urine dipstick grade from 'none' or 'trace' at baseline to a grade of ≥++), compared with none in the rosuvastatin 20 mg group and 1 in the atorvastatin 80 mg group. None of these patients had abnormal serum creatinine values at screening or the final visit. Only 2 patients (both in the rosuvastatin 40 mg group) had both proteinuria and hematuria at the final visit; however, neither of these patients had associated AEs. Overall, the number of clinically notable laboratory abnormalities was low. No clinically meaningful pattern was noted.

No safety concerns were raised for physical examination evaluations between the treatment groups.