Drug product	Rosuvastatin tablets 10, 20, 40, and 80 mg	**SYNOPSIS**	
Drug substance(s)	Rosuvastatin calcium		
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Title: A 6-week, Open-label, Dose-comparison Study to Evaluate the Safety and Efficacy of Rosuvastatin Versus Atorvastatin, Pravastatin, and Simvastatin in Subjects with Hypercholesterolemia

International Co-ordinating investigator

Study center(s)

This study was conducted in the United States (US) at 183 centers.

Publications

None at the time of writing this report

Study dates		**Phase of development**
First subject enrolled	02 April 2001	IIIb
Last subject completed	28 March 2002	

Objectives

Primary:

1. to compare the efficacy of treatment with rosuvastatin 10, 20, 40, and 80 mg with the efficacy of treatment with atorvastatin 10, 20, 40, and 80 mg; pravastatin 10, 20, and 40 mg; and simvastatin 10, 20, 40, and 80 mg in reducing low density lipoprotein-cholesterol (LDL-C) concentrations in subjects with hypercholesterolemia following 6 weeks of treatment.

2. if the dose response pairwise analyses from the first primary objective are found to be significantly different, to compare the efficacy of once daily treatment with rosuvastatin 10 mg vs. atorvastatin 10 mg and 20 mg, pravastatin 10 mg, 20 mg, and 40 mg, and simvastatin 10 mg and 20 mg; rosuvastatin 20 mg vs. atorvastatin 20 mg and 40 mg, pravastatin 20 mg and 40 mg, and simvastatin 20 mg and 40 mg; rosuvastatin 40 mg vs. atorvastatin 40 mg and 80 mg, pravastatin 40 mg, and simvastatin 40 mg and 80 mg; and rosuvastatin 80 mg versus atorvastatin 80 mg, pravastatin 40 mg, and simvastatin 80 mg in reducing LDL-C concentrations in subjects with hypercholesterolemia following 6 weeks of treatment.

Secondary:

1. to compare the efficacy of once daily treatment with rosuvastatin 10 mg versus atorvastatin 10 mg and 20 mg, pravastatin 10 mg, 20 mg, and 40 mg and simvastatin 10 mg and 20 mg; rosuvastatin 20 mg vs. atorvastatin 20 mg and 40 mg, pravastatin 20 mg and 40 mg, and simvastatin 20 mg and 40 mg; rosuvastatin 40 mg vs. atorvastatin 40 mg and 80 mg, pravastatin 40 mg, and simvastatin 40 mg and 80 mg; and rosuvastatin 80 mg vs. atorvastatin 80 mg, pravastatin 40 mg, and simvastatin 80 mg in modifying other lipids and lipoproteins following 6 weeks of treatment.

2. to compare the efficacy of once daily treatment with rosuvastatin 10 mg versus atorvastatin 10 mg and 20 mg, pravastatin 10 mg, 20 mg and 40 mg, and simvastatin 10 mg and 20 mg; rosuvastatin 20 mg vs. atorvastatin 20 mg and 40 mg, pravastatin 20 mg and 40 mg, and simvastatin 20 mg and 40 mg; rosuvastatin 40 mg vs. atorvastatin 40 mg and 80 mg, pravastatin 40 mg, and simvastatin 40 mg and 80 mg; and rosuvastatin 80 mg vs. atorvastatin 80 mg, pravastatin 40 mg, and simvastatin 80 mg in reducing LDL-C concentrations to within the NCEP (National Cholesterol Education Program), EAS (European Atherosclerosis Society), and Canadian guidelines.

3. to assess the safety of treatment with rosuvastatin to that of atorvastatin, pravastatin, and simvastatin by evaluating the incidence and severity of adverse events and abnormal laboratory values during the 6-week treatment period.

4. to assess the long-term safety of treatment with rosuvastatin.

Study design

This was an open-label, randomized, 15-arm, parallel-group, multicenter, comparator clinical study investigating the efficacy and safety of 6 weeks of treatment with a fixed dose of rosuvastatin (10, 20, 40, or 80 mg), atorvastatin (10, 20, 40, or 80 mg), pravastatin (10, 20, or 40 mg), or simvastatin (10, 20, 40, or 80 mg).

Target subject population and sample size

Male and female subjects, aged 18 and older, with primary hypercholesterolemia with fasting LDL-C concentrations of ≥160 mg/dL and <250 mg/dL not on a lipid-lowering therapy after Visit 1, and triglyceride (TG) concentrations of <400 mg/dL during the dietary lead-in period.

For each treatment comparison, a difference in mean percentage reduction in LDL-C of 6% was judged to be clinically meaningful. This consideration was also applied to the sizing of the trial and was used as the basis for statistical significance. To allow for the 25 pairwise comparisons of interest, calculations for each individual comparison were based on a 2-sided significance level of 0.20% (0.002), using a Bonferroni correction (Miller 1966), and a power of 85%. In total, 2250 subjects (approximately 150 per arm) were to be randomized into the study in order for 141 subjects to complete each arm.

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

Rosuvastatin capsules (ZD4522; rosuvastatin calcium, CRESTOR™) 10, 20, 40, or 80 mg orally once daily, or atorvastatin tablets (LIPITOR™, Pfizer) 10, 20, 40, or 80 mg orally once daily, or pravastatin tablets (PRAVACHOL™, Bristol-Myers Squibb) 10, 20, or 40 mg orally once daily, or simvastatin tablets (ZOCOR™, Merck) 10, 20, 40, or 80 mg orally once daily.

Duration of treatment

A 6-week dietary lead-in period followed by a 6-week treatment period. Eligible subjects then had the option to enter into an extension study designed to assess the long-term safety of rosuvastatin in these subjects.

Criteria for evaluation (main variables)

Efficacy

- Primary variable: Percent change from baseline in LDL-C at Week 6.
- Secondary variables: Percentage change from baseline to Week 6 in other lipids, lipoproteins, and lipid subfractions.
- Secondary variable: Percentage of subjects reaching target goals for LDL-C and other lipids to within the NCEP Adult Treatment Panel III, EAS, and Canadian guidelines.

Safety

- Secondary variable: Safety evaluation, as determined by adverse events and laboratory data at Week 6.

Statistical methods

Analyses were performed on last observations carried forward (LOCF). The primary analysis of the primary endpoint (percentage change from baseline in LDL-C at 6 weeks) and the secondary endpoints of percent change from baseline in lipids and lipoproteins was performed as LOCF in the intention-to-treat (ITT) population using analysis of covariance (ANCOVA). This analysis was performed using pair-wise comparisons of the statins versus rosuvastatin. The same model was also used to test specific comparisons of interest. For the secondary endpoint for pairwise comparisons of percentage change from baseline in lipids and liproproteins, analysis of variance (ANOVA) was used. The numbers of subjects reaching target goals were compared using logistic regression analyses. The above efficacy analyses were performed using both the ITT and per protocol (PP) population. Safety data were not subject to formal statistical analysis.

Analyses as described above for the primary and secondary endpoints were performed to compare the 10 mg to 40 mg dose range of rosuvastatin to the dose ranges of the other comparators.

Subject population

In total, 8381 subjects entered the dietary lead-in period and 2431 subjects were randomized to treatment. The majority of randomized subjects were Caucasian and between 18 and 64 years of age, with approximately equal numbers of men and women. Overall, the treatment groups were similar for demographic characteristics and baseline lipids levels.

Of 2431 randomized subjects, 2 received no study treatment and were not included in the safety population. Hence, 2429 subjects were included for safety. Of these, 2401 were analyzed for efficacy in the ITT population and 1964 in the PP population. (There were also 3 cerivastatin treatment arms, which were subsequently removed from the study due to the withdrawal of cerivastatin from all markets; 149 subjects actually received cerivastatin. These subjects are not included in the totals for the dietary lead-in period or the randomized, safety, ITT, or PP populations.)

One hundred forty-three of the 2431 subjects (5.9%) randomized to treatment with rosuvastatin, atorvastatin, pravastatin, or simvastatin discontinued the study during the randomized treatment period. The most common reason for discontinuation was adverse events. Subjects treated with rosuvastatin 80 mg and those treated with atorvastatin 40 mg had the highest percentages of discontinuations for adverse events (DAEs) (8.5% and 7.5%, respectively) relative to the other treatment groups.

Efficacy results

Results of the analysis of percent change from baseline in LDL-C at 6 weeks for the comparison of rosuvastatin 10 to 80 mg versus the comparator statins are shown in Table S1.

Table S1 Analysis of percentage change from baseline in LDL-C at Week 6 – Comparison of rosuvastatin, atorvastatin, pravastatin, and simvastatin (LOCF on ITT population)

	Dose			
	10 mg	**20 mg**	**40 mg**	**80 mg**
Rosuvastatin	N = 156	N = 160	N = 157	N = 161
Atorvastatin	N = 158	N = 155	N = 156	N = 165
Pravastatin	N = 160	N = 164	N = 161	NA
Simvastatin	N = 165	N = 162	N = 158	N = 163
% change (SD)				
Rosuvastatin	-45.87 (13.08)	-52.34 (13.64)	-54.96 (13.44)	-58.04 (14.41)
Atorvastatin	-36.73 (10.69)	-42.57 (14.32)	-47.79 (12.92)	-51.05 (13.94)
Pravastatin	-20.13 (11.30)	-24.29 (11.26)	-29.69 (12.53)	NA
Simvastatin	-28.30 (13.65)	-34.98 (10.70)	-38.81 (13.90)	-45.78 (11.85)
Analysis				
lsmean of % change (SE)				
Rosuvastatin[a]	-46.23 (0.74)	-50.55 (0.57)	-54.87 (0.56)	-59.20 (0.73)
Atorvastatin[a]	-37.99 (0.74)	-42.32 (0.57)	-46.64 (0.57)	-50.96 (0.73)
Rosuvastatin[a]	-46.52 (0.78)	-50.62 (0.56)	-54.73 (0.55)	-58.84 (0.77)
Pravastatin[a]	-20.56 (0.71)	-24.67 (0.59)	-28.77 (0.71)	NA
Rosuvastatin[b]	-45.69 (1.06)	-52.26 (1.04)	-54.87 (1.05)	-57.95 (1.04)
Simvastatin[b]	-28.15 (1.03)	-34.93 (1.04)	-38.73 (1.05)	-45.64 (1.04)
Comparisons				
Rosuvastatin vs. atorvastatin				
Difference across the dose range (SE)		-8.2 (0.7)		
95% CI of difference (LCL and UCL)		-9.7 to -6.8		
p-value[a]		<0.001		
Rosuvastatin vs. pravastatin				
Difference across the dose range (SE)		-26.0 (0.8)		

Table S1 Analysis of percentage change from baseline in LDL-C at Week 6 – Comparison of rosuvastatin, atorvastatin, pravastatin, and simvastatin (LOCF on ITT population)

	Dose			
	10 mg	**20 mg**	**40 mg**	**80 mg**
Rosuvastatin	N = 156	N = 160	N = 157	N = 161
Atorvastatin	N = 158	N = 155	N = 156	N = 165
Pravastatin	N = 160	N = 164	N = 161	NA
Simvastatin	N = 165	N = 162	N = 158	N = 163
95% CI of difference (LCL and UCL)		-27.5 to -24.4		
p-value[a]		<0.001		
Rosuvastatin 10 mg vs. simvastatin 10 mg				
Difference (SE)		-17.5 (1.46)		
95% CI of difference (LCL and UCL)		-20.4 to -14.7		
p-value[b]		<0.001		
Rosuvastatin 20 mg vs. simvastatin 20 mg				
Difference (SE)		-17.3 (1.46)		
95% CI of difference (LCL and UCL)		-20.2 to -14.5		
p-value[b]		<0.001		
Rosuvastatin 40 mg vs. simvastatin 40 mg				
Difference (SE)		-16.2 (1.48)		
95% CI of difference (LCL and UCL)		-19.0 to -13.2		
p-value[b]		<0.001		
Rosuvastatin 80 mg vs. simvastatin 80 mg				
Difference (SE)		-12.3 (1.46)		
95% CI of difference (LCL and UCL)		-15.2 to -9.4		
p-value[b]		<0.001		

Data derived from Tables T9.3.1, T9.3.2, T9.3.3.

[a] Derived from an across the dose range ANCOVA comparison. p-values <0.05 are statistically significant, and no adjustment was made for multiple testing.

[b] Derived from a dose-by-dose ANOVA comparison. p-values <0.05 are statistically significant, and no adjustment was made for multiple testing.

LDL-C Low density lipoprotein-cholesterol; LOCF Last observation carried forward; ITT Intention- to-treat; SD Standard deviation; lsmeans Least squares mean; NA not applicable; SE Standard error; CI Confidence interval; LCL Lower confidence limit; UCL Upper confidence limit.

The dose-response curves for rosuvastatin and atorvastatin and for rosuvastatin and pravastatin were parallel, and the difference between the treatments could be determined across the dose range. Across the dose range, rosuvastatin resulted in a statistically significant reduction in LDL-C compared with atorvastatin or pravastatin ($p<0.001$). Because there was a significant treatment-by-log-dose interaction for the comparison of rosuvastatin and simvastatin, the dose-response curves for the 2 treatments were not parallel and the difference between them could not be determined across the dose range. Comparisons between rosuvastatin and simvastatin separately at doses of 10 mg, 20 mg, 40 mg, and 80 mg revealed that rosuvastatin was significantly better in reducing LDL-C for each dose comparison ($p<0.001$). The difference in percent reduction in LDL-C between rosuvastatin and each of the comparators exceeded the 5 to 7% reduction considered clinically meaningful and the 6% difference on which the trial was structured.

The results of ANOVA for comparisons of interest showed the following: rosuvastatin 10 mg treatment resulted in a significantly greater percent reduction in LDL-C compared with atorvastatin 10 mg; pravastatin 10 mg, 20 mg, or 40 mg; or simvastatin 10 mg, 20 mg, or 40 mg ($p<0.001$). The effect of rosuvastatin 10 mg on LDL-C reduction was numerically greater than atorvastatin 20 mg, but the difference was not statistically significant. Rosuvastatin 20 mg treatment resulted in a significantly greater percent reduction in LDL-C compared with atorvastatin 20 mg or 40 mg; pravastatin 20 mg or 40 mg; or simvastatin 20 mg, 40 mg, or 80 mg ($p<0.002$). The effect of rosuvastatin 20 mg was numerically greater than that for atorvastatin 80 mg, but the difference was not statistically significant. Rosuvastatin 40 mg treatment resulted in a significantly greater percent reduction in LDL-C compared with atorvastatin 40 mg, pravastatin 40 mg, or simvastatin 40 mg or 80 mg ($p<0.001$). The effect of rosuvastatin 40 mg was numerically greater than that of atorvastatin 80 mg, but the difference was not statistically significant. Rosuvastatin 80 mg treatment resulted in a significantly greater percent reduction in LDL-C compared with atorvastatin 80 mg or simvastatin 80 mg ($p<0.001$).

With respect to the secondary endpoints, rosuvastatin produced an improved lipid profile with a significantly greater reduction in TC, TG, non-HDL-C, LDL-C/HDL-C ratio, TC/HDL-C ratio, non-HDL-C/HDL-C ratio, ApoB, and ApoB/ApoA-I and a significantly greater increase in HDL-C and ApoA-I for most comparisons either across the dose range or by comparison of like doses ($p<0.001$). The comparisons that were not statistically significant between rosuvastatin and comparator statins were rosuvastatin versus atorvastatin across the dose range for TG, rosuvastatin 10 mg versus atorvastatin 10 mg for HDL-C, rosuvastatin 80 mg versus atorvastatin 80 mg for ApoB, rosuvastatin 20 and 40 mg versus pravastatin 20 and 40 mg for ApoA-I, and rosuvastatin versus simvastatin for all like-dose comparisons for ApoA-I.

Results of an ANOVA comparing the various doses of rosuvastatin with those of the comparator statins for the lipid and lipoprotein parameters were consistent with the results of the analysis across the dose range or by like doses.

Specific dose comparisons revealed that a numerically greater percent of subjects treated with rosuvastatin for 6 weeks reached NCEP LDL-C, NCEP LDL-C and non-HDL-C (in subjects with TG >200 mg/dL), EAS LDL-C, Canadian LDL-C, and Canadian TC/HDL-C, and TG target goals. Statistically significant differences were evident for the majority of dose comparisons between rosuvastatin and pravastatin or simvastatin, but not for the majority of comparisons between rsouvastatin and atorvastatin ($p<0.002$).

Results of the analysis that compared the rosuvastatin 10 to 40 mg dose range to the dose ranges of the other comparators were generally consistent with the results of the analysis comparing the 10 mg to 80 mg dose range of rosuvastatin with the comparators (see Appendix 12.1.9.3). Key results of this analysis are as follows:

Rosuvastatin across the dose range of 10 to 40 mg resulted in a statistically significantly greater reduction in LDL-C compared with atorvastatin, pravastatin, or simvastatin across the dose range ($p<0.001$). The difference in percent reduction in LDL-C between rosuvastatin and each of the comparators exceeded the 5 to 7% reduction considered clinically meaningful and the 6% difference on which the trial was structured.

The key findings from the ANOVA of percentage change from baseline at Week 6 in LDL-C were as follows:

- Rosuvastatin 10 mg treatment resulted in a significantly greater percent reduction in LDL-C compared with atorvastatin 10 mg; pravastatin 10 mg, 20 mg, or 40 mg; or simvastatin 10 mg, 20 mg, or 40 mg ($p<0.001$). The effect of rosuvastatin 10 mg was numerically greater than atorvastatin 20 mg, but the difference was not statistically significant. The effect of atorvastatin 40 mg was numerically greater than rosuvastatin 10 mg, but the difference was not statistically significant.

- Rosuvastatin 20 mg treatment resulted in a significantly greater percent reduction in LDL-C compared with atorvastatin 20 mg or 40 mg ($p = 0.0015$); pravastatin 20 mg or 40 mg; or simvastatin 20 mg, 40 mg, or 80 mg ($p<0.001$). The effect of rosuvastatin 20 mg was numerically greater than atorvastatin 80 mg, but the difference was not statistically significant.

- Rosuvastatin 40 mg treatment resulted in a significantly greater percent reduction in LDL-C compared with atorvastatin 40 mg, pravastatin 40 mg, or simvastatin 40 mg or 80 mg ($p<0.001$). The effect of rosuvastatin 40 mg was numerically greater than atorvastatin 80 mg, but the difference was not statistically significant.

Rosuvastatin across the dose range of 10 to 40 mg resulted in a statistically significantly greater reduction in TC, non-HDL-C, LDL-C/HDL-C ratio, TC/HDL ratio,

non-HDL-C/HDL- ratio, ApoB, and the ApoB/Apo A-I ratio compared with atorvastatin, pravastatin, or simvastatin across the dose range ($p<0.001$).

Rosuvastatin resulted in a statistically significantly greater increase in HDL-C compared with atorvastatin for each dose comparison except 10 mg. Rosuvastatin across the dose range was significantly better than pravastatin or simvastatin across the dose range in increasing HDL-C ($p<0.001$).

Both rosuvastatin and atorvastatin decreased TG, but the difference between groups was not statistically significant. Rosuvastatin across the dose range resulted in a statistically significantly greater reduction in TG compared with pravastatin or simvastatin across the dose range ($p<0.001$).

Rosuvastatin across the dose range resulted in a statistically significantly greater increase in ApoA-I compared with atorvastatin across the dose range ($p<0.001$).

Rosuvastatin resulted in a numerically greater percentage increase in ApoA-I than did pravastatin for each dose comparison. The difference was statistically significant ($p<0.001$) only for the 10 mg dose comparison.

Across the dose range, rosuvastatin resulted in a greater percentage increase in ApoA-I than did simvastatin; the difference was not statistically significant.

The percentage changes in lipids and lipoproteins at Week 6 were generally greater with rosuvastatin treatment than with atorvastatin, pravastatin, or simvastatin. The difference between rosuvastatin and each comparator was statistically significant for the majority of dose comparisons.

Safety results

The study treatments were well tolerated. The overall incidence of AEs associated with each treatment was relatively similar. The number of deaths and SAEs were low. Subjects treated with rosuvastatin 80 mg and those treated with atorvastatin 40 mg had the highest percentages of discontinuations for adverse events (DAEs) (8.5% and 7.5%, respectively) relative to the other treatment groups.

The incidence of myalgia was higher with rosuvastatin 80 mg (7.3%), atorvastatin 20 mg (6.4%), atorvastatin 80 mg (5.4%), and pravastatin 20 mg (5.4%) relative to the other treatment groups. Changes in clinical laboratory results were generally small. Five subjects (3 atorvastatin and 2 simvastatin) had clinically important elevations in ALT (>3 x ULN on 2 consecutive visits). No cases of myopathy were observed. Three subjects (1 rosuvastatin and 2 simvastatin) had a clinically important elevation of CK (>10 x ULN on at least 1 occasion), but the elevations were not associated with muscle-related symptoms.

A >30% increase in serum creatinine was observed in 12 subjects (9 rosuvastatin [including 7 subjects treated with rosuvastatin 80 mg], 1 atorvastatin, and 2 simvastatin). Two subjects,

both treated with rosuvastatin 80 mg, had acute renal failure. Changes in vital signs and physical findings were small.

With respect to the overall safety profile of rosuvastatin, the 80 mg dose was associated with the highest incidence of mylagia (7.3%), the highest incidence of discontinuations due to myalgia (7.2%), and the largest mean change (48.9, SD 354.6) in CK relative to the 10, 20, and 40 mg doses. However, only 1 subject treated with rosuvastatin 80 mg had an increase in CK of >10 x ULN, and there were no reports of myopathy with any dose of the drug.