



Drug product: CRESTOR™ Drug substances: Rosuvastatin calcium Document No.: Edition No.: Study code: D3562C00088 (4522IL/0088) Date: 08 November 2006	SYNOPSIS	
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A Randomized, Double-blind, Placebo-controlled, Multicenter Parallel Group Phase III Study Measuring Effects on Intima Media Thickness: an Evaluation Of Rosuvastatin 40 mg (METEOR)

International coordinating investigator

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Study centres

Patients were screened and randomized into this global study at 61 centers in Europe and the United States (US): Belgium (2), Czech Republic (1), Finland (1), Germany (2), Netherlands (2), Norway (6), France (23), and the US (24 centers).

Publications

Crouse JR, Grobee DE, O’Leary DH, Bots ML, Evans GW, Palmer MK, et al. Trial design. Measuring effects on intima media thickness: An evaluation of rosuvastatin in subclinical atherosclerosis – the rationale and methodology of the METEOR study. *Cardiovascular Drugs and Therapy* 2004;18:231-38.

Crouse JR, O’Leary DH, Palmer MK, Raichlen J, for the METEOR investigators. Measuring effects on intima media thickness: An evaluation of rosuvastatin (METEOR) – baseline characteristics of randomized patients. Poster presentation at: The 75th European Atherosclerosis Society Congress, April 23-26, 2005; Prague, Czech Republic.

Study dates

First patient enrolled 08 August 2002

Last patient completed 17 May 2006

Phase of development

Therapeutic confirmatory (III)

Objectives

The primary objective of the study was to assess the effects of rosuvastatin 40 mg treatment for 104 weeks on the change in the mean maximum intima media thickness (IMT) of the 12 carotid artery segments: near and far walls of the right and left common carotid artery (CCA), carotid bulb, and the internal carotid artery (ICA). The rosuvastatin-treated patients, in whom the IMT was expected to regress over time, were compared to the placebo-treated patients, in whom the IMT was expected to progress over time. If there was a significant difference between these treatment groups, then the rosuvastatin-treated patients were examined further to determine whether there was significant regression in IMT between the beginning and the end of the treatment period.

The secondary objectives of the study were to assess the effects of rosuvastatin 40 mg treatment for 104 weeks on the following variables, with the same analyses being applied to the IMT variables:

- Change in the mean maximum IMT of the near and far walls of the right and left CCA
- Change in the mean maximum IMT of the near and far walls of the right and left carotid bulb
- Change in the mean maximum IMT of the near and far walls of the right and left ICA
- Change in the mean IMT of the near and far walls of the right and left CCA
- Change in low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), non-HDL-C, Apolipoprotein (Apo) B, ApoA-I, non-HDL-C/HDL-C, and ApoB/ApoA-I
- Change in the inflammatory marker: C-reactive protein (CRP).
- Safety was assessed by evaluations of vital signs, adverse events (AEs), clinical laboratory analyses, and electrocardiograms (ECGs).

Study design

This was a randomized, double-blind, placebo-controlled, multicenter, parallel group Phase III study, assessing the effects of rosuvastatin 40 mg treatment for 104 weeks on the change in IMT of the CCA, carotid bulb, and ICA in adults with a maximum IMT ≥ 1.2 mm and < 3.5 mm on 2 pre-randomization ultrasound measurements. Carotid IMT measurements were obtained at 26-week intervals during treatment and twice at the end of treatment.

Target patient population and sample size

To qualify for entry into the study, men were to have been ≥ 45 and ≤ 70 years of age and women were to have been ≥ 55 and ≤ 70 years of age, with both having had HDL-C ≤ 60 mg/dL

(1.6 mmol/L). At screening, patients were to have been asymptomatic, and have had either a LDL-C ≥ 120 mg/dL (3.1 mmol/L) and < 160 mg/dl (4.1 mmol/L) with a 10-year coronary heart disease (CHD) risk below 10% on the Framingham Risk Index (FRI) or a LDL-C ≥ 120 mg/dL (3.1 mmol/L) and < 190 mg/dL (4.9 mmol/L) with no additional CHD risk factor other than age. Additionally, patients were to have had TG < 500 mg/dL (5.65 mmol/L), and a maximum IMT of ≥ 1.2 mm and < 3.5 mm at any location. Eight-hundred forty patients were planned to be randomized at a 5:2 ratio between 2 treatment arms (rosuvastatin and placebo) to produce a minimum of 581 evaluable patients (415:166), with an expected average of 28 patients per study center. A total of 984 patients were actually randomized to treatment (702 in the rosuvastatin group and 282 in the placebo group).

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

The study medication was rosuvastatin 40 mg (batch numbers: PDA04V, PDA06V, TS12002, TX13074) and placebo (batch numbers: ST75016-001-FA01, TX11227) in oral tablet form for once daily use. Patients were encouraged to take the medication at the same time each day.

Duration of treatment

Rosuvastatin or placebo was administered once daily for a 104-week (2-year) treatment period.

Criteria for evaluation (main variables)

Efficacy and safety

The primary variable was change from baseline values to end of treatment in maximum carotid intima media thickness (CIMT) over the 12 carotid artery sites. This was determined using a multi-level mixed effects regression model that estimated mean annualized rate of change (mm/year) over the 2-year study period for each treatment group.

Secondary CIMT efficacy variables were segment-specific and measured as a change from baseline values to end of treatment in the following, with the same statistical analyses applied (as for the primary variable):

- Maximum CIMT over the 4 CCA sites (near and far walls of the right and left CCA)
- Maximum CIMT over the 4 carotid bulb sites (near and far walls of the right and left carotid bulb)
- Maximum CIMT over the 4 ICA sites (near and far walls of the right and left ICA)
- Mean CIMT over the 4 CCA sites (near and far walls of the right and left CCA)

Secondary laboratory efficacy variables:

- Percentage change from baseline in lipid parameters (LDL-C, TC, HDL-C, TG, non-HDL-C, TC/HDL-C, LDL-C/HDL-C, non-HDL-C/HDL-C)
- Percentage change from baseline in apolipoproteins (ApoB, ApoA-I, ApoB/ApoA-I)
- Percentage change from baseline in a circulating marker of inflammation (CRP)

Secondary safety variables:

- Safety and tolerability were monitored by evaluating the incidence and severity of AEs, abnormal laboratory values (hematology, clinical chemistry, glomerular filtration rate [GFR], and urinalysis), vital signs and weight, electrocardiograms (ECGs), and physical examination.

Statistical methods

All efficacy measures were summarized by randomized treatment group using descriptive statistics or frequency distributions (whichever was appropriate) for the raw data. For variables subjected to formal statistical analysis, the results of the analysis were presented and interpreted. A multi-level repeated-measures linear mixed effects model was used for the analysis of primary and secondary CIMT endpoints. A post-hoc p-value for the chi square comparison between the 2 treatment groups for maximum CIMT of the 12 carotid artery sites was added to the descriptive data comparing percent progression and regression between the 2 treatment groups. Analyses of lipid endpoints were performed using observed and Last Observation Carried Forward (LOCF) data, and time-weighted averages. Analyses of percentage change from baseline in lipids and lipoproteins were carried out using analysis of covariance (ANCOVA) with terms for treatment and geographic region in the model. The Wilcoxon Rank Sum test was used post hoc to analyze CRP. Statistical significance in the study was set at the $\alpha=0.05$ level; the alpha-level for the co-primary endpoints was maintained at 0.05 by a hierarchical testing procedure. No adjustments were made for multiple comparisons in the secondary endpoints.

Adverse events were classified, summarized, and listed. Hematology, clinical chemistry, urinalysis, vital signs, physical exam, and other safety data were summarized using descriptive statistics.

Patient population

The first patient was enrolled in the study on 08 August 2002 and the last patient completed the randomized treatment phase of the study on 17 May 2006. A total of 5751 patients entered the screening period. Of these, 984 (17.1%) were randomized to study treatment (702 patients were randomized to rosuvastatin and 282 patients were randomized to placebo). Of 984 randomized patients, 246 (25.0%) withdrew from treatment over the 2-year period. The percentage of patients withdrawing during randomized treatment was similar between the

2 treatment groups. For the total randomized population, the most common reason for study discontinuation was adverse events (10.3%).

Three randomized patients (2 patients in the rosuvastatin group and 1 patient in the placebo group) received no study treatment and were not included in the randomized safety population; thus, 981 patients were evaluated for safety. Of these, 876 were analyzed for efficacy in the Intent-to-Treat (ITT) population, and 863 were analyzed for efficacy in the Per-Protocol (PP) population. The treatment groups were similar with respect to the percentages of patients in the ITT and PP populations.

The majority of randomized patients were Caucasian (94.2%) and were male (59.8%). The proportions of males to females were similar between the treatment groups and both men and women were adequately represented in the study. The age range of patients in the study was 45 to 70 years; 129 patients (13.1%) were ≥ 65 years of age. Baseline characteristics were generally comparable between the 2 treatment groups. The patient population enrolled in this study was at low risk for CHD according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines published in 2001. Overall, patients in the 2 treatment groups had similar frequencies of significant medical conditions, based on medical history recorded during screening. The frequency of patients receiving concomitant medication post randomization was similar between the 2 treatment groups.

The frequency of protocol violations considered serious enough to warrant exclusion of data was similar between the treatment groups; however, the frequency of protocol deviations considered serious enough to warrant exclusion of data was slightly higher in the placebo group. The majority (>92%) of patients in the study achieved $\geq 70\%$ treatment compliance. The observed levels of compliance were similar between the treatment groups, and therefore were unlikely to have any effect on safety comparisons.

Efficacy results

Table S 1 summarizes the annualized changes from baseline values to the end of the treatment period (Week 104) in CIMT for the primary and secondary variables.

Table S 1 Annualized changes from baseline values to the end of the treatment period (Week 104) in CIMT for the primary and secondary variables (ITT population)

Annualized change (mm/year)	Rosuva 40 mg (N=624)	Placebo (N=252)	Rosuva 40 mg vs placebo (p-value)
Primary variable:			
Maximum CIMT of the 12 carotid artery sites	-0.0014	0.0131	<0.0001
Secondary variables:			
Maximum CIMT of the CCA	-0.0038	0.0084	<0.0001
Maximum CIMT of the carotid bulb	-0.0040	0.0172	<0.0001
Maximum CIMT of the ICA	0.0039	0.0145	0.0228
Mean CIMT of the CCA	0.0004	0.0088	<0.0001

CCA Common carotid artery; CIMT Carotid intima media thickness; ICA Internal carotid artery; ITT Intent-to-Treat; Rosuva Rosuvastatin.

For the primary endpoint, rosuvastatin significantly slowed the progression of carotid atherosclerosis compared to placebo. The difference in the annualized rate of change in the maximum CIMT of all 12 carotid artery sites between rosuvastatin-treated patients and placebo-treated patients was -0.0145 mm/year (95% CI -0.0196, -0.0093); this difference was statistically significant (p<0.0001). Overall, there was an absence of disease progression during the 2 years of the study, as evidenced by a negative annualized rate of change, in 52.1% of patients in the rosuvastatin group compared to 37.7% of patients in the placebo group (p=0.0002).

The annualized change from baseline for the rosuvastatin group was -0.0014 mm/year (95% CI -0.0041, 0.0014), but was not significantly different from zero (p=0.3224). There was significant progression in the placebo group (+0.0131 mm/year; 95% CI 0.0087, 0.0174; p<0.0001).

The beneficial effects of rosuvastatin were consistent across all 4 secondary IMT endpoints. Rosuvastatin significantly slowed the progression of carotid atherosclerosis compared to placebo, as evidenced by a significant difference in annualized rate of change in maximum CIMT of the following segments: CCA (p<0.0001), carotid bulb (p<0.0001), ICA (p=0.0228), and in the mean CIMT of the CCA (p<0.0001). There was significant regression in maximum CIMT of the CCA in the rosuvastatin group (-0.0038 mm/year; 95% CI -0.0064, -0.0013; p=0.0036). The annualized change was not significantly different from zero in the rosuvastatin group for the other 3 secondary IMT variables. There was significant progression in all 4 secondary IMT endpoints in the placebo group (p=0.0002 for maximum CIMT of the ICA; p<0.0001 for other endpoints).

Analyses of the CIMT data were also examined according to pre-specified subgroups. Results were robust, and consistent across all pre-specified subgroups, including age, gender, and lipid

levels. Despite baseline differences that existed regionally (between Europe and the US), there were no apparent differences in treatment effects. Sensitivity analyses were also carried out to look at the effects of missing data. The result from the main analysis was insensitive to a range of conservative assumptions about the effects of missing data.

The effect of rosuvastatin on the atherosclerotic process is a slowing, and in the majority of cases, a delaying of disease progression.

The effects of rosuvastatin on lipids, lipoproteins, and their ratios were significant and consistent with the known efficacy profile of this drug. Key baseline lipid values for the rosuvastatin group and the placebo group, respectively, were: 154.5 mg/dL and 154.3 mg/dL (LDL-C); 229.2 mg/dL and 230.2 mg/dL (TC); 49.7 mg/dL and 49.0 mg/dL (HDL-C); 125.8 mg/dL and 134.4 mg/dL (TG); and, 179.6 mg/dL and 181.2 mg/dL (non-HDL-C).

Table S 2 presents the analysis of the percent change from baseline in key lipid values at the final visit (LOCF), and the time-weighted averages for lipids, for the ITT population.

Table S 2 Analysis of percent change from baseline to final visit in key lipid values (ITT population)

	Final visit (LOCF)			Time-weighted average		
	Rosuvastatin 40 mg (N=624)	Placebo (N=252)	Rosuvastatin 40 mg vs placebo	Rosuvastatin 40 mg (N=624)	Placebo (N=252)	Rosuvastatin 40 mg vs placebo
LDL-C (mg/dL)						
n	622	251		622	251	
LSmean % change ^a	-45.3	-0.6	-44.7	-48.8	-0.3	-48.5
p-value			<0.0001			<0.0001
TC (mg/dL)						
n	622	251		622	251	
LSmean % change ^a	-31.0	0.2	-31.2	-33.7	0.3	-34.0
p-value			<0.0001			<0.0001
HDL-C (mg/dL)						
n	622	251		622	251	
LSmean % change ^a	8.9	3.7	5.2	8.0	2.8	5.2
p-value			<0.0001			<0.0001
TG (mg/dL)						
n	622	251		622	251	
LSmean % change ^a	-14.1	9.2	-23.3	-15.7	10.1	-25.7
p-value			<0.0001			<0.0001
Non-HDL-C (mg/dL)						
n	622	251		622	251	
LSmean % change ^a	-41.9	-0.4	-41.6	-45.1	0.0	-45.1
p-value			<0.0001			<0.0001

^a Least squares mean from ANCOVA with factor of region. Percent change in mean calculated as [(nominal visit week value – baseline value)/baseline value] x 100. (95% CI for the LS Mean). Percent change from baseline was calculated for those patients who had non-missing values at baseline and at the visit of interest; therefore, the number of patients included in change from baseline may have been smaller than indicated by ‘n’ column at each visit.
ANCOVA Analysis of covariance; HDL-C High-density lipoprotein cholesterol; LDL-C Low-density lipoprotein cholesterol; LOCF Last observation carried forward; LSmean Least squares mean; Non-HDL-C Non-high-density lipoprotein cholesterol; TC Total cholesterol; TG Triglycerides.

For all lipids, lipoproteins, and their ratios, there was significant improvement from baseline ($p < 0.0001$) following treatment with rosuvastatin as compared to placebo. This was noted at all post-baseline measurements and continued through the final visit (Week 104). The results were consistent for both methods of analysis (LOCF and time-weighted average).

Baseline CRP values were 0.135 mg/dL (median) for the rosuvastatin group and 0.148 mg/dL (median) for the placebo group. Median change from baseline was -36.2% in the rosuvastatin group and -2.9% in the placebo group. There was a significant improvement in CRP from baseline ($p < 0.0001$) following treatment with rosuvastatin as compared to placebo.

Safety results

The safety database in this 2-year, placebo-controlled study was appropriate for a full evaluation of safety. The extent of exposure was similar between the 2 treatment groups; mean duration was 621.7 days for the rosuvastatin group and 620.8 days for the placebo group.

The overall frequency of patients with AEs was similar between the treatment groups: 583/700 (83.3%) for the rosuvastatin group and 226/281 (80.4%) for the placebo group. One patient in the rosuvastatin group died approximately 2 months post study treatment; the cause of death was reported as Creutzfeldt-Jakob disease and was not considered to be treatment-related by the investigator. The most commonly reported AE was myalgia, reported with similar frequency for patients in both treatment groups: 89/700 (12.7%) in the rosuvastatin group and 34/281 (12.1%) in the placebo group. The frequency of patients with nonfatal treatment-emergent serious adverse events (SAEs) was higher in the rosuvastatin group than in the placebo group (63/700 [9.0%] vs 19/281 [6.8%], respectively); however, the frequency of patients with treatment-emergent SAEs considered by the investigator to be treatment-related was higher in the placebo group (1/700 [0.1%] in the rosuvastatin group vs 4/281 [1.4%] in the placebo group). The frequency of patients with treatment-emergent AEs leading to study discontinuation (DAEs) was low, but was higher in the rosuvastatin group than in the placebo group (78/700 [11.1%] vs 22/281 [7.8%], respectively). The frequency of patients with treatment-emergent DAEs considered to be treatment-related was also higher for the rosuvastatin group than in the placebo group (49/700 [7.0%] vs 9/281 [3.2%], respectively). No conclusions could be drawn about possible treatment-related differences between the groups due to the low numbers of events. The majority of patients had AEs that were characterized as mild to moderate in severity and were considered by the investigator to be unrelated to study treatment. One patient (1/689; 0.1%) receiving rosuvastatin experienced exercise-induced muscle pain associated with a clinically important CK elevation ($>10 \times$ ULN), meeting a pre-specified case definition of myopathy in the clinical study program, although not reported as myopathy by the investigator. Creatine kinase returned to normal levels while the patient continued on study treatment. The event was not considered to be treatment-related. No other patient had a clinically important CK elevation ($>10 \times$ ULN) during the course of the study. There were no cases of hepatitis, rhabdomyolysis, or renal failure.

In the rosuvastatin group, there was a slight decrease in mean platelet count that was not seen in the placebo group. It is possible that this change does represent a real effect of rosuvastatin on the platelet count. However, at the final visit, mean platelet count ($235.4 \times 10^9/L$) for rosuvastatin-treated patients remained well within the normal ranges of $140 \times 10^9/L$ to $400 \times 10^9/L$ or $130 \times 10^9/L$ to $394 \times 10^9/L$ (depending on age and sex). Individual platelet counts below $100 \times 10^9/L$ were scarce, and apparently of no clinical significance (value of $<100 \times 10^9/L$ in a patient with an artificial aortic valve and a baseline value of $97 \times 10^9/L$ that normalized with rosuvastatin treatment).

Overall, 4/689 patients (0.6%) in the rosuvastatin group and 1/276 patients (0.4%) in the placebo group experienced an elevation in ALT $>3 \times$ ULN on 2 consecutive visits at least 48 hours apart (considered clinically important). No patient in the study had a doubling of serum creatinine from baseline. The frequency of patients with proteinuria (defined as a shift in dipstick urine protein from none or trace at baseline to $\geq 2+$ post-baseline) at any time during the study was low and similar for the 2 treatment groups; 4/628 patients (0.6%) in the rosuvastatin group and 2/245 patients (0.8%) in the placebo group had proteinuria, decreasing to 2/628 patients (0.3%) in the rosuvastatin group and 1/245 patients (0.4%) in the placebo group at the final visit. The frequency of patients with hematuria (defined as a shift in dipstick urine blood from none or trace at baseline to $\geq 2+$ post-baseline) was 16/628 patients (2.5%) in the rosuvastatin group and 5/245 patients (2.0%) in the placebo group at any time during the study, decreasing to 6/628 patients (1.0%) in the rosuvastatin group and 1/245 patients (0.4%) in the placebo group at the final visit. One patient (1/628; 0.2%) in the rosuvastatin group and 1 patient (1/245; 0.4%) in the placebo group had combined proteinuria and hematuria at any time during the study, and 1 patient (1/628; 0.2%) in the rosuvastatin group and no patient (0/245) in the placebo group had combined proteinuria and hematuria at the final visit. Baseline estimated GFR was $88.18 \text{ mL}/\text{min}/1.73 \text{ m}^2$ for the rosuvastatin group and $87.58 \text{ mL}/\text{min}/1.73 \text{ m}^2$ for the placebo group. There was a small decrease in GFR for both treatment groups; absolute change from baseline to final visit was $-3.82 \text{ mL}/\text{min}/1.73 \text{ m}^2$ for the rosuvastatin group and $-4.47 \text{ mL}/\text{min}/1.73 \text{ m}^2$ for the placebo group. Changes in clinical laboratory results were generally small and the number of clinically important laboratory abnormalities was low. Safety data were consistent with the established safety profile for rosuvastatin.

Changes in vital signs, ECG, weight, and physical findings were small, and no clinically important patterns were identified.

Date of the report

08 November 2006