Drug product	CRESTOR™	**SYNOPSIS**	
Drug substance	Rosuvastatin calcium tablets 40 mg		
Study code	D3562C00076 (4522IL/0076)		
Date	1 September 2006		

A 104-Week, Open-label, Multi-center, Phase IIIb Study Evaluating the Effect of Treatment with Rosuvastatin 40 mg on Atherosclerotic Disease as Measured by Intravascular Ultrasound and Quantitative Coronary Angiography in Subjects Undergoing Coronary Angiography who have Coronary Artery Disease

A Study To Evaluate the Effect of Rosuvastatin On Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID)

Coordinating investigator

Study centers

Patients were screened at 63 centers worldwide. Patients received study drug at 53 centers: United States (21), Italy (7), Canada (5), Spain (5), Belgium (4), France (4), Australia (3), Netherlands (3), United Kingdom (1).

Publications

Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne C, et al. Effects of very high-intensity statin therapy on regression of coronary atherosclerosis. JAMA 2006;295(13):1556-65.

Nicholls SJ, Sipahi I, Colagiovanni A, Wolski K, Schoenhagen P, Crowe T, et al. Arterial wall remodeling in response to atheroma regression with very intensive lipid lowering: Insights from the ASTEROID trails. Circulation 2006b (In press). Oral presentation at the American Heart Association Scientific Sessions, Chicago 12 to 15 November 2006.

Study dates		**Phase of development**
First patient enrolled	8 November 2002	Therapeutic confirmatory (IIIb)
Last patient completed	18 November 2005	

Objectives

The primary objective of this study was to evaluate whether 104 weeks of treatment with rosuvastatin (40 mg) resulted in regression of coronary artery atheroma burden as assessed by the total atheroma volume (TAV) in the most severely diseased segment or the percent atheroma volume (PAV), as measured by intravascular ultrasound (IVUS) imaging.

Secondary objectives of this study were: to evaluate whether 104 weeks of treatment with rosuvastatin (40 mg) resulted in regression of coronary artery atheroma burden, as assessed by TAV in the total segment as measured by IVUS; to evaluate whether 104 weeks of treatment with rosuvastatin (40 mg) resulted in regression of coronary artery disease (CAD) as measured by quantitative coronary angiography (QCA); to evaluate the change in lipid and lipoprotein levels after 104 weeks of treatment with rosuvastatin (40 mg) as assessed by percent change from baseline; to evaluate the safety of rosuvastatin (40 mg) through the 104 weeks of treatment.

Study design

This was a 104-week, open-label, multi-center, Phase IIIb study evaluating whether treatment with rosuvastatin (40 mg) resulted in regression of coronary artery atheroma volume relative to baseline as measured by IVUS and QCA in patients with CAD undergoing coronary angiography for a clinical indication.

Target patient population and sample size

This study included men or women 18 years and older with a clinical indication for coronary catheterization and angiographic evidence of CAD who met specific angiographic and IVUS criteria. Use of lipid-lowering medication for more than 3 months within the previous 12 months was not allowed, but there was no restriction on baseline cholesterol levels.

If approximately 25% of patients withdrew early from the study, then approximately 450 patients allocated to study drug would yield approximately 335 completed patients, which would provide sufficient power to assess either of the 2 primary endpoints.

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

The investigational product in this study was rosuvastatin calcium 40 mg (batch numbers 2000035840, 2000047300, 2000058916, and 2000065498). Study drug was taken orally, once daily.

Duration of treatment

Eligible patients were treated with rosuvastatin 40 mg for 104 weeks.

Criteria for evaluation (main variables)

The primary efficacy variables were:

- The nominal change (end of treatment minus baseline) in TAV in the 10 mm segment of the coronary artery with the largest plaque volume at baseline (termed the most diseased subsegment) as measured by IVUS.

- The nominal change (end of treatment minus baseline) in PAV in the total segment where the total segment is the 30 to 80 mm segment of the targeted (imaged) coronary artery for all anatomically comparable slices (matched images at end of treatment and baseline with data) as measured by IVUS.

The secondary efficacy variables included:

- IVUS: The nominal change (end of treatment minus baseline) in TAV in the total segment (as described above) normalized for segment length.

- QCA: The percent change in the minimum luminal diameter (MLD) within all measured coronary segments. The mean change in the percent diameter stenosis for all lesions with >25% stenosis severity.

- Lipids: The percent change from baseline in lipid parameters (low-density lipoprotein cholesterol [LDL-C], total cholesterol [TC], triglycerides [TG], high-density lipoprotein cholesterol [HDL-C], non-HDL-C, very low-density lipoprotein cholesterol [VLDL-C], TC/HDL-C, LDL-C/HDL-C, non-HDL-C/HDL-C), the percent change from baseline in lipoprotein parameters (apolipoprotein [Apo] B, Apo A-I, Apo B/Apo A-I), and the number and percent of patients reaching National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III target goals.

The safety variables (secondary) were the incidence and severity of adverse events (AEs) and abnormal laboratory values.

Statistical methods

Patients who had an evaluable IVUS at baseline and after at least 78 weeks of treatment comprised the IVUS evaluable population. Patients who had a pre-treatment and a post-treatment coronary angiographic examination at Week 78 or later comprised the QCA evaluable population. IVUS and QCA results in the IVUS evaluable population were summarized (mean, SD, median, interquartile range). These data were not normally distributed; therefore, a Wilcoxon Signed Rank test was used. This approach is consistent with the clinical study protocol and statistical analysis plan, which pre-specified ANOVA and ANCOVA tests if the data were normally distributed or a Wilcoxon Signed Rank test if a non-parametric test was appropriate. The change from baseline was tested with a Wilcoxon Signed Rank test and the distribution free confidence interval (CI) for the median change from baseline was also calculated. To account for there being 2 primary endpoints, a 97.5% CI and

p-value <0.025 was considered significant for the change from baseline of the primary endpoints. For secondary endpoints p<0.05 was considered significant. For patients in the IVUS evaluable population, lipid parameters at each visit were summarized by last observation carried forward (LOCF), time-weighted average, and observed values and percent changes from baseline were tested by ANOVA. The frequency of patients reaching NCEP ATP III goals was also summarized.

Patients who received at least 1 dose of study drug were in the safety population. Safety data (AEs, laboratory data, vital signs, abnormal physical findings) were summarized; there was no formal statistical analysis of safety data.

Patient population

A total of 1183 patients were screened. Of the 1183, 507 patients took at least 1 dose of study drug (rosuvastatin 40 mg) and comprise the safety population. In this 104-week study 24.7% withdrew from treatment; the most common reason for withdrawal was an AE (12.4%). Of the 507 patients in the safety population, 349 (68.8%) were included in the IVUS evaluable population (IEV population). In the safety population, the mean age was 58.5 years, with 29.4% ≥65 years of age; 71.0% were men; 94.1% were Caucasian; and 93.9% had normal or mildly impaired renal function (assessed by creatinine clearance [CrCL]). All patients had CAD and were considered high risk by NCEP criteria. In regard to medical history, 95.3% had a history of hypertension, 23.9% had a prior myocardial infarction, 16.6% had an acute coronary syndrome, and 12.6% had diabetes mellitus. The demographic and baseline characteristics, as well as clinically relevant medical history, of the IEV population were similar to those of the safety population. In the IEV population, the baseline mean (SD) LDL-C was 130.4 (34.25) mg/dL and HDL-C was 43.1 (11.09) mg/dL. Compliance was high, with a mean of 97.73% in the safety population. Concomitant medications recorded were consistent with the clinical conditions of the patient population under study.

Efficacy results

Following 104 weeks of treatment with rosuvastatin (40 mg), there was significant regression of coronary atheroma volume in patients with CAD. This was supported by observations with all 3 IVUS endpoints (including the 2 primary endpoints); all had significance levels of p<0.001. Percent atheroma volume (PAV) in the total segment decreased with a median change of -0.8% from a median baseline of 39.9% (mean change of -1.0%), with a decrease in PAV observed in 222 (63.6%) of the 349 IEV patients (Table S1). Total atheroma volume (TAV) in the most diseased subsegment decreased with a median change of -5.6 mm^3 from a baseline of 65.1 mm^3 (mean change of –6.1 mm^3) (Table S1). The median percent change from baseline in TAV of the most diseased subsegment was -9.1% (mean –8.5%), with a decrease in TAV observed in 249 (78.1%) of the 319 patients evaluable for this endpoint. For the secondary IVUS endpoint, TAV in the total segment decreased with a median change of -12.5 mm^3 (mean change of –14.7 mm^3) from a median baseline of 204.7 mm^3. The median percent change from baseline in TAV of the total segment was –6.8% (mean change of -6.7%), with a decrease observed in 272 (77.9%) of the 349 IEV patients.

The percent diameter stenosis as measured by QCA decreased by an average of –1.30%. The median change was a decrease of -0.50% (95% CI: -1.00, 0.00) from a median baseline of 35.7% ($p<0.001$), with a decrease observed in 156 (53.4%) of the 292 QCA evaluable patients with baseline stenosis. The MLD measured by QCA decreased by an average of –0.021 mm. The median change was –0.010 mm (95% CI: -0.013, -0.003) from a median baseline of 2.23 mm ($p<0.001$), with a median decrease of -0.38%. Overall, 351 (94.6%) of the 371 QCA evaluable patients were clinically unchanged, with 18 (4.9%) progressing and 2 (0.5%) regressing (the clinical change in MLD was relative to a pre-specified boundary of ±0.2 mm that needed to be exceeded to consider any difference as a categorical change from baseline).

This lack of clinical change in MLD, measured by QCA, is consistent with a slowing or delaying of CAD progression in association with the decrease in atheroma volume demonstrated by IVUS. Atheroma regression is accompanied by contraction of the external elastic membrane and changes of the arterial wall; thus, the MLD findings are in the context of the dynamic nature of arterial wall remodeling and are consistent with changes in atheroma volume shown by IVUS in response to long term rosuvastatin effects on the lipid profile.

There was a significant and substantial improvement from baseline in all lipid and lipoprotein measures. This improvement was apparent at 13 weeks and stayed at roughly the same level through 104 weeks. The mean time-weighted average change from baseline was a decrease with a change of -53.2% for LDL-C and an increase of 14.7% for HDL-C. A total of 92.8% patients reached their NCEP ATP III target goals. The marked effects of rosuvastatin on the lipid profile were associated with beneficial effects on atheroma including substantial slowing or delaying of progression in the atherosclerotic disease process with evidence of regression of atheroma volume in the majority of patients.

Table S1 Change from baseline in the atheroma volume (IVUS evaluable population)

Percent atheroma volume in the total segment

	N[a]	Mean	SD	Median	IQR	Median change (CI)[b]	P-value[c]	Subjects regressing n (%)
Baseline (%)	349	39.6	8.5	39.9	33.8, 45.3	NA	NA	NA
Final[d] (%)	349	38.6	8.5	38.5	32.6, 44.3	-0.8 (-1.20, -0.53)*	<0.001	222 (63.6)

Total atheroma volume in the most diseased subsegment

	N[a]	Mean	SD	Median	IQR	Median change (CI)[b]	P-value[c]	Subjects regressing n (%)
Baseline (mm^3)	319	65.1	27.0	65.1	45.2, 82.2	NA	NA	NA
Final[d] (mm^3)	319	59.0	24.5	58.4	40.6, 76.3	-5.6 (-6.8, -4.0)*	<0.001	249 (78.1)

[a] Number of subjects with IVUS data for comparable anatomical slices at baseline and final measurement.
[b] Median change from baseline and distribution-free 97.5% CI; data were not normally distributed.
[c] P-value for change from baseline from Wilcoxon Signed Rank test. After Bonferroni adjustment to account for 2 primary endpoints, $p<0.025$ was considered statistically significant.
[d] Final visit was scheduled for Week 104, but may have occurred earlier or later. Only subjects with IVUS measurements at or after 78 weeks are included.
* Statistically significant change from baseline; the CI does not include 0. A 97.5% CI is used to account for having 2 primary efficacy variables.

CI Confidence interval; IQR Interquartile range (25^{th} to 75^{th} percentile); NA Not applicable; SD Standard deviation.

Safety results

Of the 507 patients comprising the safety population, 423 (83.4%) had a treatment-emergent AE. The most common AEs were angina pectoris (17.9%), myalgia (14.2%), hypertension (11.4%), non-cardiac chest pain (10.3%), and back pain (6.1%). There were 66 (13.0%) patients who had AEs considered by the investigator as treatment-related. The most common (n≥2) treatment-related AEs were myalgia (4.9%), ALT increased (2.2%), constipation (1.6%), CK increased (1.6%), aspartate aminotransferase increased (0.8%), muscle spasms (0.6%), musculoskeletal pain (0.6%) and urticaria (0.6%). Of the 423 patients with an AE, most (73.5%) had an AE that was mild or moderate in severity.

There were 4 deaths in this study while on treatment (the 4 deaths were due to: myocardial ischemia; ventricular fibrillation; septic shock following bronchopneumonia; and gastric cancer) and 1 death during the pre-treatment phase of the study. None of the deaths were attributed to rosuvastatin. Of the 165 (32.5%) patients with SAEs, 1 SAE (elevated CK) was considered treatment-related by the investigator. Of the 61 (12.0%) patients who discontinued due to an AE (DAE), 24 (4.7% of 507) patients had a DAE considered by the investigator to be drug-related. The review of deaths, SAEs, DAEs, and other significant adverse events (OAEs) did not raise any new safety concerns.

Changes in clinical laboratory results were generally small and no clinically meaningful patterns were identified. The number of clinically important laboratory abnormalities was low and no new safety issues were identified. Five patients met criteria for clinically important laboratory findings (with 1 patient meeting criteria for both elevated creatine kinase [CK] and serum creatinine). One (0.2%) patient had alanine aminotransferase (ALT) >3x ULN on 2 consecutive occasions more than 48 hours apart. The patient was asymptomatic and ALT temporarily improved following the discontinuation of study drug; however, the patient was later diagnosed with mildly active chronic hepatitis C with patchy periportal fibrosis. Three (0.61%) patients had CK >10x ULN identified by a local laboratory. None had muscle symptoms suggesting myopathy or rhabdomyolysis. There were 2 (0.4%) patients with an increase in serum creatinine >100% from baseline, and greater than ULN, both identified by a local laboratory. Both cases were judged not related to study drug.

Proteinuria (a shift in urine protein from none/trace at baseline to ≥2+) was infrequent and less at the final visit (3.0%) than at any visit (5.0%) indicating that proteinuria was generally transient. Six (1.3%) patients had both proteinuria and hematuria (a shift in urine blood from none/trace at baseline to ≥2+), at some time during the study, with only 1 (0.2%) patient having both at final visit. Patients with proteinuria were reviewed for time course of proteinuria, concomitant hematuria, serum creatinine, and urinary/renal AEs and no safety concerns were identified.

Date of the report

21 September 2006