AstraZeneca

**Clinical Study Report Synopsis**

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| Drug Substance | Rosuvastatin calcium |
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# **S**tudy of Coronary **A**theroma by In**T**ravascular **U**ltrasound: Effect of **R**osuvastatin Versus Atorvastati**N** (SATURN)

## A 104-week, randomized, double-blind, parallel group, multi-center Phase IIIb study comparing the effects of treatment with rosuvastatin 40 mg or atorvastatin 80 mg on atherosclerotic disease burden as measured by intravascular ultrasound in patients with coronary artery disease

**Study dates:** First patient enrolled: 22 January 2008
Last patient last visit: 16 June 2011

**Phase of development:** Therapeutic confirmatory (IIIb)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

## Study centers

This study was conducted at 234 centers in 14 countries.

## Publications

Nicholls SJ, Ballantyne CM, Barter PJ, Chapman MJ, Erbel RM, Libby P, et al. Effect of two intensive statin regimens on progression of coronary disease. N Engl J Med 2011;365:2078-87.

Nicholls SJ, Borgman M, Nissen SE, Raichlen JS, Ballantyne C, Barter P, et al. Impact of statins on progression of atherosclerosis: rationale and design of SATURN (Study of Coronary Atheroma by InTravascular Ultrasound: Effect of Rosuvastatin versus AtorvastatiN). Curr Med Res Opin 2011;27:1119-29.

Nicholls SJ, Ballantyne, C, Barter P, Chapman M, Erbel R, Libby, P, et al. Achieved lipoprotein levels and regression of coronary atherosclerosis with high dose statin therapy: Insights from SATURN. J Am Coll Cardiol 2012;59:E1499.

Nicholls SJ, Ballantyne C, Barter P, Chapman M, Erbel R, Libby P, et al. Regression of coronary atheroma volume in patients receiving high dose statin therapy: Analysis of the SATURN study. J Am Coll Cardiol 2012;59:E1502.

## Objectives and criteria for evaluation

Table S1 presents the primary and secondary objectives and outcome variables for this study. Exploratory efficacy analyses, with the exception of subgroup analyses of change in PAV and TAV by LDL-C and HDL-C, are not included in this synopsis, but can be found in the clinical study report.

**Table S1 Objectives and outcome variables**

| Objective | | | Outcome Variable |
|---|---|---|---|
| **Priority** | **Type** | **Description** | **Description** |
| Primary | Efficacy | To compare the effects of rosuvastatin 40 mg with atorvastatin 80 mg on the PAV of a coronary artery as measured by IVUS imaging following 104 weeks of treatment in patients with CAD. | The nominal change (end of treatment minus baseline) in PAV in a ≥40 mm segment of one targeted (imaged) coronary artery for all anatomically comparable slices (matched images at end of treatment and baseline), as measured by IVUS. |
| Secondary | Efficacy | Following 104 weeks of treatment in patients with CAD: | |
| | | • To determine whether rosuvastatin 40 mg or atorvastatin 80 mg shows regression of PAV in the targeted coronary artery as measured by IVUS. | The nominal change (end of treatment minus baseline) in PAV in a ≥40 mm segment of one targeted (imaged) coronary artery for all anatomically comparable slices (matched images at end of treatment and baseline), as measured by IVUS. |

| Objective | | | Outcome Variable |
|---|---|---|---|
| **Priority** | **Type** | **Description** | **Description** |
| Secondary | Efficacy *(cont.)* | • To compare the effects of rosuvastatin 40 mg with atorvastatin 80 mg on the TAV of the targeted coronary artery as measured by IVUS. | The nominal change (end of treatment minus baseline) in normalized TAV in the total segment where the total segment is a ≥40 mm segment of the targeted (imaged) coronary artery for all anatomically comparable slices (matched images at end of treatment and baseline), normalized for population segment length. |
| | | • To compare the effects of rosuvastatin 40 mg with atorvastatin 80 mg on lipid and lipoprotein metabolism. | The observed, time-weighted average, and LOCF of on-treatment levels of lipids, lipoproteins and their ratios, including LDL-C, HDL-C, TC, TG, VLDL-C, non-HDL-C, ApoB, ApoA-I, TC/HDL-C, LDL-C/HDL-C, non-HDL-C/HDL-C and ApoB/ApoA-I. |
| Secondary | Safety | To assess the safety and tolerability of rosuvastatin 40 mg and atorvastatin 80 mg during the 104-week treatment in patients with CAD. | Evaluation of type, frequency. severity, causality, and duration of reported AEs (all visits); changes in vital signs (heart rate, blood pressure), weight, and waist circumference; hepatic biochemistry and CK, clinical chemistry, hematology, and urinalysis. |

AE Adverse event; ApoA-1 Apolipoprotein A-1; ApoB Apolipoprotein B; CAD Coronary artery disease; CK Creatine kinase; CV Cardiovascular; HDL-C High density lipoprotein-cholesterol; IVUS Intravascular ultrasound; LDL-C Low density lipoprotein-cholesterol; LOCF Last observation carried forward; MI Myocardial infarction; PAV Percent atheroma volume; TAV Total atheroma volume; TC Total cholesterol; TG Triglycerides; VLDL-C Very low density lipoprotein-cholesterol.

## Study design

This was a 104-week, double-blind, parallel group, multicenter, Phase IIIb study comparing the effects of treatment with rosuvastatin versus atorvastatin on coronary artery atheroma burden as measured by intravascular ultrasound (IVUS) in patients with coronary artery disease (CAD). Patients who satisfied all inclusion/exclusion criteria, including angiographic criteria for CAD and adequate quality IVUS images, were randomized in a 1:1 ratio to receive half-maximal doses of either rosuvastatin (20 mg/day) or atorvastatin (40 mg/day) for 2 weeks. Those who achieved target low density lipoprotein-cholesterol (LDL-C) and triglyceride (TG) levels were re-randomized in a 1:1 ratio to receive maximal doses of either rosuvastatin (40 mg/day) or atorvastatin (80 mg/day) for 104 weeks (Part B) following which repeat IVUS images were acquired.

## Target subject population and sample size

Male and female patients between 18 and 75 years of age with clinical indication for coronary angiography and angiographic evidence of CAD were eligible for enrollment. For patients with no statin therapy in the 4 weeks prior to consent, LDL-C levels were to be >100 mg/dL

(2.6 mmol/L); for patients on statin therapy in the past 4 weeks, LDL-C levels were to be >80 mg/dL (2.08 mmol/L). Following pre-treatment with either rosuvastatin 20 mg/day or atorvastatin 40 mg/day for 2 weeks, all patients must have attained LDL-C levels of <116 mg/dL (3.0 mmol/L) and TG levels <500 mg/dL (5.65 mmol/L).

The primary efficacy outcome variable was defined as the nominal change in percent atheroma volume (PAV) in the targeted coronary artery by IVUS. It was estimated that a sample size of approximately 450 evaluable patients per group would be required to provide 90% power to detect a difference in PAV between the 2 treatment arms of 0.65, with a common standard deviation of 3.0, and a 2-sided alpha level of 0.05. It was anticipated that approximately 30% of the patients would discontinue early from the study or would have non-evaluable IVUS. Therefore, approximately 1300 patients were needed to be randomized in order to get the required 900 evaluable patients.

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

Study medication was administered orally with water once daily consisting of 1 capsule during the screening period (Part A), and 2 capsules during the main treatment period (Part B). Investigational product consisted of rosuvastatin 20 mg (Batch numbers 26350.1, 28220.1, 32034.1, ST75036-001-FA06, ST75036-001-FA08, ST75036-001-FA10) and, as comparator, atorvastatin 40 mg (batch numbers 26350.2, 28220.2, 32034.2, ST74019-001-FA16, ST74019-001-FA18, ST74019-001-FA19, ST74019-001-FA20, ST74019-001-FA21, ST74019-001-FA23).

**Duration of treatment**

Patients received pre-treatment with half-maximal doses of either rosuvastatin (20 mg/day) or atorvastatin (40 mg/day) for 2 weeks during the screening period (Part A), and then maximal doses of either rosuvastatin (40 mg/day) or atorvastatin (80 mg/day) for 104 weeks (Part B).

**Statistical methods**

Analyses of IVUS endpoints were performed on both the Intention-to-Treat (ITT) (primary) and Per Protocol (PP) analysis sets. These analyses only included baseline and end-of-study data.

IVUS data were not normally distributed; therefore, Wilcoxon Signed Rank tests, confidence intervals (CIs) on the median, and analysis of covariance (ANCOVA) on rank transformed data were used. ANOVA was used as the analysis method for the lipid and lipoprotein variables using the ITT analysis set. The model included factors for treatment and region. Results were presented as least-square means along with their associated 95% CIs.

Descriptive statistics and data summaries were used for the presentation of safety data using the Safety analysis set. Safety was assessed by the evaluation of types, frequencies, severity and duration of reported adverse events (AEs), examination of clinical laboratory abnormalities, and vital signs.

## Subject population

A total of 4255 patients were enrolled. Of these, 1922 patients were discontinued during the screening period and 2333 patients were randomized to Part A of the study, of whom 1578 patients were treated (783 patients in the rosuvastatin group and 795 patients in the atorvastatin group). In total, 1385 patients (695 patients in the rosuvastatin group and 690 patients in the atorvastatin group) completed Part A and were randomized to Part B of the study. Of the 1385 patients randomized to Part B (694 in the rosuvastatin group and 691 patients in the atorvastatin group), 1380 (99.6%) patients were treated (691 [99.6%] patients in the rosuvastatin group and 689 [99.7%] patients in the atorvastatin group). A total of 292 (21.1%) patients discontinued the study (148/694 [21.3%] in the rosuvastatin group and 144/691 [20.8%] patients in the atorvastatin group). Thus, 1093 (78.9%) patients (546/694 [78.7%] in the rosuvastatin group and 547/691 [79.2%] patients in the atorvastatin group) completed Part B. Of the 1385 patients randomized to treatment in Part B, 1380 (99.6%) received at least 1 dose of study medication and were evaluated for safety. A total of 1039 (75.0%) patients were included in the ITT population and 833 (60.1%) were included in the PP population with similar percentages in the treatment groups.

The demographic and baseline characteristics of the patients in this study were similar for each of the treatment groups. Mean age at randomization was 57.6 years, 74% of the patients were male, 26% were female, most were White, and the majority were hypertensive.

### Summary of efficacy results

In the primary efficacy analysis, PAV significantly decreased after 104 weeks of treatment with rosuvastatin (-1.22%, $p<0.0001$) or atorvastatin (-0.99%, $p<0.0001$) compared to baseline. The median regression was numerically greater with rosuvastatin than atorvastatin but the difference did not reach statistical significance ($p=0.1709$).

Total atheroma volume (TAV) significantly decreased after 104 weeks of treatment with rosuvastatin (-6.39 $mm^3$, $p<0.0001$) or atorvastatin (-4.42 $mm^3$, $p<0.0001$) compared to baseline. The median regression was significantly greater with rosuvastatin than atorvastatin ($p=0.0099$).

PAV regressed in 68.5% of the rosuvastatin-treated patients and 63.2% of the atorvastatin-treated patients after 104 weeks of treatment when compared to baseline but the difference between the treatment groups did not reach statistical significance ($p=0.0737$). TAV regressed in 71.3% of the rosuvastatin-treated patients and 64.7% of the atorvastatin-treated patients after 104 weeks of treatment when compared to baseline. This difference between the treatment groups was statistically significant ($p=0.0224$).

Patients treated with rosuvastatin had significantly lower levels of LDL-C and significantly higher levels of high density lipoprotein-cholesterol (HDL-C) than patients treated with atorvastatin. During 104 weeks of treatment, time-weighted least squares mean LDL-C levels were 62.64 ± 1.00 mg/dL in the rosuvastatin group and 70.18 ± 0.99 mg/dL in the atorvastatin group (mean difference, -7.53 mg/dL; $p<0.0001$). The mean HDL-C levels were 50.43 ± 0.54 mg/dL in the rosuvastatin group and 48.64 ± 0.53 mg/dL in the atorvastatin

group (mean difference, 1.79 mg/dL; p=0.0149). The rosuvastatin group also had significantly lower total cholesterol (TC) (p=0.0061), non-HDL-C (p<0.0001), LDL-C/HDL-C (p<0.0001), TC/HDL-C (p<0.0001), non-HDL-C/HDL-C (p<0.0001), Apolipoprotein B (ApoB) (p=0.0280) and ApoB/Apoprotein A-1 (ApoA-1) ratio (p<0.0001), and significantly higher levels of ApoA-1 (p<0.0001) than the atorvastatin group.

Exploratory subgroup analyses of change in PAV revealed statistical evidence of heterogeneity of benefit for rosuvastatin over atorvastatin in women, in patients with higher baseline levels of LDL-C and HDL-C, and in patients with higher on-treatment levels of HDL-C.

**Summary of safety results**

The frequency and types of treatment-emergent adverse events (TEAEs) (during Part B) were similar between the rosuvastatin and atorvastatin treatment groups and were not unexpected for a long-term study of patients with CAD. A review of the deaths, serious adverse events (SAEs), and TEAEs leading to withdrawal did not raise any new safety concerns.

The most common TEAEs (occurring in ≥5% of patients in either treatment group) were myalgia, angina pectoris, arthralgia, hypertension, non-cardiac chest pain, fatigue, and dyspnea. There were 8 deaths in the study: 5 patients in the rosuvastatin group (coronary artery insufficiency, ischemic cardiomyopathy, road traffic accident, gallbladder cancer, and metastatic lung cancer) and 3 patients in the atorvastatin group (sudden death, cerebral hemorrhage, and pulmonary embolism). There were no notable differences between the 2 treatments in the frequency or type of SAEs or TEAEs leading to withdrawal, in the incidence of skeletal muscle, hepatic, renal, or diabetes mellitus AEs, or in adjudicated major CV events.

Changes in clinical laboratory results were generally small and no clinically meaningful trends were observed. The number of clinically important laboratory abnormalities was low in both treatment groups. There were essentially no changes in vital signs or physical findings over the course of the study in either treatment group.