AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Rosuvastatin calcium
Study Code	D3560L00030 (4522US/0011)
Edition Number	
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JUPITER

Justification for the **U**se of statins in **P**rimary prevention: an **I**ntervention **T**rial **E**valuating **R**osuvastatin

A Randomized, Double-Blind, Placebo Controlled, Multicenter, Phase III Study of Rosuvastatin (CRESTOR™) 20 mg in the Primary Prevention of Cardiovascular Events Among Subjects with Low Levels of LDL-Cholesterol and Elevated Levels of C-Reactive Protein

Study dates:	First subject enrolled: 05 February 2003 Last subject completed: 20 August 2008
Phase of development:	Therapeutic confirmatory (III)

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

Study centre(s)

The study subjects were randomized at 1348 centers in 26 countries.

The first subject entered the study on 05 February 2003. The last subjected completed the study on 20 August 2008.

Publications

1. Glynn RJ, MacFadyen JG, Ridker PM. Tracking of high-sensitivity C-reactive protein after observation of an initially increased concentration: the JUPITER study. Clin Chem 2009;55:305-312.

2. Ridker PM. Rosuvastatin in the primary prevention of cardiovascular disease among patients with low levels of low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein: rationale and design of the JUPITER trial. Circulation 2003;108:2292-7.

3. Ridker PM, Fonseca FAH, Genest J, Gotto AM, Kastelein JJP, Khurmi NS, et al on behalf of the JUPITER Trial Study Group. Baseline Characteristics of Participants in the JUPITER Trial, A Randomized Placebo-Controlled Primary Prevention Trial of Statin Therapy Among Individuals With Low Low-Density Lipoprotein Cholesterol and Elevated High-Sensitivity C-Reactive Protein. Am J Cardiol 2007;100:1659-64.

4. Ridker PM, Danielson ED, Fonseca FAH, Genest J, Gotto AM, Kastelein JJP, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359(21):2195-207.

Objectives

The primary objective was to investigate whether long-term treatment with rosuvastatin 20 mg compared with placebo would decrease the rate (based on time to first event after randomization) of major cardiovascular events (combined endpoint of cardiovascular death, stroke, myocardial infarction, unstable angina or arterial revascularization) among individuals with low levels of low density lipoprotein-cholesterol (LDL-C)(<130 mg/dL [3.3 mmol/L]) who were at high vascular risk on the basis of an enhanced inflammatory response, as determined by elevated levels of C-reactive protein (CRP)(≥2.0 mg/L).

The secondary objectives were to investigate the safety of long-term treatment with rosuvastatin compared with placebo through comparisons of total mortality, noncardiovascular mortality and adverse events, and to investigate whether therapy with rosuvastatin reduced the incidence of diabetes mellitus, venous thromboembolic events, and the incidence of bone fractures.

Study design

This was a randomized, double-blind placebo-controlled, multicenter, Phase III study evaluating rosuvastatin 20mg/day in the prevention of cardiovascular events, defined as cardiovascular death, stroke, myocardial infarction (MI), unstable angina, or arterial revascularization.

Target subject population and sample size

The study recruited men aged ≥50 years and women aged ≥60 years, who had no prior history of MI, unstable angina, stroke, arterial revascularization, or diabetes mellitus and who, on initial screening, were found to have LDL-C levels <130 mg/dL (3.3 mmol/L) and high sensitivity CRP (hsCRP) levels ≥2.0 mg/L.

Sample size determination: In order to detect a 25% reduction from the placebo event rate with 90% power, the study needed to observe 514 events. This was rounded to 520 events. The estimate was based on a 2-sided alpha of 0.05, which took into account the planned interim analyses to be performed by the Independent Data Monitoring Board (IDMB). If the accrual period was 1 year and the mean follow-up was 3.5 years, then 12,000 subjects would have needed to be randomized. Allowing for various situations that would reduce power, such as a low placebo event rate of 1.0 events per 100 person-years of follow-up, or an annual loss (non-cardiovascular deaths or drop-outs) exceeding 5%, or the need for extended accrual or follow-up periods; the sample size estimate was raised to 15,000 randomized subjects. The trial actually randomized and evaluated 17802 subjects, with 8901 subjects in the rosuvastatin treatment group and 8901 in the placebo treatment group.

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

Table S1 presents the details of treatment used in the JUPITER study. The list of batch numbers is extensive and is therefore presented in the CSR.

Table S1 Details of investigational product and any other study treatments

Investigational product or test drug	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Formulation number
Rosuvastatin tablets	20 mg	AstraZeneca	F12673
Placebo to match rosuvastatin tablets	0 mg	AstraZeneca	F12832

Duration of treatment

After a 4-week placebo run-in period, subjects meeting the study inclusion criteria and having none of the exclusion criteria were allocated to receive either rosuvastatin 20 mg/day or matching placebo.

The study was planned to last until at least 520 primary endpoints had occurred, but was stopped early upon recommendation of the IDMB, with concurrence of the Steering Committee, due to clear evidence of benefit with rosuvastatin compared with placebo. At the time of the IDMB recommendation on 29 March 2008, 328 endpoints had been adjudicated by the Clinical Event Committee at Duke University.

Criteria for evaluation - efficacy (main variables)

Primary efficacy: time to first occurrence of a major cardiovascular event (cardiovascular death, stroke, MI, unstable angina, or arterial revascularization).

Secondary efficacy: time to first occurrence of total mortality, noncardiovascular mortality, discontinuation of blinded study medication due to adverse effects, development of diabetes mellitus, development of venous thromboembolic events (deep vein thrombosis or pulmonary embolism), and bone fractures.

Criteria for evaluation - safety (main variables)

Incidence of adverse events (AEs) and abnormal laboratory values

Statistical methods

Efficacy analyses of the primary and secondary variables were analyses of time from randomization to first occurrence of event. The Intent-to-treat (ITT) population was used in the primary analyses of both primary and secondary variables. Only events occurring on or before 30 March 2008 and adjudicated and confirmed as MCEs by the Clinical Events Committee were included in the primary efficacy analysis. Deaths with insufficient information to adjudicate as either cardiovascular or non-cardiovascular were included in the analysis of total mortality, but they were excluded from analyses of cardiovascular death, non-cardiovascular death, and composite endpoints including cardiovascular death.

The primary efficacy analysis used a likelihood ratio test based on a proportional hazards model to test the null hypothesis of no association between rosuvastatin treatment and risk of the primary variable with an unadjusted proportional hazards model to estimate the hazard ratio with 95% confidence interval.

The validity of the proportional hazards assumption was checked through evaluation of trend over time of scaled Schoenfeld residuals.

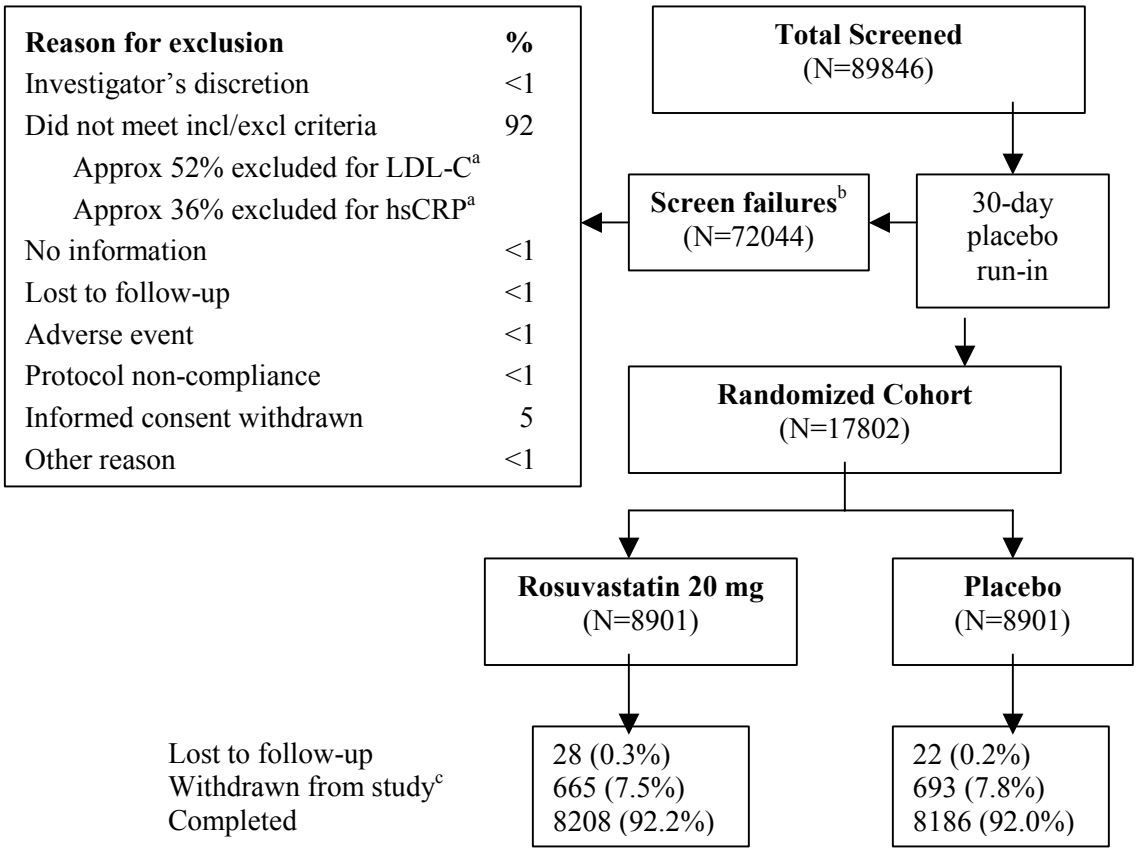
Kaplan-Meier plots were presented for time-to-event variables. Descriptive analyses used the Kaplan-Meier estimates of the probability of remaining free of event for each treatment.

Subject population

Figure S1 shows the disposition of study subjects in the JUPITER trial. The study population was 62% male and 38% female with an average age at randomization of 66 years. The majority of the population was Caucasian (71%). with Blacks and Hispanics making up 13%

each of the overall study population. Demographics and baseline characteristics were similar among treatment groups.

Figure S1 Disposition of JUPITER study subjects



NOTE: Withdrawn and lost to follow-up status were indicated on case report forms. Withdrawn indicates subjects refused all study contact; vital status was obtained at the end of the study from public records where available. For lost to follow-up subjects, no information, including vital status, was obtainable at the end of the study. Completed subjects were those who did not withdraw and had vital status information available.

[a] These numbers reported in Ridker et al 2008.

[b] There were 72044 screen failure subjects; there were 5 additional subjects (E2111/0003, E2111/0007, E2111/0011, E8453/0027, and E8477/0063) who were not screen failure subjects but who did not get randomized.

[c] Withdrawn from study in this figure does not include those subjects lost to follow-up. The number of subjects lost to follow-up is listed separately.

All of the JUPITER study subjects had an hsCRP ≥2.0 mg/L and at least 1 conventional risk factor for coronary heart disease (CHD) upon entering the trial (older age). Over 75% of subjects had 2 or more conventional risk factors. In JUPITER, 60% of subjects were considered intermediate or high risk (≥10%) according to the Framingham risk algorithm and 52% were high risk (≥5%) according to the European SCORE risk criteria. As targeted, the

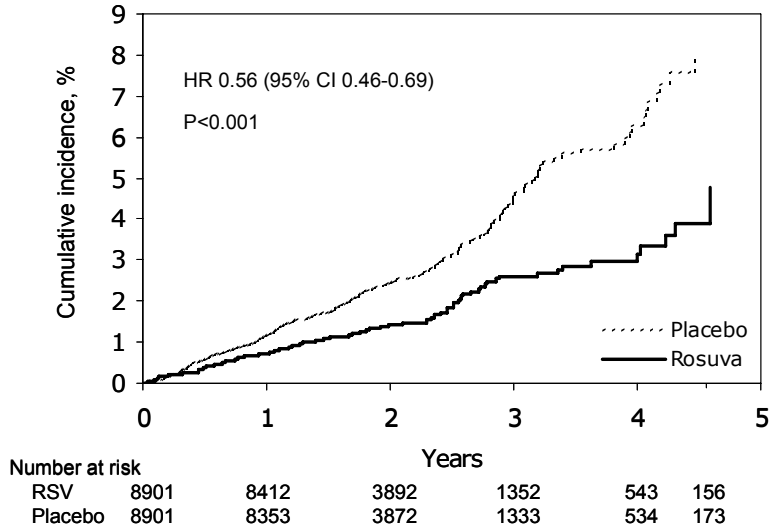
randomized population had low baseline LDL-C levels (mean 104 mg/dL [2.7 mmol/L]). At baseline, the median hsCRP level was 4.3 mg/L. Approximately 70% of subjects had hsCRP >3 mg/L and 30% of subjects had an hsCRP ≤3 mg/L, an "average hsCRP risk" based on CDC/AHA recommendations.

Summary of efficacy results

The results for the primary efficacy variable of time to first occurrence of a major cardiovascular event (MCE) are depicted graphically in Figure S2. An MCE is the occurrence of any of the following events: cardiovascular death, MI, stroke, unstable angina, or arterial revascularization. Only events occurring on or before 30 March 2008 and adjudicated and confirmed as MCEs by the Clinical Events Committee were included in the primary efficacy analysis.

Rosuvastatin treatment was effective in prolonging the time until a first MCE occurred (see Figure S2). Subjects treated with rosuvastatin were 44% less likely to have a first MCE compared with subjects treated with placebo (Hazard ratio [HR]: 0.56; 95% Confidence interval [CI] 0.46, 0.69; p <0.001). Median follow up was 1.9 years.

Figure S2 Kaplan-Meier plot for the primary composite endpoint



As seen in Figure S2, there was early separation of the primary event curves. A post-hoc analysis showed that the reduction in MCEs was statistically significant within 6 months of randomization with rosuvastatin treatment (HR 0.62; 95% CI 0.40, 0.96; p=0.029). This significant treatment difference was continued throughout the trial.

The distribution of MCEs contributing to the primary endpoint for both the rosuvastatin and placebo treatment groups is summarized in Table S2. This table, as in the figure, shows only 1 MCE for each subject, since the composite primary endpoint is defined as the first occurrence of any MCE. As seen in Table S2, each of the primary endpoint components occurred less frequently in the rosuvastatin treatment group than in the placebo group.

Table S2 Number of events by treatment group for the composite primary endpoint (ITT population)

	Number of first events	
	Rosuva 20 mg (N=8901)	**Placebo (N=8901)**
	n	**n**
First MCE[a]	142	252
Cardiovascular death	29	37
Nonfatal MI	21	61
Non fatal Stroke	30	57
Hospitalized unstable angina	15	27
Arterial revascularization	47	70

	Event rate/1000-patient years			
	Rosuva 20 mg	**Placebo**	**HR (95% CI)**	**P value**
First MCE	7.6	13.6	0.56 (0.46, 0.69)	<0.001

CI Confidence interval; HR Hazard ratio; ITT Intent-to-treat; Rosuva Rosuvastatin.

[a] An MCE is the occurrence of any of the following events: cardiovascular death, stroke, MI, unstable angina or arterial revascularization. Event occurrence counts only 1 MCE for each subject. If subject had more than 1 MCE on the same day, only 1 event is shown in Table S2, according to the following hierarchy: 1) unstable angina, 2) MI, 3) arterial revascularization, 4) nonfatal stroke, 5) cardiovascular death.

Robustness of clinical findings was supported by the treatment effects observed in analyses of the composite endpoints death or MCE, all-cause death/MI/stroke, and cardiovascular death/MI/stroke, as well as the analyses of fatal or nonfatal MI and fatal or nonfatal stroke. In addition, statistically significant benefits with rosuvastatin treatment were observed in subgroups by age, gender, race, smoking status, hypertension, geographic region, body mass index, baseline HDL-C, LDL-C, triglycerides, hsCRP, or fasting glucose levels.

Although there was a similar proportional reduction in the risk of sustaining major cardiovascular events in subjects with various baseline characteristics, absolute risk reduction was greater among subjects with a higher baseline risk of CHD.

There was a 20% reduction in risk of death due to any cause (HR:0.80, 95% CI: 0.67,0.97; p=0.021) and a 43% reduction in risk of venous thromboembolic events (HR:0.57, 95% CI: 0.35, 0.91; p=0.018) in the rosuvastatin treatment group compared to the placebo treatment group. Rosuvastatin did not significantly reduce noncardiovascular mortality, investigator-reported diabetes mellitus, or bone fracture rates.

Summary of safety results

Table S3 summarizes the AEs occurring during the JUPITER trial by category. Numbers of patients with treatment-emergent AEs, serious AEs (SAE), and discontinuations from the study due to AEs (DAE) were similar in the 2 treatment groups. AEs leading to death were less frequent among rosuvastatin-treated patients.

Table S3 Number (%) of subjects who had a treatment-emergent adverse event in any category during the randomized treatment period (ITT population)

Category of adverse event (AE)	Rosuva 20 mg (N=8901) n (%)	Placebo (N=8901) n (%)
Any AE	6968 (78.3)	6907 (77.6)
AE leading to death	141 (1.6)	179 (2.0)
AE leading to discontinuation from the study (DAE)	143 (1.6)	158 (1.8)
Serious AE (SAE)[a]	1341 (15.1)	1372 (15.4)

Note: Number of subjects with adverse events based on randomized treatment. Subjects may be included in more than one AE category.

[a] Primary endpoints (cardiovascular death, stroke, MI, hospitalization for unstable angina, and arterial revascularization), occurring before 31 March 2008, that were adjudicated to be MCEs were not captured as SAEs in this study.

AE Adverse event; CSR Clinical study report; DAE discontinuation from study due to an adverse event; ITT Intent-to-Treat; Rosuva Rosuvastatin.

Overall, the most common AEs with rosuvastatin were consistent with prior knowledge and current labeling. Although fasting glucose levels were no different in the rosuvastatin and placebo groups during the period of follow-up, there was a larger number of subjects with investigator-reported diabetes mellitus in the rosuvastatin treatment group compared to the placebo treatment group (251 [2.8%] vs 205 [2.3%]). Diabetes was not an adjudicated endpoint.