AstraZeneca

Advisory Committee Briefing Document

Drug substance Rosuvastatin calcium

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CRESTOR® (rosuvastatin calcium)
NDA 21-366/S-016

Briefing Document for Endocrinologic and Metabolic Drugs Advisory Committee Meeting of December 15, 2009

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1. EXECUTIVE SUMMARY

Cardiovascular disease causes substantial disability and continues to be the leading cause of death worldwide despite preventative efforts including statin treatment (Rosamond et al 2008, Waldman and Terzic 2007).

Statins are highly effective cholesterol-lowering agents that have been proven to reduce cardiovascular events in numerous clinical studies. The Cholesterol Treatment Trialists' meta-analysis of over 90000 statin study subjects concluded that statin therapy can safely reduce the incidence of major cardiovascular events largely irrespective of the initial lipid profile or other presenting characteristics such as age, sex, or the presence or absence of diabetes or prevalent coronary heart disease (CHD)(CTT Collaborators 2005).

Current cardiovascular disease prevention guidelines recommend statin use, particularly among patients with hypercholesterolemia, cardiovascular disease, or with multiple CHD risk factors (such as older age, cigarette smoking, hypertension, low levels of high density lipoprotein-cholesterol [HDL-C], or a family history of premature CHD) (Expert Panel (NCEP) 2001, Graham et al 2007). However, at least half of all future cardiovascular events occur in individuals with "normal" cholesterol levels who were not recommended for cholesterol-lowering treatment based on current guidelines (Sachdeva et al 2009, Ridker et al 2002). Many of these individuals have elevated levels of the inflammatory biomarker C-reactive protein (CRP) when measured with a high sensitivity assay or "hsCRP," which has been shown to be an independent predictor of cardiovascular risk in numerous epidemiologic studies (Ridker et al 1998, Danesh et al 2000).

AstraZeneca conducted the "Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin," (subsequently referred to as the JUPITER study) to assess the long-term safety and efficacy of rosuvastatin in reducing cardiovascular events. The study was conducted in a population of adults who had an increased cardiovascular risk (identified initially based on age and the presence of an elevated hsCRP level at a screening visit), but who were not recommended for cholesterol-lowering treatment based on current guidelines. This allowed AstraZeneca to ethically conduct a placebo-controlled study and, at the same time, address the need for improved cardiovascular disease prevention. The main results of the JUPITER study were the statistically significant 44% reduction in the risk of sustaining a major cardiovascular event (cardiovascular death, stroke, myocardial infarction, unstable angina, or arterial revascularization) and 20% reduction in total mortality observed in the rosuvastatin compared to the placebo group.

AstraZeneca is therefore seeking approval for use of rosuvastatin to reduce the risk of major cardiovascular events in patients at increased cardiovascular risk on the basis of the results of the JUPITER study.

Overview of the JUPITER study

JUPITER was a randomized, placebo-controlled, double-blind Phase III study conducted in 17802 adult subjects (8901 rosuvastatin, 8901 placebo), who had an increased risk of cardiovascular disease based on their age (≥50 years for men, ≥60 years for women) and the presence of an hsCRP level ≥2.0 mg/L at an initial screening visit. Although these study subjects frequently had multiple risk factors for cardiovascular disease, they were not recommended for cholesterol-lowering treatment based on National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines (Expert Panel (NCEP) 2001). The study treatment intervention was rosuvastatin 20 mg once daily, with no up- or down-titration.

The primary objective in the JUPITER study 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 (cardiovascular death, nonfatal myocardial infarction [MI], nonfatal stroke, unstable angina, or arterial revascularization). Clinical information obtained from study subjects who died or experienced a suspected nonfatal cardiovascular endpoint event was provided to a Clinical Events Committee for adjudication in order to identify the primary endpoint events. The Clinical Events Committee was blinded to treatment assignment. Secondary objectives were to assess total mortality, noncardiovascular mortality, and the long-term safety and tolerability of rosuvastatin and to investigate whether therapy with rosuvastatin reduced the incidence of diabetes, venous thromboembolic events, or bone fractures. These secondary efficacy endpoints were not centrally adjudicated.

During the development of the JUPITER study, AstraZeneca sought guidance from the Food and Drug Administration (FDA). Design features, such as the study population, sample size, and primary outcome variable were discussed, and FDA recommendations incorporated.

JUPITER study data were first analyzed by the academic study statistician (Robert Glynn, PhD) and Principal Investigator (Paul Ridker MD, MPH) and published by the JUPITER Study Group in the *New England Journal of Medicine* (Ridker et al 2008). AstraZeneca conducted a separate analysis of the study data in accordance with the Clinical Study Protocol and Statistical Analysis Plan. The study results reported in this document are from the AstraZeneca analyses. Because the academic researchers and the sponsor performed independent analyses, there are differences between the published manuscript (Ridker et al 2008, see Appendix C) and the sponsor reports. These differences did not alter the interpretation of the JUPITER study results.

Study population

The JUPITER study population comprised 17802 subjects from 26 countries with a mean age of 66 years. The cohort included 38% women, 12.5% black, 12.7% Hispanic and 1.6% Asian subjects. At baseline, mean low-density lipoprotein-cholesterol was 104 mg/dL, and median hsCRP was 4.3 mg/L. The randomized treatment groups were well balanced with regard to baseline characteristics.

The estimated baseline coronary heart disease risk of the JUPITER study population was 11.6% over 10 years based on the Framingham Risk Score algorithm, with 75% of subjects having had at least 2 ATP III major CHD risk factors at baseline: age (100%), hypertension (58%), low HDL-C levels (23%), cigarette smoking (16%) or a family history of premature CHD (12%).

Summary of primary and secondary endpoint results

Table 1 provides a summary of the primary and secondary endpoint results.

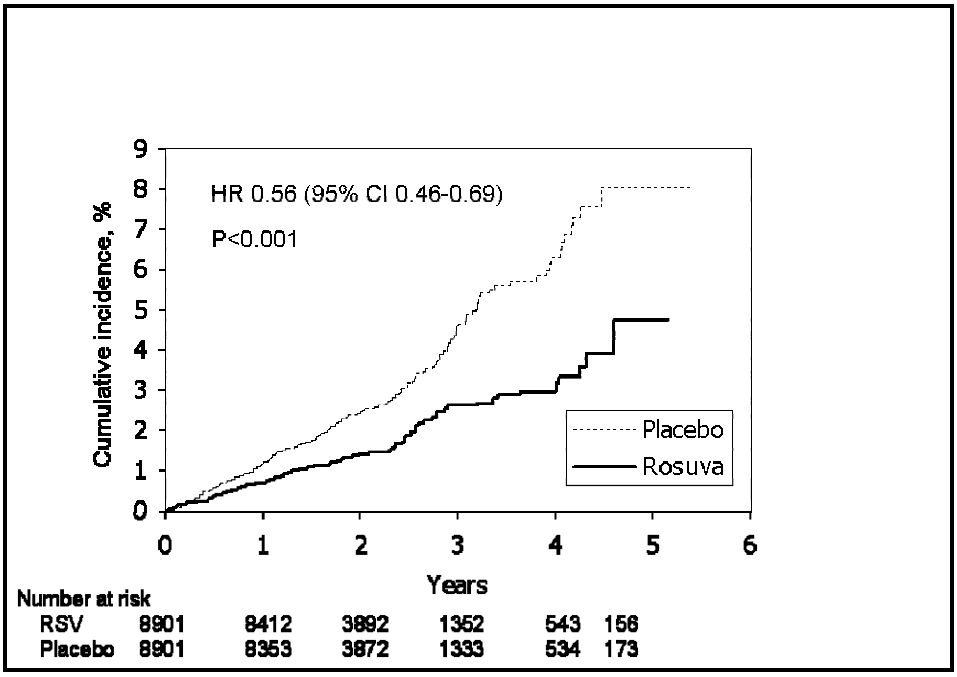
Table 1 Primary and secondary endpoint results

	Rosuvastatin (N=8901)	Placebo (N=8901)		
	n (%)	n (%)	HR (95% CI)	p value
Primary endpoint (CV death, stroke, MI, unstable angina or arterial revascularization)	142 (1.6)	252 (2.8)	0.56 (0.46-0.69)	<0.001
Secondary endpoints				
Total mortality	198 (2.2)	247 (2.8)	0.80 (0.67-0.97)	0.021
Noncardiovascular mortality	105 (1.2)	126 (1.4)	0.84 (0.65-1.08)	0.172
Discontinuation of study medication due to AEs	495 (5.6)	486 (5.5)	1.02 (0.90-1.06)	0.758
Investigator-reported diabetes	251 (2.8)	205 (2.3)	1.27 (1.05-1.53)	0.015
Venous thromboembolism	26 (0.3)	46 (0.5)	0.57 (0.35-0.91)	0.018
Bone fracture	226 (2.5)	214 (2.4)	1.06 (0.88-1.28)	0.548

The study was stopped before accrual of the planned 520 endpoints upon recommendation of the Independent Data Monitoring Board due to clear evidence of benefit with rosuvastatin. The median follow-up was 1.9 years.

There were 142 (1.6%) study subjects in the rosuvastatin group and 252 (2.8%) study subjects in the placebo group who experienced a primary endpoint event (cardiovascular death, nonfatal stroke, nonfatal MI, unstable angina, or arterial revascularization), which represents a 44% reduction in the risk of sustaining a major cardiovascular event (Figure 1).

Figure 1 Kaplan-Meier plot for the primary composite endpoint



CI Confidence interval; HR Hazard ratio; RSV Rosuvastatin

There were 198 deaths in the rosuvastatin group and 247 deaths in the placebo group, which represents a 20% reduction in total mortality (HR: 0.80, 95% CI: 0.67-0.97; p=0.021). There were 105 deaths attributed to a noncardiovascular cause in the rosuvastatin group and 126 deaths attributed to a noncardiovascular cause in the placebo group. The difference was not statistically significant (HR: 0.84, 95% CI 0.65-1.08, p=0.172).

There was no difference in the percentage of study subjects who discontinued study medication due to an adverse event (AE) (HR: 1.02, 95% CI 0.90-1.06, p=0.758).

With regard to the secondary efficacy endpoints, diabetes was reported by investigators in 251 (2.8%) study subjects in the rosuvastatin group and 205 (2.3%) study subjects in placebo group (HR: 1.27, 95% CI 1.05-1.53, p=0.015). Although no significant differences in mean plasma fasting glucose or the percentage of subjects whose fasting glucose levels increased to a level ≥126 mg/dL were observed between treatment groups (see Section 6.9), there was an approximate 0.1% greater increase in Hb_{A1c} from baseline to the final visit in the rosuvastatin than the placebo group (p<0.001). In post-hoc analyses, time to initiation of anti-diabetic medication was not different in the 2 treatment groups (p=0.671). Approximately 80% of the excess in investigator-reported diabetes cases in the rosuvastatin compared to the placebo group occurred among study subjects who had baseline fasting glucose levels ≥100 mg/dL (Impaired Fasting Glucose or IFG). The subset of the JUPITER study population who had IFG at baseline had a 34% reduction in the risk of major cardiovascular events (HR: 0.66, 95% CI 0.47-0.93, see Table 11, Section 5.1.1).

There were 26 study subjects in the rosuvastatin group and 46 study subjects in the placebo group with a reported venous thromboembolic event (HR: 0.57, 95% CI 0.35-0.91, p=0.018). Bone fracture was reported in 226 (2.5%) study subjects in the rosuvastatin group and 214 (2.4%) study subjects in the placebo group (HR:1.06, 95% CI 0.88-1.28, p=0.548).

Summary of Safety

Table 2 summarizes the adverse events (AEs) reported during the JUPITER study by category. Numbers of subjects with treatment-emergent AEs and serious AEs (SAE) were similar in the 2 treatment groups in both the intention-to-treat (ITT) and Safety populations. AEs leading to death were less frequent among rosuvastatin-allocated subjects.

Table 2 Number (%) of subjects who had a treatment-emergent AE in any category during the randomized treatment period (ITT population)

Category of adverse event (AE)	RSV 20 mg (N=8901) n (%)	Placebo (N=8901) n (%)
Any AE	6968 (78.3)	6907 (77.6)
Any Serious AE (SAE)[a]	1341 (15.1)	1372 (15.4)
AE leading to death	141 (1.6)	179 (2.0)

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 (the date of study closure) were not captured as SAEs in this study.

AE Adverse event; ITT Intent-to-Treat; RSV Rosuvastatin; SAE Serious adverse event.

The most commonly reported treatment-emergent AEs that occurred to a greater extent in rosuvastatin patients versus placebo were: urinary tract infection (8.7% versus 8.6%), followed by nasopharyngitis (7.6% versus 7.2%), back pain (7.6% versus 6.9%), myalgia (7.6% versus 6.6%), bronchitis (7.2% versus 7.1%), and arthritis (5.8% versus 5.6%).

In the JUPITER study, findings with respect to muscle, liver, or renal-related AEs were consistent with the known safety profile in the US Prescribing Information (PI) for CRESTOR. There was approximately a 0.1% increase in Hb_{A1c} and a higher frequency of investigator-reported diabetes in the rosuvastatin compared to the placebo group. Elevated glucose is included as a laboratory abnormality in the US PI for CRESTOR.

Conclusions

The principal results of the JUPITER study were that subjects who received rosuvastatin (20 mg once daily) compared to placebo had a 44% reduction ($p<0.001$) in the primary study endpoint, which was a composite of cardiovascular death, nonfatal stroke, nonfatal MI, unstable angina, or arterial revascularization). There was also a 20% reduction (p=0.021) in total mortality. Rosuvastatin was well tolerated with an AE profile that was consistent with its known safety profile, based on controlled clinical trials data as well as postmarketing experience, and as described in the current US PI for CRESTOR. There was approximately a

0.1% increase in Hb_{A1c} level in the rosuvastatin group compared to the placebo group and an increased frequency of diabetes as reported by investigators (2.8% rosuvastatin subjects versus 2.3% placebo subjects).

Since the benefits of rosuvastatin treatment outweighed the risks in the JUPITER study, AstraZeneca is seeking approval for the use of rosuvastatin to reduce the risk of major cardiovascular events in patients at increased cardiovascular risk on the basis of the JUPITER study results.

2. INTRODUCTION

Current national and international cardiovascular disease prevention guidelines provide recommendations for statin use, particularly among subjects with hypercholesterolemia, CHD or multiple CHD risk factors (such as older age, cigarette smoking, hypertension, low HDL-C, or a family history of premature CHD) (Expert Panel (NCEP) 2001, Graham et al 2007). Despite the presence of these treatment recommendations and the availability of effective treatment methods, cardiovascular disease remains the leading cause of death worldwide (Rosamond et al 2008, Waldman and Terzic 2007).

2.1 Rosuvastatin

Rosuvastatin (CRESTOR™) is a synthetic 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, a member of the statin class of lipid-lowering agents. It was approved in the United States (US) on 12 August 2003. Currently, rosuvastatin has marketing authorization in over 100 countries. The cumulative worldwide market exposure is approximately 17.3 million patients, with more than 16.9 million person-years of post-marketing experience cumulatively through 30 April 2009. The safety and tolerability profile of rosuvastatin has been established on the basis of controlled clinical trials as well as postmarketing experience.

2.2 Rosuvastatin development program leading up to the JUPITER study

The AstraZeneca clinical development program for rosuvastatin included studies designed to assess effects on the atherogenic lipid profile, effects on atherosclerosis, and a clinical outcomes program.

Studies in dyslipidemic populations found that 50% reductions of LDL-C were achievable when rosuvastatin was administered in its usual recommended dose range of 10 to 40 mg once daily (Jones et al 2003). In addition to greater reductions of LDL-C, rosuvastatin has been shown to have greater effects on other lipids and lipoproteins in comparison to other statins across their respective dose ranges (Table 3).

Table 3 Percent change from baseline across the dose range of rosuvastatin, atorvastatin, pravastatin, and simvastatin—STELLAR study

	Range of least squares means of % change from baseline to week 6					
	TC	**TG**	**HDL-C**	**LDL-C**	**Non-HDL-C**	**ApoB**
Rosuvastatin 10-40 mg	-33 to -40	-20 to -24	8 to 10	-46 to -55	-42 to -50	-37 to -45
Atorvastatin 10-80 mg	-28 to -39	-21 to -27	2 to 6	-37 to -51	-36 to -48	-29 to -43
Pravastatin 10-40 mg	-15 to -21	-8 to -12	4 to 5	-20 to -30	-19 to -26	-16 to -23
Simvastatin 10-80 mg	-20 to -33	-14 to -18	5 to 6	-28 to -46	-26 to -42	-22 to -35

ApoB Apolipoprotein B; TC Total cholesterol; TG Triglycerides; HDL-C High-density lipoprotein cholesterol; LDL-C Low-density lipoprotein cholesterol.

The METEOR study, which was conducted in patients with elevated LDL-C, at low risk for symptomatic coronary artery disease, and with subclinical atherosclerosis as evidenced by carotid intimal-medial thickness (cIMT), identified a highly significant reduction in the annualized change in cIMT with rosuvastatin 40 mg relative to placebo (-0.0145 mm/year; 95% CI for difference -0.0196, -0.0093; $p<0.0001$) (Crouse et al 2007). The clinical relevance of this observed effect of rosuvastatin on the progression of cIMT is supported by findings from a meta-analysis of 7 statin-intervention studies that included cIMT measurements. These investigators reported that a cIMT progression difference in statin-treated subjects versus placebo of -0.012 mm/year was associated with an approximate halving of cardiovascular risk (odds ratio of 0.48 [95% CI 0.30, 0.78]) (Espeland et al 2005).

AstraZeneca also undertook a program of clinical outcomes studies, which were placebo-controlled studies to further assess the efficacy and safety of rosuvastatin treatment. One of the studies was conducted in patients with heart failure and was called "CORONA" (Kjekshus et al 2007). Another study of patients with heart failure (GISSI-HF) utilized rosuvastatin as a treatment intervention, but was not conducted by AstraZeneca. The main results of the trial are included in this discussion for completeness (GISSI-HF investigators 2008). JUPITER was the only study that AstraZeneca conducted in a population whose cardiovascular prognosis was largely dictated by their risk of sustaining an atherosclerosis-related cardiovascular event.

CORONA included approximately 5000 patients with chronic symptomatic systolic heart failure (New York Heart Association class [NYHA] II-IV) of ischemic etiology. GISSI-HF included approximately 4500 patients with chronic symptomatic systolic heart failure (NYHA II-IV) of either ischemic or nonischemic etiology. These studies were placebo controlled and used a 10 mg dose of rosuvastatin. Most of the cardiovascular events that occurred in the CORONA and GISSI-HF study populations were heart failure related rather than acute atherothrombotic in etiology. Although rosuvastatin was well-tolerated in these study populations, it did not reduce total mortality of the risk of major cardiovascular events.

AstraZeneca also conducted a study of patients with endstage renal disease who were receiving chronic hemodialysis called "AURORA" (Fellstrom et al 2009). The AURORA study included approximately 2800 patients who were randomized to rosuvastatin 10 mg or placebo and followed for an average of 3.8 years. Rosuvastatin 10 mg was well tolerated but did not reduce the composite primary endpoint of cardiovascular death, MI or stroke. These results are in agreement with a previously published study that investigated the use of atorvastatin in patients undergoing dialysis (Wanner et al 2005). Like CORONA and the GISSI-HF study, a relatively small proportion of the major cardiovascular events that occurred were atherothrombotic in etiology in AURORA study subjects.

3. JUPITER RATIONALE, DESIGN, AND CONDUCT

3.1 Rationale for JUPITER

JUPITER was designed to investigate the effects of rosuvastatin in a patient population at increased cardiovascular risk, but for whom statin use was not recommended based on guidelines. The rationale behind conducting the JUPITER study follows:

- Cardiovascular events frequently occur even in adults with "normal" levels of LDL-C (<130 mg/dL) (Section 3.1.1)
- hsCRP levels have been shown to identify individuals at increased cardiovascular risk, independent of LDL-C levels (Section 3.1.2)
- A post-hoc, hypothesis-generating analysis from the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) suggested that statin therapy reduced cardiovascular events among individuals with elevated levels of hsCRP, but "normal" LDL-C (Section 3.1.3)

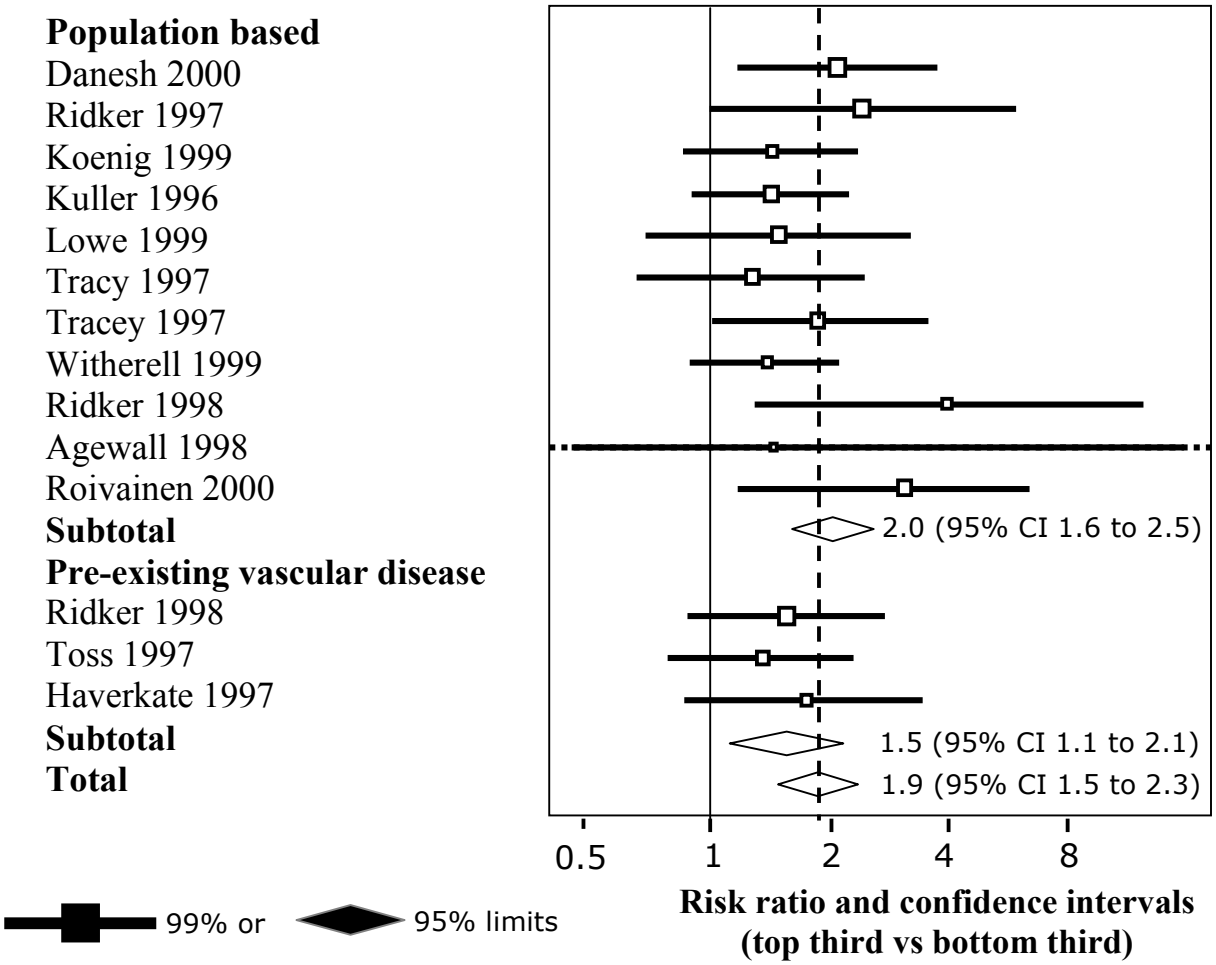
3.1.1 Cardiovascular events frequently occur in people with "normal" levels of LDL-C (<130 mg/dL)

Many individuals considered at low cardiovascular risk, and for whom cholesterol-lowering drug treatment is not recommended, nevertheless experience major cardiovascular events such as MI or stroke (Ridker et al 2002). For example, in an analysis of 136905 hospitalizations for CHD in the US, where lipid levels were obtained in the first 24 hours of hospitalization, the mean LDL-C was 105±40 mg/dL. Almost half of patients hospitalized with CHD had LDL-C<100 mg/dL and 17.6% had LDL<70 mg/dL. Thus, a substantial proportion of patients presenting with their first or a recurrent CHD event fall well within current guideline-recommended targets for LDL-C (Sachdeva et al 2009).

3.1.2 hsCRP levels identify individuals at increased cardiovascular risk, independent of LDL-C

Data from epidemiologic studies reported prior to initiation of the JUPITER study provided evidence that levels of the inflammatory biomarker hsCRP tended to be higher in individuals with recognized risk factors for cardiovascular disease, but that hsCRP nonetheless independently predicted major cardiovascular events (Figure 2) (Danesh et al 2000, Ford and Giles 2000, Kjekshus et al 2007, Koenig et al 1999, Kuller et al 1996, Pradhan et al 2002, Ridker et al 1997, Ridker et al 1998, Ridker et al 2000, Ridker et al 2002, Rost et al 2001, Zimmermann et al 1999).

Figure 2 **Prospective studies of hsCRP and CHD: Relative CHD risk in subjects with hsCRP in top vs bottom third at baseline (Danesh et al 2000)**



The Centers for Disease Control (CDC) and the American Heart Association (AHA) convened an international panel of experts to review data relevant to the association of hsCRP levels and

cardiovascular risk. In 2002, this CDC/AHA panel of experts recommended that risk assessments based on hsCRP levels be modeled in a manner similar to the approach used to characterize risk based on blood lipid levels (Pearson et al 2003). The recommendations, which were published after initiation of the JUPITER study, included a classification of hsCRP into 3 levels:

low risk hsCRP	<1 mg/L
average risk hsCRP	1-3 mg/L
high-risk hsCRP	>3 mg/L

3.1.3 A post-hoc, hypothesis-generating analysis (AFCAPS/TexCAPS) suggested that statin therapy reduced cardiovascular events among individuals with elevated levels of hsCRP, but "normal" LDL-C

Prior to initiation of the JUPITER study, a post-hoc analysis of data from the AFCAPS/TexCAPS study supported the hypothesis that individuals who have elevated concentrations of hsCRP are at increased cardiovascular risk and could benefit from statin treatment. As seen in Table 4, AFCAPS/TexCAPS study subjects in the placebo group who had lower LDL-C but higher hsCRP levels at baseline, had cardiovascular event rates that were similar to the rates among subjects with higher baseline LDL-C levels. In addition, the relative risk reductions observed in statin-treated (lovastatin) subjects were similar in the low LDL-C/high hsCRP and the high LDL-C groups (Downs et al 2001). In this analysis, "low" LDL-C was <149 mg/dL and "high" hsCRP was >1.6 mg/L.

Table 4 Event rates and relative risks (RR) associated with lovastatin allocation according to baseline LDL-C and hsCRP levels in AFCAPS/TexCAPS[a]

	Lovastatin		Placebo		
	N	Rate	N	Rate	RR (95% CI)
Low LDL-C, low hsCRP	19/726	0.026	17/722	0.024	1.08 (0.56-2.08)
Low LDL-C, high hsCRP	22/718	0.031	37/710	0.052	0.58 (0.34-0.98)
High LDL-C, low hsCRP	15/709	0.021	37/711	0.052	0.38 (0.21-0.70)
High LDL-C, high hsCRP	29/741	0.039	40/705	0.057	0.68 (0.42-1.10)

Data derived from Ridker et al 2001.
CI Confidence interval; hsCRP High sensitivity C-reactive protein; LDL-C Low-density lipoprotein cholesterol; RR Relative risk reduction.
[a] Baseline LDL-C and hsCRP characterized as "low" or "high" based on median values for the AFCAPS/TexCAPS population (median LDL-C: 149 mg/dL, median hsCRP: 1.6 mg/L).

Evidence that inflammation plays an important role in atherogenesis (Libby et al 2002), in conjunction with clinical data obtained in studies that were available prior to initiation of the JUPITER study, provided support for the hypotheses that:

1) elevated hsCRP could identify a population of subjects who were not recommended for statin treatment based on guidelines, but who nevertheless had an increased risk of cardiovascular disease, and

2) these individuals at increased risk could benefit from treatment with rosuvastatin.

3.2 Rationale for the JUPITER study design

During the development of the JUPITER study, AstraZeneca sought guidance from the FDA. Design features, such as the study population, sample size, and primary outcome variable were discussed and FDA recommendations incorporated.

JUPITER was designed as a placebo-controlled, double-blind, randomized study. A placebo-control group allowed assessment of the impact of rosuvastatin on cardiovascular events and allowed for optimal assessment of the long-term safety of rosuvastatin treatment. A placebo group was also appropriate since participation was restricted to individuals who were not recommended for statin treatment based on the NCEP ATP III guideline (Expert Panel (NCEP) 2001).

Subjects with clinical evidence of pre-existing cardiovascular disease or diabetes were excluded from the study because the benefits of statin therapy had already been established in these high-risk groups (The Scandinavian Simvastatin Survival Study Group 1994, Sacks et al 1996, Heart Protection Study Collaborative Group 2002). Thus, inclusion of such subjects in a placebo-controlled study would be unethical. Similarly, subjects with hypercholesterolemia (LDL-C ≥130 mg/dL) were excluded from the study. The JUPITER inclusion requirement of LDL C <130 mg/dL was based on NCEP ATP III guidelines (Expert Panel (NCEP) 2001) to ensure that subjects recommended for cholesterol-lowering treatment would not enroll in this placebo-controlled study.

Although subjects with pre-existing cardiovascular disease, diabetes, or hypercholesterolemia were excluded from the study, study subjects were considered to have an increased risk of cardiovascular disease based on their age (≥50 years for men, ≥60 years for women) and were also required to have an hsCRP level ≥2.0 mg/L at an initial screening visit. The hsCRP entry criterion (≥2.0 mg/L) was chosen as the qualifying level for JUPITER because it approximated the median level (1.6 mg/L) in the AFCAPS/TexCAPS study (Ridker et al 2001), which showed that risk of a major cardiovascular event was similar for subjects with low LDL-C/high hsCRP and those with high LDL-C.

The JUPITER study intervention was based on randomized assignment to rosuvastatin 20 mg or a matching placebo. The 20 mg dose of rosuvastatin was selected anticipating that it would reduce LDL-C levels by approximately 50% and maintain a favorable safety and tolerability profile (STELLAR study data 2001 subsequently published in Jones et al 2003 [see Table 4],

Shepherd et al 2002 updated in Shepherd et al 2007). JUPITER subjects were initiated on the 20 mg dose of rosuvastatin or placebo, and continued on the same dose for the duration of the study.

The primary endpoint, a composite of cardiovascular death, stroke, MI, hospitalization for treatment of unstable angina, or arterial revascularization, was selected to include clinically meaningful events that represented complications of atherosclerosis. All components of the primary endpoint were defined in the protocol and Clinical Events Committee Process Document (see Section 3.3.2 for details of adjudication process). In particular, categorizing a death as cardiovascular death required definitive evidence of antecedent MI, heart failure or stroke. Sudden deaths were evaluated on a case-by-case basis, but not categorized as cardiovascular deaths by default.

Secondary endpoints were the occurrence of:

- total mortality
- noncardiovascular mortality
- discontinuation of blinded study medication due to adverse events
- development of diabetes
- venous thromboembolic events (deep vein thrombosis or pulmonary embolism)
- bone fractures

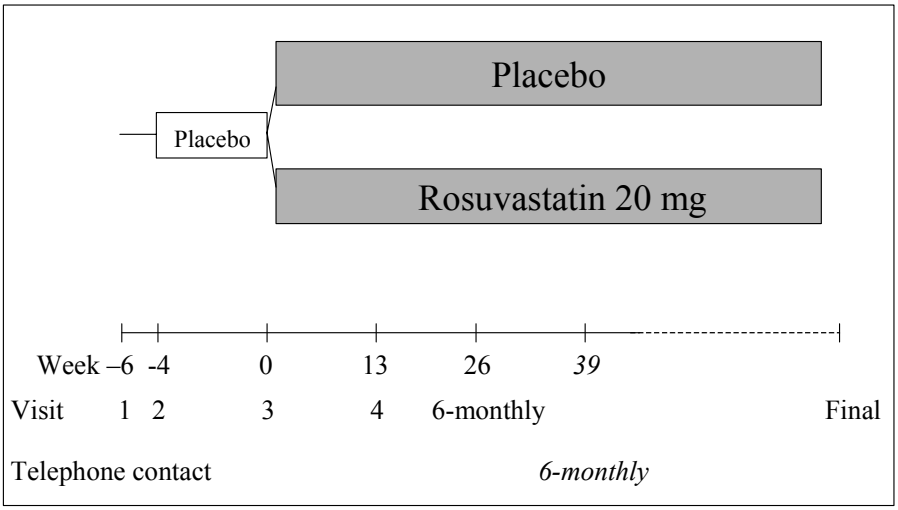
Of the above secondary endpoints, total mortality, noncardiovascular mortality, investigator-reported diabetes, and discontinuation of study medication due to an AE were in the original study protocol. Secondary endpoints of bone fracture and venous thromboembolic events were added to the JUPITER protocol (Amendment 1) in January 2003 (prior to first subject enrolled), at a time of increased interest around actions of statins beyond lipid modulation. Information from all study subjects who died or experienced a suspected JUPITER primary endpoint event was reviewed by a Clinical Events Committee, blinded to treatment assignment. Development of diabetes, venous thromboembolic events, and bone fracture were not centrally adjudicated endpoints.

3.3 Study design

The study design comprised a 2-week screening period, a 4-week placebo run-in period to assess subject compliance with study medication, followed by a double-blind, randomized treatment period (Figure 3). There was no rosuvastatin tolerability run-in period prior to randomization. At the end of the placebo run-in period, eligible subjects were randomly assigned to double-blind treatment with rosuvastatin 20 mg or matching placebo once daily. The randomization ratio between rosuvastatin and placebo was 1:1, stratified by center. Refer to Appendix A for the Clinical Study Protocol pages with the inclusion and exclusion criteria,

as well as the schedule of assessments. The study was designed as an event-driven study, which was to continue until 520 subjects experienced a primary endpoint event.

Figure 3 Study design



NOTE: The placebo run-in phase is the interval between Visits 2 and 3. The randomized treatment phase is from Visit 3 onward.

3.3.1 Independent Data Monitoring Board (IDMB)

The JUPITER study utilized an IDMB. The primary purpose of the IDMB (chaired by Professor Rory Collins) was to protect the interests of study subjects with regard to the safety and efficacy of their investigational treatment. The IDMB functioned independently of the Steering Committee, investigators, and AstraZeneca. The IDMB was appointed by, and was advisory to, the Steering Committee (chaired by Paul Ridker, MD MPH). The Steering Committee was appointed by the Sponsor to provide scientific, ethical, and clinical oversight, and to ensure the study was conducted in accordance with GCP.

The IDMB reviewed unblinded safety data approximately twice a year, including laboratory data, concomitant medications and AEs. Two interim analyses were planned, at 37.5% (195 confirmed endpoints) and 75% (390 confirmed endpoints) of primary events. The final analysis was planned when at least 520 primary endpoints had been confirmed.

The interim analyses used a group sequential design to preserve the overall type 1 error probability of 0.05 (false positive efficacy result). The group sequential boundaries for the 3 scheduled analyses were 2.947, 2.411, and 2.011, which correspond to nominal p values of 0.003, 0.016 and 0.044, respectively. These boundaries were based on an alpha-spending function that approximated an O'Brien-Fleming boundary in the setting of unequal analysis times (O'Brien and Fleming 1979, Lan and DeMets 1983).

3.3.2 Clinical endpoint assessment and adjudication process

Study subjects were asked about possible primary clinical endpoints every 3 months. Supporting documentation for possible primary endpoints was collected and reviewed by the Duke Clinical Research Institute (DCRI) Clinical Events Committee (Durham, NC). Two physicians from a group of 2 to 5 DCRI physician reviewers assigned to the JUPITER project independently adjudicated each suspected endpoint using documentation from CRFs and subjects' medical records. If the 2 physician reviewers agreed in their adjudication of the suspected endpoint, the adjudication was considered complete. If the reviewers did not agree, the event was adjudicated by a Phase II committee of at least 3 DCRI faculty physicians. Final adjudication results were recorded on a clinical event adjudication form and sent for data entry.

The required source documentation for each type of endpoint is summarized in Table 5.

Table 5 Source documentation for Clinical Events Classification group review

Endpoint	Required source documentation
MI	Event CK, CK-MB and/or troponin (lab print outs) Critical diagnostic electrocardiograms (ECG) Angiographic report (if done) Discharge summary Or the clinical equivalent if the above unavailable
Revascularization	Operative and/or interventional procedure report Discharge summary Or the clinical equivalent if the above unavailable
Stroke	Hospital discharge summary CT report (if done) MR report (if done) Neurological consult reports Or the clinical equivalent if the above unavailable
Hospitalization for unstable angina	Event CK, CK-MB and/or troponin (lab print outs) Critical diagnostic ECGs Angiographic report (if done) Discharge summary Or the clinical equivalent if the above unavailable
Death	Death note and relevant source documents if in hospital Death note from Principal Investigator if death at home For some cases, information on subjects' deaths was not obtained during the study, but via limited external data such as public death records. Available information on these individuals was reviewed.

CK Creatine kinase; CK-MB Creatine kinase MB band isoenzyme; CT Computed tomography; ECG Electrocardiogram; MR Magnetic resonance imaging study.

Categorizing a death as cardiovascular death required definitive evidence of antecedent MI, heart failure, or stroke. Sudden deaths were evaluated on a case-by-case basis, but not

categorized as cardiovascular deaths by default. If insufficient documentation was provided to determine whether or not an endpoint occurred or to determine the specific classification, the physician reviewer could request additional source documentation. It was anticipated that there would be cases for which minimal source documentation was available. In such cases, the DCRI required documentation from the sponsor designee that due diligence was exercised in attempting to collect source documents, and that no additional data would be available. In cases where the data was insufficient to adjudicate, the event was not considered an event for the primary endpoint.

3.3.3 Summary of efficacy objectives, variables, and analyses

Objectives, outcome variables, and statistical analyses are summarized in Table 6.

Table 6 Objectives and outcome variables related to each objective

Objective	Outcome variable (s)	Statistical analysis or data presentation
Primary		
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 among individuals with low LDL-C (<130 mg/dL) who are at high cardiovascular risk on the basis of an enhanced inflammatory response, as determined by elevated levels of hsCRP (≥2.0 mg/L).	Combined endpoint of cardiovascular death, stroke, MI, unstable angina, or arterial revascularization	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 (HR) with 95% confidence interval (CI). Kaplan-Meier plots are presented. To look for consistency of effect, separate analyses were done for each component of the primary endpoint. In these analyses, subjects were followed until the first occurrence of a specific event, even if the event occurred after a prior non-fatal event. In addition, analyses of the composite of cardiovascular death/MI/stroke, fatal/nonfatal MI, and fatal/nonfatal stroke were prespecified, as were analyses of the primary composite endpoint in several subgroups.

Table 6 Objectives and outcome variables related to each objective

Objective	Outcome variable (s)	Statistical analysis or data presentation
Secondary To investigate the safety of long-term treatment with rosuvastatin compared with placebo through comparisons of total mortality, noncardiovascular mortality, and AEs, and to investigate whether therapy with rosuvastatin reduced the incidence of diabetes, venous thromboembolic events, or the incidence of bone fractures.	▪ total mortality ▪ noncardiovascular mortality ▪ discontinuation of blinded study medication due to AEs[a] ▪ development of diabetes[a] ▪ development of venous thromboembolic events (deep vein thrombosis or pulmonary embolism) ▪ development of bone fractures.	Likelihood ratio tests based on a proportional hazards model to test the null hypothesis of no association between rosuvastatin treatment and risk of the secondary variable with an unadjusted proportional hazards model to estimate the HR with 95% CI.

AE Adverse event; hsCRP High sensitivity C-reactive protein; LDL-C Low-density lipoprotein cholesterol; MI Myocardial infarction.

[a] The secondary variables discontinuation of blinded study medication due to AEs and development of diabetes are discussed in the safety section.

Subjects who had an event could stay in the study but were to discontinue study medication and initiate open-label statin therapy in addition to standard of care.

3.3.3.1 Statistical analysis

Analyses for the primary investigator's publication (Ridker et al 2008, Appendix C) were performed independently by statisticians at the Center for Cardiovascular Disease Prevention, Brigham and Women's Hospital, Boston, MA. AstraZeneca conducted a separate analysis of the study data in accordance with the Clinical Study Protocol and Statistical Analysis Plan. The study results reported in this document are from the AstraZeneca analyses. The statistical analysis plan (SAP) was provided to FDA prior to database lock and before unblinding of the data.

Primary endpoint analysis

The primary endpoint analysis was based on time from randomization to first occurrence of a first major cardiovascular event (CV death, stroke, MI, unstable angina, or arterial revascularization). The ITT population, defined as all randomized subjects, was used in the primary endpoint analysis. A subject might have had one or more major cardiovascular event; however, only a subject's first occurring event contributed to the analysis of the primary variable. Only events occurring on or before 30 March 2008 and adjudicated and confirmed as major cardiovascular events by the Clinical Events Committee were included in the primary efficacy analysis. 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 HR with 95% CI (Cox 1972).

The validity of the proportional hazards assumption was checked through evaluation of trend over time of scaled Schoenfeld residuals. If a violation of the proportional hazards assumption was observed with a significant ($p<0.01$) correlation between scaled residuals and the log of time (Therneau and Grambsch 2000), then estimates of the effects of rosuvastatin would have been obtained from proportional hazards models fit to data from each year of follow-up. However, the overall estimate from a single model fit to all years of follow-up would continue to serve as the best single estimate of the average treatment effect over the follow-up period.

The study was designed to provide sufficient power for the composite primary endpoint but not the individual components; however, to look for consistency of effect across components, separate analyses were done for each component of the primary endpoint: cardiovascular death, stroke, MI, unstable angina, and revascularization. In these separate analyses of the events of the composite endpoint, subjects were followed until the first occurrence of the specific event, even if the event occurred after a prior non-fatal event. For analysis of cardiovascular death, a subject who died of a non-cardiovascular cause would have been censored at the time of death. Similarly, in the analysis of the secondary endpoint, non-cardiovascular death, a subject who died of a cardiovascular cause would be censored at the time of death.

The protocol did not specify control for multiplicity of testing variables that were used to assess robustness of the primary endpoint. The SAP introduced control for 3 variables. The plan for analysis was that if the primary variable was statistically significant, the following variables would be tested in sequential order, each at a 5% level of significance. Statistical testing was to stop if significance was not reached for any of these variables:

- cardiovascular death, nonfatal stroke, or nonfatal MI
- fatal or nonfatal MI
- fatal or nonfatal stroke

Prespecified subgroups for analysis of the primary endpoint:

Exploratory proportional hazards models of major cardiovascular event and of the composite endpoint including cardiovascular death, nonfatal MI, and nonfatal stroke determined whether simultaneous control for pre-specified baseline cardiovascular risk factors had any effect on the relative risk associated with randomized treatment. Only adjudicated events were used in the analyses. Each risk factor was included in a model, separately, with treatment. The likelihood ratio test was used to test for statistical significance of the interaction. Continuous variables were also tested as continuous variables. A forest plot showed HRs and CIs of treatment effects within subgroups. Potential risk factors evaluated were age, sex, age by sex,

race, smoking, body mass index (BMI), hypertension (blood pressure ≥140/90 mm Hg or on an antihypertensive medication), geographic region (US or US/Canada versus other countries), HDL-C, LDL-C , (continuous; and below versus at or above median), triglycerides (TG), hsCRP (continuous; and below versus at or above median), LDL-C and hsCRP (categories defined by medians).

An analysis was done stratified by the date of the protocol amendment changing the age inclusion criterion (20 September 2005). There was also an analysis of the subgroup of subjects included by this amendment (men 50 to <55; women 60 to <65; versus the older subjects). Additional analyses were performed for subjects whose baseline Framingham risk (Expert Panel (NCEP) 2001) was ≤10% over 10 years or >10% over 10 years, for subjects with a baseline fasting glucose <100 mg/dl or ≥100 mg/dL, and for subjects with a baseline Hb_{A1c} <6.5 % or ≥6.5%.

There were several exploratory analyses:

- Descriptive analyses explored the potential impact of missing data on the primary major cardiovascular event variable from subjects who withdrew early from the study. Baseline characteristics of withdrawn subjects were tabulated. Kaplan-Meier estimates of time to censoring without a major cardiovascular event were done to examine the pattern of censoring on the 2 treatment arms. A sensitivity simulation, assuming no treatment effect, was done to explore the influence of withdrawals on the primary efficacy analysis. In this simulation, withdrawals were assigned the same event rate as the observed placebo group for the remainder of their potential time on study.

- There was an exploratory analysis of the primary variable, based on adjudicated events, in the subsets of subjects who had or did not have metabolic syndrome at baseline. Subjects had metabolic syndrome if they had 3 or more of the following 5 factors (Grundy et al 2005): waist circumference >40 inches (101.6 cm) [men] or >35 inches (88.9 cm) [women], TG ≥150 mg/dL, HDL-C <40 mg/dL [men] or <50 mg/dL [women], diastolic blood pressure ≥85 mmHg or systolic blood pressure ≥130 mmHg; or taking prescribed medication for hypertension, fasting blood glucose ≥100 mg/dL.

Secondary endpoint analyses

Analyses of secondary endpoints were based on time to occurrence of each of the secondary endpoint events, which included:

- total mortality

- noncardiovascular mortality

- discontinuation of blinded study medication due to adverse events

- development of diabetes
- venous thromboembolic events (deep vein thrombosis or pulmonary embolism)
- bone fractures

Noncardiovascular mortality and discontinuations of study medications were pre-specified safety endpoints. Diabetes, venous thromboembolism, and bone fracture were not adjudicated endpoints.

Safety analysis

Data from all subjects who entered the screening period (Visit 1 onwards) were included in the evaluation of safety. Results from the screening period were presented separately from results after randomization. AEs starting during the screening period were reported separately. For subjects who withdrew during the screening period, demography, end of study status, and SAEs were summarized.

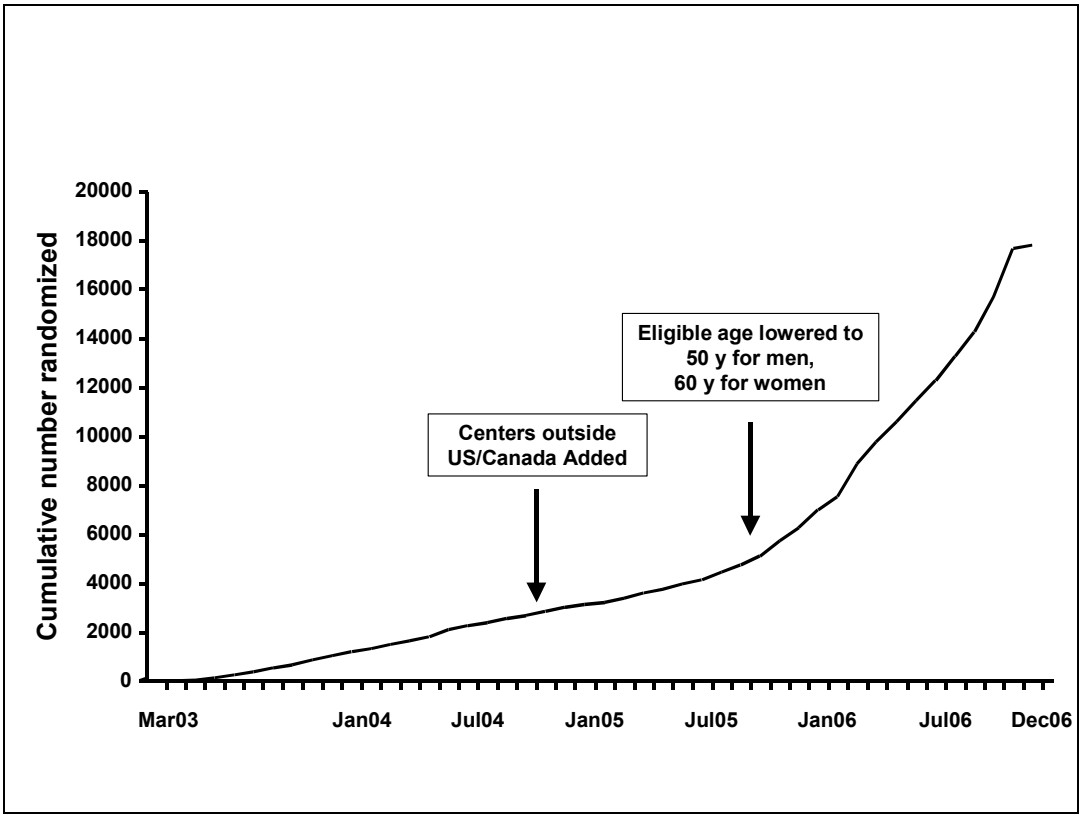
The primary population for safety analyses was the ITT population. Analyses based on treatment emergent adverse events in the safety population were also performed. Emerging SAEs were reported for 30 days following a subject's final visit. The proportions of subjects experiencing AEs were tabulated by treatment received according to the Medical Dictionary for Regulatory Activities (MedDRA). Incidence rates of AEs were also presented for key tables. Summaries of all treatment-emergent AEs, treatment-emergent SAEs, and treatment-emergent AEs leading to death are presented. Primary endpoints occurring on or before 30 March 2008 that were adjudicated to be major cardiovascular events were not captured as SAEs in this study. There was analysis of time to discontinuation of study medication (randomized treatment) due to an AE. There were summaries of subjects with ALT >3xULN on 2 occasions (at least 48 hours apart), ALT >3xULN on at least 1 occasion, CK >10xULN, or serum creatinine >100% increase from baseline. Complete blood count, ALT, creatinine, CK, and urinalyses were summarized using descriptive statistics at each scheduled measurement.

3.4 Conduct of JUPITER

3.4.1 Protocol amendments

Protocol amendments after initiation of recruitment added Canadian sites and excluded subjects with creatinine >2 mg/dL (Amendment 2, April 2003), added sites outside the US/ Canada and a telephone contact between visits (Amendment 3, October 2004) and lowered eligible age from 55 to 50 years for men and from 65 to 60 years for women, added a subgroup analysis for age at entry to evaluate the impact of this change, and excluded subjects with prior unstable angina (Amendment 4, September 2005). The impact of these changes on recruitment is summarized in Figure 4. Prespecified analyses of the primary endpoint using 1) events before and after the date of Amendment 4, and 2) including only subjects meeting the original age requirement, were conducted (Section 5.1.1).

Figure 4 Recruitment curve



3.4.2 Recruitment of subjects

From February 2003 to December 2006, 89846 subjects were screened in 26 countries (Figure 5) to randomize 17802 subjects, 8901 to each treatment group. Of those screened, 80% were ineligible (see Appendix A for criteria). The major inclusion criteria leading to screen failure were LDL-C ≥130 mg/dL (52%) and hsCRP <2 mg/L (36%) (Ridker et al 2008).

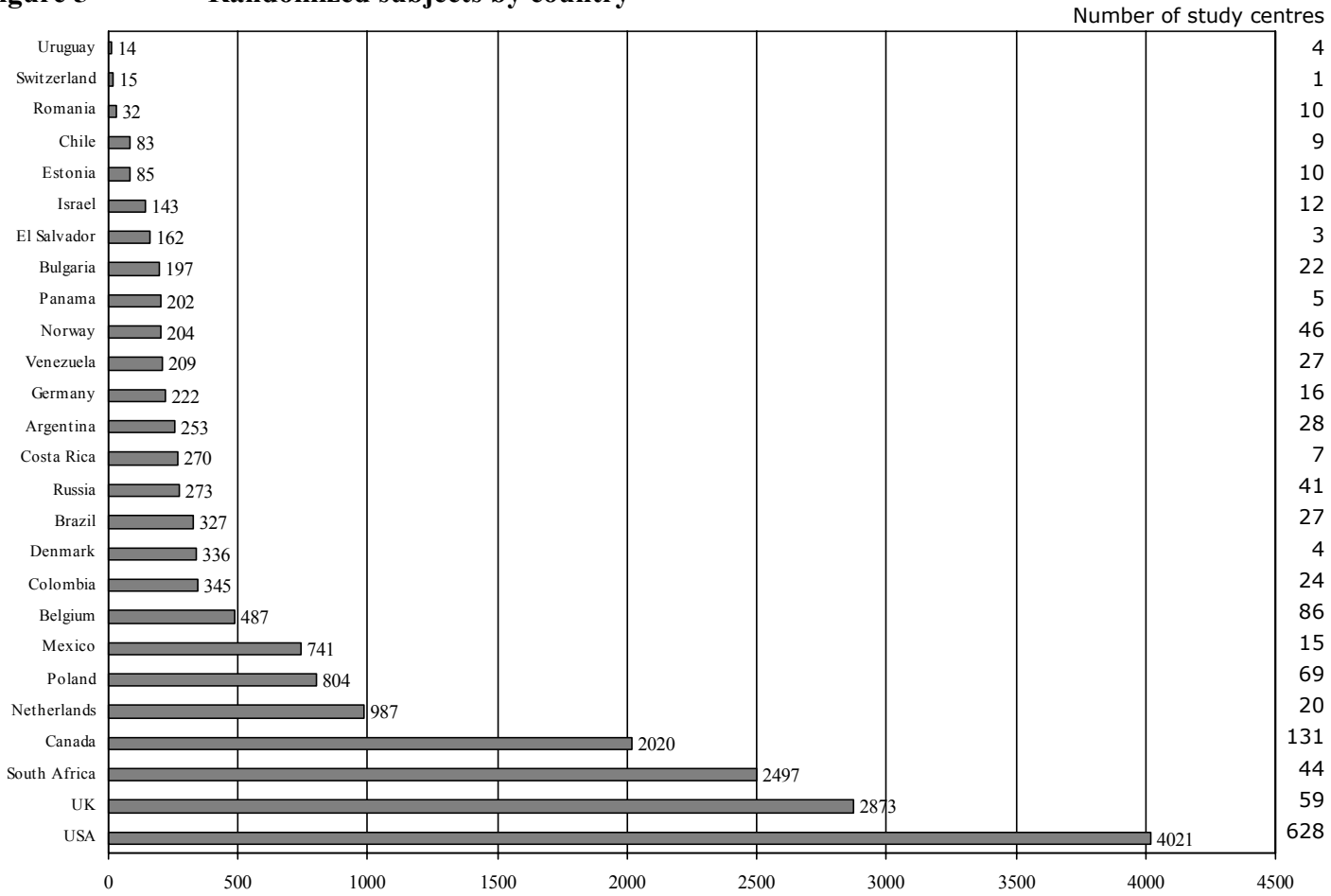
The US accounted for 22.6% of the randomized population, Canada for 11.3%, Europe for 36.6%, Latin America for 14.6%, South Africa for 14%, and Israel for 0.8%. The study was initiated in the US with sites in Canada being added in 2003. Clinical sites outside US/Canada (countries listed in Figure 5) were added in 2004.

3.4.3 IDMB recommendation for early study stop

The IDMB conducted the first protocol-specified interim analysis on 07 September 2007 and recommended the study continue as planned, but elected to schedule another meeting in 6 months. At that meeting on Saturday, 29 March 2008, 328 primary endpoints had been confirmed (63% of the planned 520 endpoints). The study was to be terminated early if both the IDMB and Steering Committee concurred that it was necessary to do so based on safety or efficacy data available at the time of their interim review. This did occur and the study was stopped on the basis of clear evidence of benefit; closeout visits began the following Monday, 31 March 2008.

Study subjects were asked to continue study medication until their final visit for collection of on-treatment laboratory measures. All efficacy data up to and including 30 March 2008 were included in the primary analysis. These primary endpoints were not reported as AEs. After 30 March 2008, primary endpoint events were reported as AEs. They were also documented and adjudicated by the same procedures as primary endpoints. Events confirmed by the Clinical Events Committee as meeting criteria for primary endpoints between 30 March 2008 and the final visit are summarized in Section 5.1.3.

Figure 5 Randomized subjects by country



4. JUPITER STUDY POPULATION

4.1.1 Baseline characteristics of the study population

Baseline characteristics are summarized (Table 7). The mean age of the study population was 66 years. The study included 6801 women and 5119 non-Caucasian subjects. Approximately 75% of the study subjects had 2 or more major cardiovascular risk factors (age, hypertension, low HDL-C, cigarette smoking, or a family history of premature CHD).

Table 7 Demographic and baseline characteristics (ITT population)

		Treatment group		
		RSV 20 mg (N=8901)	**Placebo (N=8901)**	**Overall (N=17802)**
Demographic characteristics				
Age (years) at entry	Mean (SD)	66.0 (7.64)	66.0 (7.79)	66.0 (7.71)
	Range	49 to 94	50 to 97	49 to 97
Sex, n (%) of subjects	Male	5475 (61.5)	5526 (62.1)	11001 (61.8)
	Female	3426 (38.5)	3375 (37.9)	6801 (38.2)
Race, n (%)	Caucasian	6358 (71.4)	6325 (71.1)	12683 (71.2)
	Black	1100 (12.4)	1124 (12.6)	2224 (12.5)
	Asian	147 (1.7)	136 (1.5)	283 (1.6)
	Hispanic	1121 (12.6)	1140 (12.8)	2261 (12.7)
	Other	173 (1.9)	176 (2.0)	349 (2.0)
	Not recorded	2 (0.02)	0	2 (0.01)
Baseline characteristics				
Current smoking		1400 (15.7)	1420 (16.0)	2820 (15.8)
Hypertension, n (%)		5079 (57.1)	5129 (57.6)	10208 (57.3)
Family history of CHD, n (%)		997 (11.2)	1048 (11.8)	2045 (11.5)
Low HDL, <40 mg/dL, n (%)		1980 (22.2)	2023 (22.7)	4003 (22.5)
Fasting glucose ≥100 mg/dL[a]		2755 (31.0)	2817 (31.6)	5572 (31.3)
Body mass index, kg/m^2	Mean (SD)	29.1 (6.69)	29.0 (5.67)	29.0 (6.20)
Metabolic syndrome[b]	Yes	3652 (41.0)	3725 (41.8)	7377 (41.4)
	No	5218 (58.6)	5146 (57.8)	10364 (58.2)
	Unknown	31 (0.3)	30 (0.3)	61 (0.3)
Risk categories				
Framingham risk score	Mean (SD)	11.6 (7.0)	11.6 (6.9)	11.6 (7.0)
Framingham risk category[c]	Low, n (%)	3615 (40.6)	3602 (40.5)	7217 (40.5)
	Intermediate, n (%)	4485 (50.4)	4516 (50.7)	9001 (50.6)
	High, n (%)	786 (8.8)	772 (8.7)	1558 (8.8)
	Not recorded, n (%)	15 (0.2)	11 (0.1)	26 (0.1)

Table 7 Demographic and baseline characteristics (ITT population)

		Treatment group		
		RSV 20 mg (N=8901)	Placebo (N=8901)	Overall (N=17802)
Lipoproteins and hsCRP				
Total cholesterol, mg/dL	Mean (SD)	183 (24.7)	183 (24.2)	183 (24.4)
Triglycerides, mg/dL	Median	118 (73.4)	118 (73.5)	118 (73.4)
HDL-C, mg/dL	Mean (SD)	51 (15.3)	51 (15.2)	51 (15.3)
LDL-C, mg/dL	Mean (SD)	104 (18.9)	105 (18.5)	104 (18.7)
hsCRP, mg/L[d]	Median	4.2	4.3	4.3

CHD Coronary heart disease; HDL-C High-density lipoprotein cholesterol; hsCRP High-sensitivity assay C-reactive protein; ITT Intent-to-treat; LDL-C Low-density lipoprotein cholesterol; RSV Rosuvastatin; SD Standard deviation.

[a] As stated in the Conventions section, fasting serum glucose ≥100 mg/dL is considered impaired fasting glucose or prediabetes (ADA 2008).

[b] Subjects had metabolic syndrome if they had 3 or more of the following 5 factors (Grundy et al 2005): 1) Waist circumference >40 inches (men) or >35 inches (women), 2) TG ≥150 mg/dL, 3) HDL-C <40 mg/dL (men) or <50 mg/dL (women), 4) Diastolic blood pressure ≥85 mmHg or systolic blood pressure ≥130 mmHg; or taking prescribed medication for hypertension, 5) Fasting blood glucose ≥100 mg/dL.

[c] Framingham risk category: Low <10% 10-year CHD risk; intermediate 10-20%; high >20%.

[d] hsCRP was measured at Visits 1 and 2. hsCRP at Visit 1 had to be ≥2 mg/L to qualify for the study. Baseline, as reported in table, was the average of Visits 1 and 2. hsCRP levels are not normally distributed, so are reported as median.

Baseline data were used to provide estimates of cardiovascular risk using the Framingham algorithm. The Framingham algorithm utilizes age, sex, total cholesterol and HDL-C levels, systolic blood pressure, antihypertensive medication use, and cigarette smoking as risk assessment parameters. As seen in Table 7, the overall study population had an intermediate level of risk (estimated to be an 11.6% risk of MI/CHD death over 10 years, based on Framingham criteria), but included subjects spanning the cardiovascular risk spectrum; 41% of JUPITER subjects would be categorized as low risk (10-year risk of MI/CHD death of <10%) and 59% as intermediate or high risk (10-year risk of MI/CHD death of 10 to 20%), (Expert Panel (NCEP) 2001).

4.1.2 Time on study

For the entire JUPITER study population, time on study during the randomized treatment period was similar for the rosuvastatin (mean: 796 days) and placebo groups (mean: 797 days). There were 4483 (50.4%) rosuvastatin-treated subjects and 4495 (50.5%) placebo subjects who remained in the study for over 2 years; 1459 (16.4%) rosuvastatin and 1488 (16.7%) placebo subjects remained in the study for over 3 years.

For subjects in the US, mean time on study during the randomized treatment period was 1034 days for the rosuvastatin group and 1042 days for the placebo group. There were 1471 (73.9%) rosuvastatin-treated subjects and 1501 (73.9%) placebo subjects who remained

in the study for over 2 years; 923 (46.4%) rosuvastatin and 955 (47.0%) placebo subjects remained in the study for over 3 years. As observed, subjects in the US had longer times in the study than the overall population, which is due to the fact that recruitment in countries other than the US was not started until CSP amendments in 2003 and 2004 (Section 3.4.1).

4.1.3 Subject disposition and compliance

During follow-up, 665 rosuvastatin (7.5%) and 693 placebo (7.8%) subjects discontinued active study participation. The occurrence of an AE was given as the reason for discontinuation in 143 (1.6%) rosuvastatin and 158 (1.8%) placebo subjects. Myalgia was the most frequent AE leading to discontinuation of study medication in the rosuvastatin group. Data obtained prior to withdrawal from the study were included in analyses of the ITT population. Vital status was ascertained for 97.2% of the study subjects. There were 28 rosuvastatin and 22 placebo subjects who were lost to follow-up.

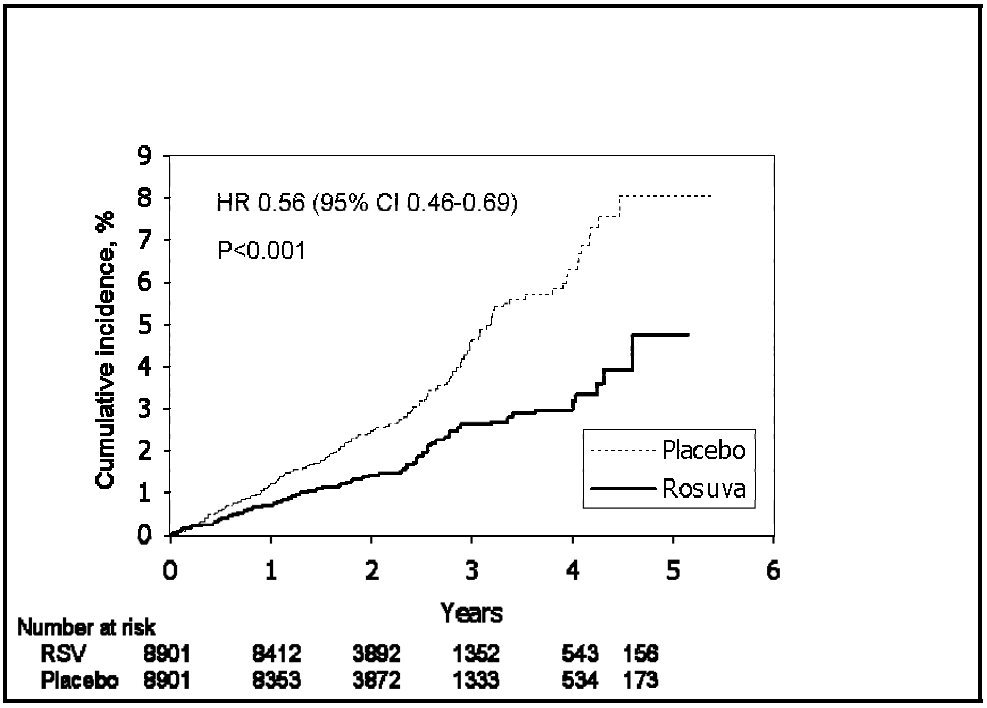
Treatment compliance was high and similar in the rosuvastatin and placebo group. Approximately 85% of subjects took >80% of prescribed study medication (based on pill counts). The percentage of randomized subjects permanently discontinuing study medication was 19.2% for the rosuvastatin group and 21.6% for the placebo group. Thus, there were no substantial treatment group differences in adherence to study medication or discontinuation of study medication. Open-label statin use was infrequent; reported by 1.6% of subjects assigned to rosuvastatin and 3.3% assigned to placebo.

5. JUPITER PRIMARY AND SECONDARY ENDPOINT RESULTS

5.1 Primary endpoint results: reduction in the risk of major cardiovascular events

The results for the primary efficacy variable of time to first occurrence of a major cardiovascular event are depicted graphically in Figure 6, rosuvastatin-treated subjects experienced a highly statistically significant 44% reduction in the risk of experiencing a primary endpoint event (HR 0.56; 95% CI 0.46-0.69; p<0.001,). There were 142 rosuvastatin and 252 placebo subjects who had a primary endpoint event (Figure 6, Table 8)

Figure 6 Kaplan-Meier plot for the primary composite endpoint



The distribution of major cardiovascular event contributing to the primary endpoint for the rosuvastatin and placebo groups is summarized (Table 8). This table, as in Figure 6, counts only 1 major cardiovascular event for each subject, since the composite primary endpoint is defined as the first occurrence of any major cardiovascular event. Each of the primary endpoint components occurred less frequently in the rosuvastatin group than the placebo group (Table 8),

Table 8 Number of events by treatment group for the composite primary endpoint (ITT population)

	Number of first events	
	RSV 20 mg (N=8901)	**Placebo (N=8901)**
First major cardiovascular event[a]	142	252
Cardiovascular death	29	37
Nonfatal Stroke	30	57
Non fatal MI	21	61
Unstable angina	15	27
Arterial revascularization	47	70

	Event rate/1000-subject years			
	RSV 20 mg	**Placebo**	**HR (95% CI)**	**p value**
First major cardiovascular event	7.6	13.6	0.56 (0.46-0.69)	<0.001

CI Confidence interval; RR Relative risk; HR Hazard ratio; ITT Intent-to-treat; RSV Rosuvastatin.

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

To look for consistency of effect across components, a separate analysis was done for each component of the primary endpoint: cardiovascular death, nonfatal stroke, nonfatal MI, unstable angina and revascularization. In these individual analyses of specific primary endpoint components, subjects were followed until the first occurrence of the specific event, even if the event occurred after a different prior nonfatal event (Table 9). In this table, if a subject had more than 1 type of major cardiovascular event (eg, 1 stroke and 1 MI), they were counted once for each event, in contrast to events presented in Table 8.

Table 9 Number of first events by treatment group for each individual cardiovascular endpoints (ITT population)

	Number (%) of subjects with event			
	RSV 20 mg (N=8901) n (%)	Placebo (N=8901) n (%)	HR (95% CI)	P value
Cardiovascular death	35 (0.4)	44 (0.5)	0.80 (0.51-1.24)	0.315
Nonfatal stroke	30 (0.3)	58 (0.7)	0.52 (0.33-0.80)	0.003
Nonfatal myocardial infarction	22 (0.2)	62 (0.7)	0.35 (0.22-0.58)	<0.001
Unstable angina	16 (0.2)	27 (0.3)	0.59 (0.32-1.10)	0.093
Arterial revascularization	71 (0.8)	131 (1.5)	0.54 (0.41-0.72)	<0.001

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

Thus, as seen in Table 8 and Table 9, each of the individual components contributed to the overall result of the composite endpoint in terms of the reduction in major cardiovascular event with rosuvastatin treatment.

As seen in Figure 6, there was early separation of the primary endpoint event curves. A post-hoc analysis showed that the reduction in major cardiovascular event was statistically significant within 6 months of randomization to rosuvastatin (HR 0.62; 95% CI 0.40-0.96; p=0.029). This significant treatment difference continued throughout the study (Table 10). The consistency of hazard ratios observed for the different time-periods after randomization provides reassurance that early stopping of the study did not lead to an overestimate of the effect size.

Table 10 Number of primary endpoint events, percentage of subjects with an event, and hazard ratio (95% CI) for the primary endpoint by time since randomization

Time since randomization	RSV (N=8901) n (%)	Placebo (N=8901) n (%)	HR (95% CI)	p value
6 months	32 (0.4)	52 (0.6)	0.62 (0.40-0.96)	0.029
12 months	63 (0.7)	103 (1.2)	0.61 (0.45-0.84)	0.002
18 months	93 (1.0)	147 (1.7)	0.63 (0.49-0.82)	<0.001
2 years	109 (1.2)	186 (2.1)	0.58 (0.46-0.74)	<0.001
2.5 years	120 (1.3)	204 (2.3)	0.59 (0.47-0.73)	<0.001
3 years	133 (1.5)	228 (2.6)	0.58 (0.47-0.72)	<0.001

CI Confidence interval; HR Hazard ratio; RSV Rosuvastatin.

5.1.1 Pre-specified subgroup analyses in support of primary efficacy endpoint

To support the primary analysis and provide evidence of clinical robustness, a number of analyses of subpopulations were pre-specified, and are summarized in Table 11.

The treatment effect of rosuvastatin was similar in older and younger subjects, men and women, those who had or did not have hypertension, for subjects who had or did not have a low HDL-C level, for smokers compared to nonsmokers, and for study subjects who had or did not have a family history of premature CHD. There was evidence of a treatment benefit with rosuvastatin irrespective of whether any of these individual risk markers was present.

Table 11 Analyses of the primary efficacy endpoint by pre-specified subgroups

Baseline characteristic		N of events		HR (95% CI)	p value for interaction
		RSV 20 mg (N=8901) n (rate)[a]	Placebo (N=8901) n (rate)[a]		
Age	≤65 years at baseline	42 (4.9)	90 (10.3)	0.48 (0.33-0.69)	0.338
	>65 years at baseline	100 (9.9)	162 (16.6)	0.60 (0.47-0.77)	
Sex	Female	39 (5.6)	70 (10.4)	0.54 (0.37-0.80)	0.817
	Male	103 (8.8)	182 (15.5)	0.57 (0.45-0.73)	
Race	Caucasian	111 (7.8)	202 (14.4)	0.54 (0.43-0.69)	0.561
	Non-Caucasian	31 (7.0)	50 (11.1)	0.63 (0.40-0.99)	
Region	US	58 (10.7)	94 (16.9)	0.63 (0.45-0.87)	0.395
	Countries other than US	84 (6.4)	158 (12.2)	0.52 (0.40-0.68)	
	US or Canada	81 (9.7)	137 (16.3)	0.60 (0.45-0.78)	0.536
	Countries other than US/Canada	61 (6.0)	115 (11.4)	0.52 (0.38-0.71)	
Baseline hsCRP	below median (4.2 mg/L)	53 (5.6)	124 (13.5)	0.42 (0.30-0.58)	0.015
	above median (4.2 mg/L)	89 (9.7)	128 (13.7)	0.71 (0.54-0.92)	
LDL-C	≤100 mg/dL	55 (8.7)	86 (13.5)	0.65 (0.46-0.91)	0.304
	>100mg/dL	87 (7.1)	166 (13.7)	0.52 (0.40-0.67)	
Hypertension	No	53 (6.6)	86 (10.8)	0.61 (0.43-0.86)	0.559
	Yes	89 (8.5)	166 (15.8)	0.54 (0.42-0.70)	
HDL-C	≥40 mg/dL	110 (7.7)	187 (13.1)	0.58 (0.46-0.74)	0.512
	<40 mg/dL	32 (7.6)	65 (15.3)	0.50 (0.33-0.76)	
Cigarette Smoking	No	110 (6.9)	190 (12.1)	0.58 (0.46-0.73)	0.644
	Yes	32 (11.7)	62 (22.6)	0.51 (0.34-0.79)	
Family history of CHD	No	124 (7.7)	204 (12.7)	0.61 (0.48-0.76)	0.077
	Yes	17 (7.3)	48 (20.6)	0.35 (0.20-0.61)	
Fasting glucose	<100 mg/dL	87 (6.9)	167 (13.3)	0.52 (0.40-0.67)	0.257
	≥100 mg/dL	55 (9.4)	84 (14.2)	0.66 (0.47-0.93)	

Table 11 Analyses of the primary efficacy endpoint by pre-specified subgroups

Baseline characteristic		N of events		HR (95% CI)	p value for interaction
		RSV 20 mg (N=8901) n (rate)[a]	Placebo (N=8901) n (rate)[a]		
BMI	≤30	94 (8.2)	179 (15.9)	0.52 (0.04-0.67)	0.31
	>30	47 (6.6)	73 (10.2)	0.65 (0.45-0.94)	
Metabolic syndrome	No	75 (6.9)	149 (14.0)	0.50 (0.38-0.66)	0.167
	Yes	67 (8.7)	102 (13.1)	0.67 (0.49-0.91)	

BMI Body mass index; CHD Coronary heart disease; CI Confidence interval; HDL-C High-density lipoprotein-cholesterol; hsCRP High sensitivity C-reactive protein; HR Hazard ratio; LDL-C Low-density lipoprotein-cholesterol; RSV Rosuvastatin; US United States.
Note: Age to enter study was required to be ≥50 years for men and ≥60 years for women.
[a] Number of events and event rate/1000-person years. The denominator is the time at risk on study in days, summed across the relevant subjects and divided by 365.25. The numerator is 1000 x number of events.

Additional prespecified examinations of the primary endpoint evaluated events before (HR: 0.60; 95% CI 0.45-0.78) and after (HR: 0.52; 95% CI 0.38-0.71) the date of Amendment 4, which expanded recruitment outside the US/Canada, and showed no significant interaction (p=0.536). An additional analysis included only subjects meeting the original age requirement of >55 years for men and >65 years for women (HR: 0.57; 95% CI 0.46-0.70).

Primary efficacy endpoint by Framingham risk strata

Table 12 summarizes results of analyses of subjects by Framingham risk strata. Both lower risk and higher risk Framingham subsets of the JUPITER study population derived similar proportional risk reduction from rosuvastatin. As expected, the magnitude of the absolute reduction in rate of major cardiovascular event was greater among subjects with a higher baseline level of risk (8.8 per 1000 person-years for >10% Framingham risk versus 3.2 for ≤10%, Section 5.4.1, Table 19).

Table 12 Analyses of the primary efficacy endpoint by Framingham risk strata

	RSV 20 mg			Placebo				
	n of subjects	n of MCE	rate[c]	n of subjects	n of MCE	rate[c]	HR (95% CI)	p value for interaction
Framingham risk[a,b]								
≤10%	4440	38	4.2	4434	67	7.4	0.57 (0.38-0.85)	0.899
>10%	4446	103	10.8	4456	185	19.6	0.55 (0.43-0.70)	

CI Confidence interval; HR Hazard ratio; MCE Major cardiovascular events; RSV Rosuvastatin.
[a] Framingham risk category: Low <10% 10-year CHD risk; intermediate 10-20%; high >20.
[b] The SAP specified that the HR and 95% CI were to be calculated for categories ≤10 and >10 only; the latter category includes high-risk and most intermediate-risk subjects.
[c] rates are per 1000 person-years. The denominator is the time at risk on study in days, summed across the relevant subjects and divided by 365.25 and the numerator is 1000 x number of events.

Taken together, the data presented in Table 11, and Table 12 indicate the following:

- there was no specific risk factor(s) required for subjects to benefit from rosuvastatin treatment and
- the magnitude of the absolute cardiovascular benefit derived from rosuvastatin treatment increased with increasing levels of cardiovascular risk, as assessed using the Framingham global risk assessment.

5.1.2 Other cardiovascular efficacy endpoints analyzed in support or primary efficacy endpoint

Analyses of several other pre-specified and exploratory cardiovascular endpoints were conducted to further support the robustness of benefit observed with rosuvastatin for the primary study endpoint (Table 13).

As observed in Table 13, there was a statistically significant treatment benefit with rosuvastatin treatment for each of the 3 prespecified cardiovascular composite endpoints (cardiovascular death/MI/stroke, fatal or nonfatal MI, fatal or nonfatal stroke). Rosuvastatin reduced the clinical endpoint composite of cardiovascular death, stroke, or MI by 48%. In addition, there was a 48% reduction in risk of having a fatal or nonfatal stroke and a 54% reduction in the risk of having a fatal of nonfatal MI. Finally, the results remained highly statistically significant ($p<0.001$) when total mortality was substituted for cardiovascular death in composite endpoints of death or major cardiovascular event and death, stroke, or MI, an analysis requested by the FDA. Based on this analysis, there were 135 fewer patients who died or experienced a nonfatal major cardiovascular event in the rosuvastatin compared to the placebo group.

Table 13 Other cardiovascular efficacy endpoints (ITT population)

	Number of events (% with an event)			
	RSV 20 mg	Placebo	HR (95% CI)	p value
Pre-specified endpoints				
CV death/MI/stroke	83 (0.9)	158 (1.8)	0.52 (0.40-0.68)	<0.001
Fatal or nonfatal MI	31 (0.3)	68 (0.8)	0.46 (0.30-0.70)	<0.001
Fatal or nonfatal stroke	33 (0.4)	64 (0.7)	0.52 (0.34-0.79)	0.002
Post-hoc analyses				
Primary endpoint + all-cause mortality	265 (3.0)	400 (4.5)	0.66 (0.56-0.77)	<0.001
Death/MI/stroke	208 (2.3)	312 (3.5)	0.66 (0.56-0.79)	<0.001

CV Cardiovascular; CI Confidence interval; HR Hazard ratio; ITT Intent-to-treat; MI Myocardial infarction; RSV Rosuvastatin.

These results support the positive findings of the primary endpoint analysis presented in Section 5.1.

5.1.3 Major cardiovascular events reported between 31 March 2008 and final visit

The ITT analyses discussed in the previous sections included all primary events from the date of each subject's randomization through 30 March 2008.

Clinical events occurring between 31 March 2008 and each subject's final visit were reported as SAEs. They were also documented and adjudicated by the same procedures as primary endpoints. Events confirmed by the Clinical Events Committee as meeting criteria for primary endpoints after 30 March 2008 and before the final visit are summarized here. Among subjects randomized to rosuvastatin, 2 events were reported (1 cardiovascular death, 1 revascularization). Among subjects assigned to placebo, 12 events were reported (2 MIs, 4 strokes, 1 unstable angina, 5 revascularizations). Of these events, 3 were identified after the study blind had been broken; however, the Clinical Events Committee classified these events blinded to treatment assignment.

A post-hoc analysis of the primary endpoint including these major cardiovascular events occurring after 30 March and before the subject's final visit supported the primary analysis (HR: 0.55; 95% CI 0.45-0.68; p<0.001).

5.1.4 Cardiovascular events reported after final visits

These events were spontaneously reported for 30 days after subjects' final visits. They were not classified as endpoints by clinic physicians nor adjudicated by the Clinical Events Committee. They included 9 apparent cardiovascular events among individuals assigned to rosuvastatin while on-study, and 6 among those assigned to placebo: arterial stent insertion (placebo 1), cardiac arrest (placebo 1), cardiac death (rosuvastatin 2, placebo 1), cerebrovascular accident (rosuvastatin 2, placebo 1), myocardial infarction (rosuvastatin 1), sudden cardiac death (rosuvastatin 1), and sudden death (rosuvastatin 3, placebo 2).

Assessment of these events is limited by the spontaneous nature of their reporting and lack of confirmation by either clinic investigator or central adjudicator.

5.2 Secondary endpoint results

The secondary endpoint results of the JUPITER study are summarized in Table 14.

Table 14 Secondary endpoint results

	Rosuvastatin (N=8901)	Placebo (N=8901)		
	n (%)	n (%)	HR (95% CI)	p value
Total mortality	198 (2.2)	247 (2.8)	0.80 (0.67-0.97)	0.021
Noncardiovascular mortality	105 (1.2)	126 (1.4)	0.84 (0.65-1.08)	0.172
Discontinuation of study medication due to AEs	495 (5.6)	486 (5.5)	1.02 (0.90-1.06)	0.758
Investigator-reported diabetes	251 (2.8)	205 (2.3)	1.27 (1.05-1.53)	0.015
Venous thromboembolism	26 (0.3)	46 (0.5)	0.57 (0.35-0.91)	0.018
Bone fracture	226 (2.5)	214 (2.4)	1.06 (0.88-1.28)	0.548

Results for total mortality, venous thromboembolism, and bone fracture will be discussed in this section. Results for noncardiovascular mortality, discontinuation of study medications due to AEs, and investigator-reported diabetes will be discussed in the safety results section (Section 6). The results for investigator-reported diabetes as well as fasting glucose and Hb_{A1c} levels (which were measured in a central laboratory in the JUPITER study) are discussed in the safety section (Section 6.9) since there were more study subjects in the rosuvastatin group than the placebo group with investigator-reported diabetes.

5.2.1 Total mortality

Overall, there were 445 total deaths, 198 (2.2%) in rosuvastatin-treated subjects versus 247 (2.8%) in placebo subjects (Table 15). Death from any cause was reduced by 20% in subjects treated with rosuvastatin compared to placebo (HR 0.80, 95% CI 0.67-0.97, p=0.021; Figure 7).

Figure 7 Kaplan-Meier plot of time to death from any cause

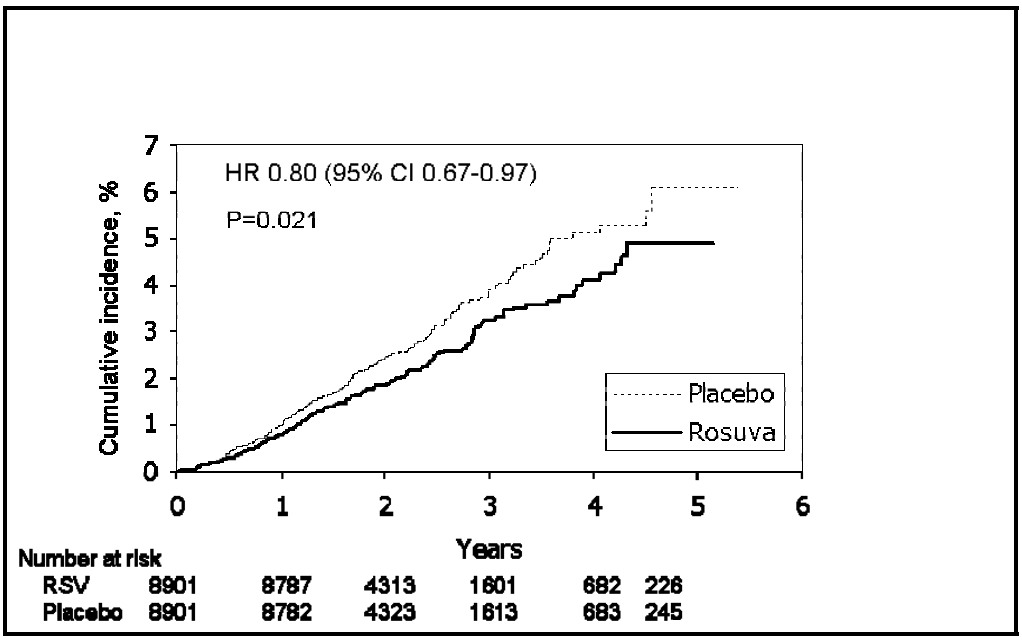


Table 15 Number of events by treatment group time to death from any cause (total mortality)—analysis including external vital status data (ITT population)

	Number of events (% of subjects having an event)						
	RSV 20 mg (N=8901)		Placebo (N=8901)				
	n	(%)	n	(%)	HR	95% CI	p value
Death from any cause	198	(2.2)	247	(2.8)	0.80	0.67-0.97	0.021

CI Confidence interval; HR Hazard ratio; RSV Rosuvastatin.
Note: Includes deaths on or before the 30 March 2008 efficacy cut-off date.

Results for venous thromboembolism and bone fracture are summarized in Table 16. The risk of venous thromboembolism was reduced 43% among subjects assigned to rosuvastatin (p=0.018). Bone fracture occurred with similar frequency in the 2 treatment groups.

Table 16 Venous thromboembolism and bone fracture (ITT population)

	Number of events (% with an event)			
	RSV 20 mg (N=8901)	Placebo (N=8901)	HR (95% CI)	p value
Venous thromboembolism	26 (0.3)	46 (0.5)	0.57 (0.35-0.91)	0.018
Bone fractures	226 (2.5)	214 (2.4)	1.06 (0.88-1.28)	0.548

ITT Intent-to-treat; RSV Rosuvastatin.

5.3 Lipoprotein and hsCRP laboratory results

Values for lipoproteins and hsCRP are summarized in Table 17.

Table 17 Summary of key lipoproteins and hsCRP values throughout the study (ITT population)

	Baseline		After 12 months		At Final visit (LOCF)	
	RSV 20 mg	**Placebo**	**RSV 20 mg**	**Placebo**	**RSV 20 mg**	**Placebo**
TC (mg/dL)						
N	8899	8901	7962	7928	8157	8151
Mean (SD)	183.23 (24.71)	183.39 (24.16)	139.15 (33.31)	188.85 (30.02)	144.02 (35.87)	187.18 (31.24)
Median	186.00	185.00	133.00	188.00	137.00	188.00
HDL-C (mg/dL)						
N	8899	8901	7960	7927	8157	8151
Mean (SD)	51.36 (15.34)	51.26 (15.20)	54.66 (16.33)	52.22 (15.60)	55.36 (17.29)	53.26 (16.50)
Median	49.00	49.00	52.00	50.00	52.00	50.00
LDL-C (mg/dL)						
N	8899	8899	7949	7909	8154	8150
Mean (SD)	104.34 (18.91)	104.57 (18.51)	61.64 (27.57)	109.10 (25.02)	65.72 (30.39)	107.15 (25.99)
Median	108.00	108.00	55.00	110.00	57.00	108.00
TG (mg/dL)						
N	8899	8901	7962	7928	8157	8151
Mean (SD)	137.76 (73.42)	137.80 (73.46)	114.91 (64.90)	138.39 (75.71)	115.25 (68.80)	134.39 (82.07)
Median	118.00	118.0	99.00	119.00	99.00	115.00
hsCRP (mg/L)[a]						
N	8901	8901	7950	7923	8613	8630
Mean (SD)	6.629 (8.588)	6.923 (9.169)	4.535 (9.857)	6.010 (10.259)	5.213 (10.720)	6.755 (12.051)
Median	4.200	4.300	2.200	3.500	2.600	3.700

HDL-C High-density lipoprotein cholesterol; hsCRP High sensitivity C-reactive protein; ITT Intent-to-treat; LDL-C Low-density lipoprotein cholesterol; LOCF Last observation carried forward; SD Standard deviation; TC Total cholesterol; TG Triglycerides.

[a] hsCRP was measured at Visits 1 and 2. hsCRP at Visit 1 had to be ≥2 mg/L to qualify for the study. Baseline, as reported in table, was the average of Visits 1 and 2.

Changes (least squares mean) in lipoproteins and hsCRP are summarized in Table 18. At year 1, mean LDL-C was 45% lower and median LDL-C was 51% lower among subjects assigned to rosuvastatin treatment compared with placebo. At year 1, hsCRP levels were 47% lower among subjects assigned to rosuvastatin and 20% lower among subjects assigned to placebo. Treatment group differences were maintained throughout the duration of the study ($p<0.001$ at each timepoint).

Table 18 Summary of percent changes in key lipoproteins and hsCRP after 1 year of study treatment and at final visit (ITT population)

	After 12 months		At Final visit (LOCF)	
	RSV 20 mg	**Placebo**	**RSV 20 mg**	**Placebo**
TC				
N	7961	7928	8155	8151
LsMean (SE)	-23.57 (0.177)	3.30 (0.177)	-20.93 (0.190)	2.44 (0.190)
p value	<0.001		<0.001	
Difference (95% CI)	-26.87 (-27.36- -26.38)		-23.37 (-23.90- -22.84)	
HDL-C				
N	7959	7927	8155	8151
LsMean (SE)	7.61 (0.199)	2.98 (0.199)	8.97 (0.211)	4.97 (0.211)
p value	<0.001		<0.001	
Difference (95% CI)	4.63 (4.08-5.18)		4.00 (3.42-4.59)	
LDL-C				
N	7948	7907	8152	8148
LsMean (SE)	-39.93 (0.292)	5.36 (0.293)	-35.98 (0.310)	3.61 (0.310)
p value	<0.001		<0.001	
Difference (95% CI)	-45.29 (-46.10- -44.48)		-39.59 (-40.45- -38.72)	
TG				
N	7961	7928	8155	8151
LsMean (SE)	-9.43 (0.432)	6.80 (0.433)	-8.87 (0.494)	4.92 (0.494)
p value	<0.001		<0.001	
Difference (95% CI)	-16.23 (-17.43- -15.04)		-13.78 (-15.15- -12.41)	
hsCRP[a]				
N	7950	7923	8613	8630
LsMean (SE)	-12.94 (2.258)	15.65 (2.262)	1.49 (2.432)	27.68 (2.430)
p value[b]	<0.001		<0.001	
Difference (95% CI)	-28.59 (-34.86- -22.33)		-26.20 (-32.94- -19.46)	
Median % change from baseline (SD)	-46.86 (199.46)	-20.00 (203.18)	-40.91 (220.11)	-13.64 (231.17)

CI Confidence interval; hsCRP High sensitivity C-reactive protein; HDL-C High-density lipoprotein cholesterol; ITT Intent-to-treat; LDL-C Low-density lipoprotein cholesterol; LOCF Last observation carried forward; LsMean Least squares mean; RSV Rosuvastatin; SD Standard deviation; SE Standard Error; TC Total cholesterol; TG Triglycerides.

[a] hsCRP was measured at Visits 1 and 2. hsCRP at Visit 1 had to be ≥2 mg/L to qualify for the study. Baseline, as reported in table, was the average of Visits 1 and 2.

[b] p value for hsCRP from ANOVA.

5.4 Conclusions: efficacy of rosuvastatin for prevention of major cardiovascular events

The principal efficacy findings in the JUPITER study were the 44% reduction in the risk of major cardiovascular event (cardiovascular death, nonfatal stroke, nonfatal MI, unstable angina, or arterial revascularization; p<0.001) and the 20% reduction in total mortality (p=0.021) in the rosuvastatin treatment group compared to placebo. Rosuvastatin-treated study subjects had a 48% reduction in the combined endpoint of cardiovascular death, stroke, or MI (p<0.001), a 48% reduction in fatal or nonfatal stroke (p=0.002), and a 54% reduction in fatal or nonfatal myocardial infarction (p<0.001).

5.4.1 Greater absolute risk reduction was seen in JUPITER subjects with higher absolute risk

There was evidence of a treatment benefit across a wide range of population subsets within the JUPITER study population. As expected, the greatest absolute reduction in cardiovascular risk was observed among study subjects at higher absolute risk based on assessment of conventional cardiovascular risk factors. Table 19 summarizes the relative and absolute risk reductions according to the presence or absence of the major coronary heart disease factors in the ATP III guidelines and among JUPITER study subjects who had an estimated 10-year coronary heart disease risk that was ≤10% or >10%.

Table 19 Relative and absolute risk reduction for primary endpoint in the JUPITER population by ATP III major coronary heart disease risk factors and Framingham risk at entry

	Rosuvastatin Event Rate[a]	Placebo Event Rate[a]	Relative risk reduction	Absolute risk reduction[a]
Age				
≤65 years	4.9	10.3	52%	5.4
>65 years	9.9	16.6	40%	6.7
Hypertension				
No	6.6	10.8	39%	4.2
Yes	8.5	15.8	46%	7.3
Low HDL-C (<40 mg/dL)				
No	7.7	13.1	42%	5.4
Yes	7.6	15.3	50%	7.7
Cigarette Smoking				
No	6.9	12.1	42%	5.2
Yes	11.7	22.6	49%	10.9
Family history of CHD				
No	7.7	12.7	39%	5.0
Yes	7.3	20.6	65%	13.3

Table 19 Relative and absolute risk reduction for primary endpoint in the JUPITER population by ATP III major coronary heart disease risk factors and Framingham risk at entry

	Rosuvastatin Event Rate[a]	Placebo Event Rate[a]	Relative risk reduction	Absolute risk reduction[a]
Framingham Risk				
Low, ≤10%	4.2	7.4	43%	3.2
Intermediate-High >10%	10.8	19.6	45%	8.8

CHD Coronary heart disease; HDL-C High-density lipoprotein cholesterol
[a] Event rates and absolute risk reduction per 1000 subject-years.

Results obtained in the JUPITER study are robust and consistent with data from other statin outcome studies. Statistically significant risk reductions with rosuvastatin were seen regardless of baseline characteristics (Table 11). Although relative risk reductions were similar in all subgroups, as expected, greater absolute risk reductions were seen in subjects at higher absolute cardiovascular risk.

6. JUPITER SAFETY RESULTS

6.1 Safety background

The purpose of the safety evaluation in JUPITER was to assess the long-term safety and tolerability of treatment with rosuvastatin at a dose of 20 mg daily. The 20 mg dose was maintained for the entire duration of the JUPITER study with no up or down titration.

Primary endpoint events collected on or before the 30 March 2008 efficacy cut-off date were not reported as AEs. After this date, primary endpoint events were reported as AEs and as such, were collected until 30 days after stopping study medication, and are included in the analyses of safety data.

All safety analyses are reported for the ITT population (all randomized subjects) since this is the largest population; exposure is reported for the safety population (all randomized subjects who started treatment). Analyses of treatment emergent adverse events were also performed in the safety population showed similar results and are not reported in this document.

6.2 Exposure

An overview of exposure for the Safety population, in terms of actual days on treatment since randomization is presented in Table 20.

Table 20 Overview of exposure during randomized treatment period (Safety population)

Exposure by duration of treatment (days)[a]	RSV 20 mg (N=8864)	Placebo (N=8869)
Mean (SD)	700.5 (358.19)	689.5 (352.00)
Median	657.0	648.0

Note: The safety population was reported by actual treatment received.
SD Standard deviation.
[a] Duration of treatment calculated as number of days from the day of randomization to date of last dose on the completion/withdrawal page of case report form.

The total duration of exposure to rosuvastatin 20 mg was approximately 17000 subject years. The mean duration of exposure to rosuvastatin was approximately 11 days longer than for subjects assigned to placebo, representing approximately 270 more subject-years of exposure to rosuvastatin compared with placebo (Table 20). The size and diversity of the study population and duration of exposure was sufficient to evaluate the safety of the 20 mg rosuvastatin dose.

6.3 Adverse events

Categories of treatment emergent AEs are summarized by treatment group for the entire JUPITER study population in Table 21. Numbers of subjects with treatment-emergent AEs, or SAEs were similar in the 2 treatment groups. AEs leading to death were less frequent among rosuvastatin-treated subjects (n=141, 1.6%) than placebo subjects (n=179, 2.0%) (see Section 6.4.1).

Table 21 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)	RSV 20 mg (N=8901) n (%)	Placebo (N=8901) n (%)
Any AE	6968 (78.3)	6907 (77.6)
Serious AE (SAE)	1341 (15.1)	1372 (15.4)
AE leading to death	141 (1.6)	179 (2.0)

AE Adverse event; ITT Intent-to-treat; RSV Rosuvastatin; SAE Serious adverse event.

For subjects from the US only, categories of treatment-emergent AEs are summarized by treatment group in Table 22. As with the entire JUPITER population, numbers of subjects with treatment-emergent AEs and SAEs were similar in the 2 treatment groups. AEs leading to death were less frequent among rosuvastatin-treated subjects (n=29, 1.5%) than placebo subjects (n=49, 2.4%).

Table 22 US subjects only—Number (%)who had a treatment-emergent adverse event in any category during the randomized treatment period (ITT population)

Category of adverse event (AE)	RSV 20 mg (N=1990) n (%)	Placebo (N=2031) n (%)
Any treatment-emergent AE	1704 (85.6)	1725 (84.9)
Serious AE (SAE)	417 (21.0)	411 (20.2)
AE leading to death	29 (1.5)	49 (2.4)

AE Adverse event; ITT Intent-to-treat; RSV Rosuvastatin; SAE Serious adverse event.

For the entire JUPITER study population, treatment-emergent AEs during randomized treatment, summarized by MedDRA System Organ Class (SOC), are shown in Table 23.

Table 23 Treatment-emergent adverse events, summarized by MedDRA system organ class, during the randomized treatment phase (ITT population)

System organ class	RSV 20 mg (N=8901) n	(%)	Placebo (N=8901) n	(%)
Infections and infestations	3873	(43.5)	3941	(44.3)
Musculoskeletal and connective tissue disorders	3293	(37.0)	3037	(34.1)
Gastrointestinal disorders	2231	(25.1)	2209	(24.8)
Respiratory, thoracic and mediastinal disorders	1445	(16.2)	1429	(16.1)
Nervous system disorders	1424	(16.0)	1492	(16.8)
Injury, poisoning, and procedural complications	1342	(15.1)	1255	(14.1)
General disorders and administration site conditions	1238	(13.9)	1228	(13.8)
Skin and subcutaneous tissue disorders	1106	(12.4)	1145	(12.9)
Vascular disorders	937	(10.5)	1095	(12.3)
Investigations	865	(9.7)	810	(9.1)
Renal and urinary disorders	812	(9.1)	817	(9.2)
Metabolism and nutrition disorders	684	(7.7)	752	(8.4)
Eye disorders	631	(7.1)	665	(7.5)
Psychiatric disorders	625	(7.0)	646	(7.3)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	608	(6.8)	676	(7.6)
Reproductive system and breast disorders	551	(6.2)	602	(6.8)
Cardiac disorders	543	(6.1)	636	(7.1)
Ear and labyrinth disorders	438	(4.9)	452	(5.1)
Blood and lymphatic system disorders	295	(3.3)	292	(3.3)
Hepatobiliary disorders	189	(2.1)	187	(2.1)
Immune system disorders	142	(1.6)	144	(1.6)

Table 23 Treatment-emergent adverse events, summarized by MedDRA system organ class, during the randomized treatment phase (ITT population)

System organ class	RSV 20 mg (N=8901) n	(%)	Placebo (N=8901) n	(%)
Endocrine disorders	100	(1.1)	101	(1.1)
Congenital, familial, and genetic disorders	42	(0.5)	28	(0.3)
Surgical and medical procedures	5	(0.1)	3	(0)
Social circumstances	4	(0)	14	(0.2)

Note: Number of subjects with AEs based on randomized treatment. Subjects who had more than 1 AE within the same system organ class were counted once in that system organ class total.
AE Adverse event; ITT Intent-to-Treat; MedDRA Medical Dictionary for Regulatory Activities; RSV Rosuvastatin.

The most common treatment-emergent AEs during randomized treatment, summarized by MedDRA Preferred Term (PT), are shown in Table 24 (cut-off at a frequency of ≥5% in the rosuvastatin group).

Table 24 Most common treatment-emergent adverse events (≥5%), summarized by MedDRA preferred term, sorted by decreasing order of frequency in the rosuvastatin group during the randomized treatment phase (ITT population)

Preferred term	RSV 20 mg (N=8901) n	(%)	Placebo (N=8901) n	(%)
Most common treatment-emergent AE				
Urinary tract infection	772	(8.7)	764	(8.6)
Nasopharyngitis	679	(7.6)	642	(7.2)
Back pain	679	(7.6)	616	(6.9)
Myalgia	678	(7.6)	590	(6.6)
Bronchitis	643	(7.2)	631	(7.1)
Upper respiratory tract infection	630	(7.1)	676	(7.6)
Hypertension	624	(7.0)	695	(7.8)
Arthritis	516	(5.8)	495	(5.6)
Cough	475	(5.3)	472	(5.3)
Bone pain	449	(5.0)	451	(5.1)

Note: Number of subjects with AEs based on randomized treatment. Subjects who had more than 1 AE assigned to the same MedDRA preferred term were counted once for that event.
AE Adverse event; CSR Clinical study report; ITT Intent-to-Treat; MedDRA Medical Dictionary for Regulatory Activities; RSV Rosuvastatin.

Myalgia was the only treatment-emergent AE that was reported in ≥1% more subjects in the rosuvastatin group than in the placebo group.

Key observations regarding subjects with treatment-emergent AEs in the JUPITER study were as follows:

- The overall AE profile associated with each treatment group by SOC was similar (Table 23).
- By SOC, the most commonly reported treatment-emergent AEs were in Infections and infestations (rosuvastatin 43.5%, placebo 44.3%), with similar frequencies for the 2 treatment groups, and Musculoskeletal disorders (rosuvastatin 37.0%, placebo 34.1%); the increase in the rosuvastatin group was predominantly due to differences in back pain and myalgia (Table 23).
- There were no treatment group differences in the frequency of treatment-emergent AEs in hepatobiliary or renal and urinary disorders organ systems (Table 23).
- By MedDRA PT, the most common treatment-emergent AEs that were more frequently reported in rosuvastatin patients versus placebo were: urinary tract infection (8.7% versus 8.6%), followed by nasopharyngitis (7.6% versus 7.2%), back pain (7.6% versus 6.9%), myalgia (7.6% versus 6.6%), bronchitis (7.2% versus 7.1%), and arthritis (5.8% versus 5.6%) (Table 24).

6.4 Deaths and serious adverse events

6.4.1 Deaths

The Clinical Events Committee classified deaths as cardiovascular or noncardiovascular, but organ-specific causality of noncardiovascular deaths was not adjudicated. Treatment-emergent AEs leading to death were reported for 141 subjects assigned to rosuvastatin treatment (1.6%) and 179 assigned to placebo (2.0%) (Table 25). Note that cardiovascular deaths were classified as endpoints, not AEs, if the occurrence of the event was on or before 30 March 2008, and therefore these deaths are not included in this table.

Table 25 Number (%) of subjects with treatment-emergent adverse events leading to death, by System Organ Class, sorted by decreasing order of frequency in the rosuvastatin group during the randomized treatment phase (ITT population)

System organ class	RSV 20 mg (N=8901)		Placebo (N=8901)	
	n	(%)	n	(%)
Any death	**141**	**(1.6)**	**179**	**(2.0)**
Neoplasms benign, malignant and unspecified (includes cysts and polyps)	40	(0.4)	65	(0.7)
General disorders and administration site conditions	39	(0.4)	40	(0.4)
Infections and infestations	22	(0.2)	24	(0.3)
Respiratory, thoracic, and mediastinal disorders	14	(0.2)	20	(0.2)
Gastrointestinal disorders	13	(0.1)	1	(0.01)
Cardiac disorders	8	(0.1)	8	(0.1)
Injury, poisoning, and procedural complications	3	(0.03)	8	(0.1)
Nervous system disorders	3	(0.03)	4	(0.04)
Psychiatric disorders	3	(0.03)	1	(0.01)
Metabolism and nutrition disorders	2	(0.02)	0	
Vascular disorders	2	(0.02)	5	(0.1)
Blood and Lymphatic system disorders	1	(0.01)	0	
Hepatobiliary disorders	1	(0.01)	1	(0.01)
Renal and urinary disorders	1	(0.01)	4	(0.04)

ITT Intent-to-Treat; RSV Rosuvastatin.

Gastrointestinal AE-related deaths

In the Gastrointestinal (GI) disorder SOC, there were 13 rosuvastatin subjects and 1 placebo subject who died resulting from a treatment-emergent AE. Of the subjects receiving rosuvastatin, 1 (E12800011) died of a subdural hematoma in a setting of gastroesophageal reflux disease (GERD) and depression, both of which (along with the subdural hematoma) were listed as having resulted in death. The patient had been off study medication for 329 days and should not have been counted as a GI death.

A discussion of the additional deaths attributed to GI-related AEs follows:

- 3 rosuvastatin-treated subjects died of esophageal disorders—1 subject (E11300006) with a long-standing history of GERD had an esophageal rupture; 1 subject (E54820269) with a history of alcoholic cirrhosis and recurrent bleeding varices apparently had a fatal esophageal hemorrhage; and 1 subject (E72160031), with a hiatal hernia and esophagitis on endoscopy, died at home of an upper GI hemorrhage.

- 2 rosuvastatin-treated subjects (E10350011) and (E10350050) had fatal pancreatitis. In the JUPITER study, pancreatitis was reported in 8 (0.09%) rosuvastatin-treated subjects and 11 (0.12%) placebo-treated subjects; pancreatitis acute was reported in 10 (0.11%) rosuvastatin-treated subjects and 6 (0.07%) placebo-treated subjects; pancreatitis chronic was reported in 1 (0.01%) rosuvastatin and 0 placebo-treated subjects.

- 2 rosuvastatin-treated subjects (E12650001) and (E86170009) hemorrhaged while receiving a vitamin K antagonist anticoagulant for atrial fibrillation. One had been off study medication (rosuvastatin) for 25 days, the other for 66 days.

- 2 rosuvastatin-treated subjects (E41450037) and (E60260034) apparently died of complications of malignancy—gastric and liver cancer respectively. The subject with gastric cancer had been off study medication for 44 days. Another rosuvastatin-treated subject (E50020367) died of a duodenal ulcer; he had ongoing bladder cancer at the time. Another rosuvastatin-treated subject (E60420370) died of peritonitis and an additional rosuvastatin-treated subject (E77760042) died from sepsis following bowel perforation during herniorrhaphy.

- 1 placebo-treated subject (E77540020) died of complications of a gastric bypass procedure.

Based on a review of the rosuvastatin controlled study database, and careful review of the JUPITER data, the imbalance in gastrointestinal AEs leading to death in the JUPITER study was not considered to represent a safety signal. No pattern was seen among investigator-reported gastrointestinal AEs leading to death in the JUPITER study and an increased incidence of fatal gastrointestinal AEs has not been observed in previous rosuvastatin clinical studies. In a pooled analysis of Phase II/III controlled trials including METEOR (N for rosuvastatin 5 to 40 mg=11487); there were no AEs in the Gastrointestinal disorders SOC leading to death in any of the rosuvastatin dose groups or in the placebo group (N=764). Additionally, there was no increase in gastrointestinal deaths with rosuvastatin treatment observed in the previously reported long-term studies, CORONA (heart failure patients) and AURORA (end-stage renal disease treated by hemodialysis) (Table 26). While there is a numerical difference in cases between the rosuvastatin treatment group and the placebo group, the accounting of the individual cases underlines the conclusion in JUPITER that the higher number of gastrointestinal deaths in the rosuvastatin group was due to small numbers of death that were widely dispersed among specific gastrointestinal organs and had no specific pattern.

Table 26 Number (%) of subjects with treatment-emergent gastrointestinal adverse events leading to death in the CORONA and AURORA clinical studies

	Rosuvastatin			Placebo		
Gastrointestinal system organ class	**N**	**n**	**(%)**	**N**	**n**	**(%)**
CORONA	2514	5	(0.2)	2497	22	(0.9)
AURORA	1389	29	(2.1)	1378	29	(2.1)

Cancer deaths

There were 40 (0.4%) deaths attributed to cancer in the rosuvastatin group and 65 (0.7%) attributed to cancer in the placebo group. As seen in Table 27, Section 6.4.2, there were 286 (3.2%) subjects in the rosuvastatin group and 306 (3.4%) subjects in the placebo group who had a cancer-related SAE. Thus, there was no evidence of an increase in cancer-related morbidity and mortality with rosuvastatin in the JUPITER trial. This is consistent with previously reported studies with other statins (CTT Collaborators 2005).

Summary of AEs leading to death

Key observations regarding subject deaths during JUPITER were as follows:

- The frequency of treatment-emergent AEs leading to death was 1.6% in the rosuvastatin treatment group and 2.0% in the placebo group (Table 25). This difference does not take into account the lower number of adjudicated cardiovascular deaths that occurred in the rosuvastatin group (n=35) compared to the placebo group (n=44).

- The SOCs with the greatest number of fatal AEs were Neoplasms (rosuvastatin group, n=40 [0.4%], placebo group, n=65 [0.7%]) and General disorders and administration site conditions (rosuvastatin group, n=39 [0.4%], placebo group, n=40 [0.4%]).

- There were 13 rosuvastatin-treated subjects who had treatment-emergent gastrointestinal AEs leading to death versus 1 placebo subject, based on investigator-reported causes of death. Upon review of the individual cases, the imbalance was not considered to represent a safety signal. In addition, a review of previously reported rosuvastatin studies showed no increase in the frequency of gastrointestinal-related deaths compared to placebo.

6.4.2 Serious adverse events

The most common SAEs (occurring in ≥2% of either treatment group) are summarized in Table 27.

Table 27 Number and percentage of subjects with treatment-emergent serious adverse events (≥2%), by system organ class (ITT population)

System organ class	RSV 20 mg (N=8901)		Placebo (N=8901)	
	n	(%)	n	(%)
Any SAEs	**1341**	**(15.1)**	**1372**	**(15.4)**
Neoplasms benign, malignant, and unspecified (includes cysts and polyps)	286	(3.2)	306	(3.4)
Infections and infestations	215	(2.4)	234	(2.6)
Gastrointestinal disorders	193	(2.2)	172	(1.9)
Cardiac disorders	157	(1.8)	181	(2.0)

ITT Intent-to-Treat; RSV Rosuvastatin; SAE Serious adverse event.

The SOCs with the greatest number of SAEs were Neoplasms (286 [3.2%] rosuvastatin, 306 [3.4%] placebo), Infections and infestations (215 [2.4%] rosuvastatin, 234 [2.6%] placebo), and Gastrointestinal disorders (193 [2.2%] rosuvastatin, 172 [1.9%] placebo). A slightly higher frequency of treatment-emergent gastrointestinal disorder SAEs was seen in the rosuvastatin treatment group.

During the randomized treatment phase, 1341 (15.1%) subjects in the rosuvastatin treatment group and 1372 (15.4%) subjects in the placebo group had treatment-emergent SAEs. The number and percentage of subjects with SAEs that were in the musculoskeletal and connective tissues, hepatobiliary, or renal and urinary disorders SOCs were similar in the rosuvastatin and placebo groups.

6.5 Hepatic, muscle, and renal safety

6.5.1 CRESTOR post-marketing safety database

In the JUPITER study, findings with respect to musculoskeletal AEs, including myopathy, myalgia, myositis, and CK elevations, renal-related AEs including proteinuria and hematuria, and hepatic AEs and individual clinically important changes in ALT were consistent with the known safety profile of rosuvastatin, based on data from controlled clinical trials and post-marketing experience.

Select hepatic, muscular, and renal safety parameters are presented in subsequent sections.

6.5.2 Hepatic, muscle, and renal adverse events in JUPITER

Hepatic, muscle, and renal treatment-emergent AEs and laboratory findings of special interest are summarized in Table 28.

Table 28 Number and percentage of subjects with AEs and laboratory abnormalities reported as treatment-emergent AEs by investigators, and with laboratory findings of interest detected in the central laboratory during the randomized treatment phase (ITT population)

System organ class Preferred term or Laboratory finding	RSV 20 mg (N=8901) n (%)	Placebo (N=8901) n (%)
Any hepatic-related AE	210 (2.4)	181 (2.0)
ALT increased	160 (1.8)	130 (1.5)
Hepatic cirrhosis	3 (0.03)	4 (0.04)
Hepatitis	3 (0.03)	2 (0.02)
Jaundice	1 (0.01)	6 (0.1)
Chronic hepatic failure	2 (0.02)	0
Hepatic failure	0	2 (0.02)
ALT >3 x ULN	124 (1.4)	87 (1.0)
ALT >3 x ULN on 2 consecutive occasions	23 (0.3)	17 (0.2)
Any muscle-related AE	1353 (15.2)	1268 (14.2)
Myalgia	678 (7.6)	590 (6.6)
Myositis	9 (0.1)	8 (0.1)
Myopathy	0	1
Rhabdomyolysis[a]	1	0
Creatine kinase >10 x ULN	2 (0.02)	1 (0.01)
Any renal-related AE	478 (5.4)	439 (4.9)
Haematuria	216 (2.4)	181 (2.0)
Proteinuria	127 (1.4)	113 (1.3)
Renal failure	25 (0.3)	23 (0.3)
Renal failure chronic	23 (0.3)	28 (0.3)
Renal failure acute	19 (0.2)	16 (0.2)
Renal impairment	11 (0.1%)	8 (0.1%)
Serum creatinine >100% above baseline	10 (0.1)	6 (0.1)

AE Adverse event; ALT Alanine aminotransferase; ITT Intent-to-treat; ULN Upper limit of normal.
[a] occurred while on study medication, but after the study closed; attributed to influenza and trauma, not study medication.

6.5.2.1 Hepatic AEs

Treatment-emergent hepatic AEs were reported for 210 subjects assigned to rosuvastatin (2.4%) and 181 assigned to placebo (2.0%)(Table 28). These were predominantly laboratory abnormalities (Investigations SOC): rosuvastatin 160 (1.8%), placebo 130 (1.5%). AstraZeneca separately analyzed the central clinical laboratory results for abnormal ALT values. ALT>3xULN at any time during the study was identified for 124 (1.4%) subjects in the rosuvastatin group and 87 (1.0%) in the placebo group. ALT>3xULN on 2 consecutive occasions was identified for 23 (0.3%) subjects in the rosuvastatin group versus 17 (0.2%) in the placebo group.

There were more reports of the following preferred terms in the placebo group versus the rosuvastatin group: hepatic failure (0 rosuvastatin, 2 placebo) and jaundice (1 rosuvastatin, 6 placebo). The rosuvastatin-allocated subject with jaundice was diagnosed with pancreatic cancer. Neither of the 2 rosuvastatin subjects with the reported AE of chronic hepatic failure met the clinical and laboratory criteria for drug-induced liver injury.

Key observations regarding JUPITER subjects with hepatic AEs of interest and clinically important changes in ALT are as follows:

- Overall, hepatic AEs occurred with similar frequency among subjects assigned to rosuvastatin (2.4%) and placebo (2.0%). The numerical difference in the number of hepatic AEs in the rosuvastatin treatment group was primarily due to laboratory abnormalities (Investigations).

- The percentage of subjects with ALT>3xULN was slightly greater in the rosuvastatin treatment group compared to the placebo group (1.4% and 1.0%, respectively). Elevations of ALT>3xULN on 2 consecutive occasions were uncommon and occurred with similar frequency in the 2 treatment groups (rosuvastatin 0.3%, placebo 0.2%).

- No cases of drug induced liver injury, liver-related deaths, or liver transplantations due to liver failure were observed in the rosuvastatin group.

These findings are consistent with the known safety profile of rosuvastatin.

6.5.2.2 Muscle-related AEs

As observed in Table 28, treatment-emergent muscle-related AEs were reported for 1353 (15.2%) of subjects assigned to rosuvastatin treatment and 1268 (14.2%) assigned to placebo treatment. Myalgia was the most common AE, reported for 7.6% of rosuvastatin and 6.6% of placebo subjects. This largely accounted for the difference in reported events within the Musculoskeletal disorders SOC between the treatment groups. Myositis was reported for 9 rosuvastatin subjects (0.1%) and 8 placebo subjects (0.1%). Myopathy was reported for 1 subject (placebo) and rhabdomyolysis for 1 subject (rosuvastatin). The latter occurred after study closure in a 90-year-old man (Subject E1778/0001) still taking study medication pending his final visit. He developed laboratory-confirmed influenza and lay on the floor at home for at least 24 hours, unable to arise due to weakness. At the hospital, his CK value was 13,000 U/L and his creatinine value was 1.5 mg/dL, (baseline creatinine 4 years prior was 1.3 mg/dL. Following hydration, he recovered fully; his creatinine value at the final visit was 1.1 mg/dL. The clinic investigator reported the influenza as an SAE, but did not report rhabdomyolysis as an SAE and attributed neither to study medication. Viral influenza A and B are known causes of rhabdomyolysis, as is post-traumatic prolonged immobilization.

AstraZeneca separately analyzed the clinical laboratory results for CK values >10xULN. CK was measured at baseline, final visit and in subjects with muscle symptoms (see

Appendix D). CK >10xULN was identified in 3 subjects (2 rosuvastatin, 1 placebo) during the study.

Key observations regarding JUPITER study subjects with AEs of interest related to skeletal muscle and individual clinically important changes in CK are as follows:

- Musculoskeletal symptoms were observed in both treatment groups. Myalgia was reported for 7.6% of rosuvastatin and 6.6% of placebo subjects.
- There were no subjects who had a serious muscle-related AE attributed to rosuvastatin.

These findings are consistent with the known safety profile of rosuvastatin.

6.5.2.3 Renal-related AEs

Renal-related AEs were reported for 478 subjects assigned to rosuvastatin (5.4%) and 439 assigned to placebo (4.9%) Table 28. Hematuria and proteinuria were the most commonly reported renal AEs with a numerical difference between treatment groups (hematuria: rosuvastatin 2.4%, placebo 2.0%; proteinuria: rosuvastatin 1.4%, placebo 1.3%). Results of the urinalysis from samples obtained according to the JUPITER study protocol are summarized in Section 6.7.4. Acute, chronic and unspecified renal failure and renal impairment were uncommon and reported with similar frequency in the 2 treatment groups.

AstraZeneca separately analyzed the central clinical laboratory results, which are summarized in Section 6.7.4. The number and percentage of the subjects with serum creatinine elevations increased >50% above the baseline value at any time was 161 (2.1%) in the rosuvastatin group and 168 (2.2%) in the placebo group. The number and percentage with an increase >100% (doubling of serum creatinine) was 10 (0.1%) in the rosuvastatin group and 6 (0.1%) in the placebo group.

JUPITER enrolled 3257 subjects with baseline eGFR<60 ml/min. In this subgroup with impaired renal function, eGFR was stable during follow up (Table 29) and AEs of renal impairment or renal failure were reported with similar frequency in the 2 treatment groups. When compared with placebo, both major cardiovascular event (HR 0.56; 95% CI 0.37-0.85) and all-cause mortality (HR 0.55; 95% CI 0.38-0.82) were statistically significantly lower in the rosuvastatin group.

Table 29 JUPITER outcomes in patients with impaired renal function (eGFR <60 ml/min/1.73 m^2)

	Rosuvastatin (N=1632)	Placebo (N=1625)
eGFR (ml/min/1.73 m^2)		
Baseline, mean (SD)	54 (6.1)	54 (6.2)
Final visit, mean (SD)	54 (10.0)	54 (10.2)
Renal adverse events, n (%)		

Table 29 JUPITER outcomes in patients with impaired renal function (eGFR <60 ml/min/1.73 m^2)

	Rosuvastatin (N=1632)	Placebo (N=1625)
Renal impairment	5 (0.3)	5 (0.3)
Renal failure acute	8 (0.5)	11 (0.7)
Renal failure chronic	16 (1.0)	22 (1.3)
Renal failure (unspecified)	10 (0.6)	17 (1.0)
Death from any cause, n (rate)[a]	34 (9.1)	61 (16.7)
MCEs, n (rate)[a]	40 (10.8)	72 (19.9)

[a] rate per 1000 patient years.
eGFR Estimated glomerular filtration rate; MCE Major cardiovascular events.
NOTE: Total mortality HR 0.56, 95% CI 0.37-0.85; MCEs HR 0.55, 95% CI 0.38-0.82.

Key observations regarding JUPITER study subjects with renal AEs of interest and individual clinically important changes in serum creatinine are as follows:

- Proteinuria (rosuvastatin 1.4%, placebo 1.3%) and hematuria (rosuvastatin 2.4%, placebo 2.0%) were slightly more frequent among subjects assigned to rosuvastatin treatment.
- No treatment group difference was seen in reported renal failure (rosuvastatin 25 [0.3%], placebo 23 [0.3%]), renal failure acute (rosuvastatin 19 [0.2%], placebo 16 [0.2%]), renal failure chronic (rosuvastatin 23 [0.3%], placebo 28 [0.3%]), or renal impairment (rosuvastatin 11 [0.1%], placebo 8 [0.1%]).
- Elevations of serum creatinine >100% above baseline occurred with similar frequency in the 2 treatment groups (0.1% in each group).
- Among subjects with impaired renal function, rosuvastatin reduced major cardiovascular events and total mortality with no apparent adverse effect on renal function.

These observations are consistent with the known safety profile of rosuvastatin.

6.6 Neuropsychiatric disorders

There have been previous reports of impaired cognitive function in statin-treated patients and memory loss is included as an AE in the US PI for CRESTOR. For these reasons, the JUPITER database was explored for AEs related to cognition, as well as other neuropsychiatric disorders (Table 30). The JUPITER study was not designed for the purpose of assessing cognitive function and no specific cognitive testing was performed. Overall frequencies of cognition-related AEs were similar in the 2 treatment groups (Table 30).

Table 30 Number and percentage of subjects with treatment-emergent neuropsychiatric adverse events by MedDRA System Organ Class and Preferred Term (ITT population)

System Organ Class	Preferred term	RSV 20 mg (N=8901) n (%)	Placebo (N=8901) n (%)
Any adverse event	**Any adverse event**	**568 (6.4)**	**586 (6.6)**
Nervous system disorders	Any adverse event	69 (0.8)	76 (0.9)
	Amnesia	30 (0.3)	36 (0.4)
	Memory impairment	18 (0.2)	16 (0.2)
	Dementia	12 (0.1)	9 (0.1)
	Dementia alzheimer's type	7 (0.1)	7 (0.1)
	Disturbance in attention	3 (0.03)	1 (0.01)
	Amnestic disorder	2 (0.02)	1 (0.01)
	Global amnesia	2 (0.02)	1 (0.01)
	Senile dementia	1 (0.01)	2 (0.02)
	Cognitive disorder	0	6 (0.1)
	Vascular dementia	0	1 (0.01)
Psychiatric disorders	Any adverse event	515 (5.8)	533 (6.0)
	Insomnia	226 (2.5)	208 (2.3)
	Depression	184 (2.1)	214 (2.4)
	Anxiety	128 (1.4)	157 (1.8)
	Confusional state	18 (0.2)	4 (0.04)
	Depressed Mood	12 (0.1)	12 (0.1)
	Nervousness	8 (0.1)	7 (0.1)
	Generalized anxiety disorder	2 (0.02)	1 (0.01)
	Major depression	2 (0.02)	0

Note: Number of subjects with AEs based on randomized treatment. Subjects who had more than 1 AE assigned to the same MedDRA term were counted once for that event. Subjects who had more than 1 AE within the same SOC were counted once in that SOC total. For that reason, the separate AE totals may not sum to the SOC total.
ITT Intent-to-treat; RSV Rosuvastatin.

Confusional state was reported for 18 subjects in the rosuvastatin group and 4 in the placebo group. A review of these cases was performed and is summarized in Table 31.

Table 31 Summary of JUPITER subjects with reports of Confusional State AEs

ID	Treatment group	Verbatim Term as Reported	On study medication (+30 days) at event onset?	Duration of treatment with study medication at the onset of the event (days)	Overall duration of treatment with study medication (days)	Investigator assessed causality	Clinical history
E1031.0031	RSV	Confusion	Yes	670	1247	No	76 yo woman with concurrent acute cholecystitis with fever, nausea, abdominal pain, vomiting
E1244.0018	RSV	Intermittent confusion	No	1159	722	No	55 yo man with concurrent atrial fibrillation, depression, constipation, dyspnea, headache, muscle spasms, weight gain (digoxin, amiodarone, lisinopril, sular)
E1282.0013	RSV	Confusion	Yes	1190	1269	No	74 yo man: antecedent AEs - Fall with scalp laceration day 1069, Anxiety disorder day 1101, Kidney stone day 1136 (toradol, promethazine)
E1668.0124	RSV	Confusion	Yes	250	607	No	82 yo woman: antecedent meningioma, concurrent bacteremia, hypoxia, aphagia, leukocytosis
E1802.0113	RSV	Confusion (SAE)	Yes	79	373	No	87 yo man: concurrent renal hemorrhage
E2067.0021	RSV	Confusion	No	911	186	No	84 yo woman: concurrent depression
E2249.0001	RSV	Confusion	Yes	12	1167	No	69 yo woman: dizziness & muscular weakness before study entry. Concurrent AEs of urinary hesitation, bronchitis and blurred vision (levaquin)
E2324.0019	RSV	Confusion (SAE)	Yes	327	327	No	67 yo woman: hospitalized for joint pain exacerbation, found to have leukocytosis, acute renal failure, dehydration, bilateral Babinski signs, possible posterior communicating artery aneurysm
E4010.0060	RSV	Confusion	Yes	250	246	No	72 yo man: concurrent pneumonia
E4048.0074	RSV	Confusion	Yes	377	725	No	77 yo man with concurrent pericarditis, atrial fibrillation, thyrotoxicosis (oxazepam, morphine, tapazole, cortisone, metoprolol, ativan)
E4099.0006	RSV	Confusion	Yes	454	1616	No	70 yo man: concurrent insomnia, depression, anxiety, Parkinson's disease (celexa, zyprexa, sinemet, clonazepam, oxazepam)
E4141.0044	RSV	Confusion	No	550	302	No	74 yo man: off drug, B cell lymphoma

Table 31 Summary of JUPITER subjects with reports of Confusional State AEs

ID	Treatment group	Verbatim Term as Reported	On study medication (+30 days) at event onset?	Duration of treatment with study medication at the onset of the event (days)	Overall duration of treatment with study medication (days)	Investigator assessed causality	Clinical history
E5001.1388	RSV	"Confusion is due to opioid (sic) use"	Yes	591	819	No	62 yo man: concurrent COPD, pneumonia
E5007.0782	RSV	Confusion (SAE)	Yes	655	726	No	74 yo woman: concurrent hypokalemia, hyponatremia, urinary tract infection
E5037.0069	RSV	Intermittent confusion	No	312	79	No	76 yo man: off drug, transient ischemic attack
E6410.0023	RSV	Acute confusional state (SAE)	Yes	461	952	No	81 yo man: hospitalized for confusion, recovered
E7154.0002	RSV	Acute syndrome confusional	Yes	170	176	No	77 yo man: concurrent pneumonia and endocarditis
E8487.0008	RSV	Confused (SAE)	Yes	396	396	No	82 yo woman: concurrent septic shock with multiorgan failure

AE Adverse event; COPD Chronic obstructive pulmonary disease; RSV Rosuvastatin; SAE Serious adverse event; yo Year old.

Based on the JUPITER study data, there is no evidence that rosuvastatin was associated with an alteration in cognitive function or neuropsychiatric disorders.

6.7 Laboratory safety

6.7.1 Hematology

Laboratory findings for hematology indicated that the mean platelet count decreased slightly from baseline to final visit in both treatment groups. This decrease was not associated with clinically significant thrombocytopenia or an increased risk of bleeding. There were no clinically relevant changes in red or white blood cell counts.

6.7.2 Hepatic biochemistry

With respect to hepatic biochemistry, there was no difference in mean change in ALT from baseline between the 2 treatment groups (Table 32).

Table 32 Change from baseline to final visit in ALT (ITT population)

ALT (U/L)	RSV 20 mg (N=8901)	Placebo (N=8901)
Baseline		
N	8892	8891
Mean (SD)	16.0 (7.7)	16.0 (7.7)
Median	14.0	14.0
Change from baseline to final visit		
N	7175	7072
Mean (SD)	1.4 (17.4)	–0.1 (8.76)
Median	1.0	0.0

ALT Alanine aminotransferase; ITT Intent-to-Treat; RSV Rosuvastatin; SD Standard deviation.

6.7.3 Skeletal muscle biochemistry

Laboratory findings for skeletal muscle biochemistry revealed no clinically meaningful difference in mean change in CK from baseline between the 2 treatment groups (Table 33). These findings are consistent with the known safety profile of rosuvastatin.

Table 33 Change from baseline to final visit in CK (ITT population)

CK (U/L)	RSV 20 mg (N=8901)	Placebo (N=8901)
Baseline		
N	8897	8896
Mean (SD)	68.8 (42.9)	70.0 (47.2)
Median	58.0	58.0
Change from baseline to final visit		
N	7169	7069
Mean (SD)	11.1 (147.2)	2.3 (52.1)
Median	5.0	1.0

CK Creatine kinase; ITT Intent-to-Treat; RSV Rosuvastatin; SD Standard deviation.

6.7.4 Renal biochemistry

With respect to renal biochemistry, change from baseline in mean serum creatinine on treatment was similar in the rosuvastatin and placebo groups (Table 34). The percentage of subjects who had a doubling of their baseline serum creatinine level was also similar in the 2 treatment groups.

Table 34 Change from baseline to final visit in serum creatinine (ITT population)

Serum creatinine (µmol/L)	RSV 20 mg (N=8901)	Placebo (N=8901)
Baseline		
N	8897	8898
Mean (SD)	89.1 (17.1)	89.2 (17.1)
Median	88.4	88.4
Change from baseline to final visit		
N	7170	7070
Mean (SD)	8.5 (15.8)	9.1 (14.5)
Median	8.8	8.8

ITT Intent-to-Treat; RSV Rosuvastatin; SD Standard deviation.

Table 35 shows the number and percent of subjects with urine protein and urine blood shifts from “none” or “trace” at baseline to ++ or greater post-baseline. Development of persistent dipstick positive proteinuria (an increase from a baseline value that was “none” or “trace” to a level that was ++ or greater at a minimum of the last 2 visits during the study occurred in 19 out of 7803 (0.2%) subjects in the rosuvastatin group and 17 out of 7816 (0.2%) of subjects in the placebo group. Development of persistent dipstick positive hematuria (an increase from a

baseline value that was "none" or "trace" to a level that was ++ or greater at a minimum of the last 2 visits during the study occurred in 38 out of 7921 (0.5%) subjects in the rosuvastatin group and 28 out of 7890 (0.4%) subjects in the placebo group. Proteinuria and hematuria were reported as AEs more frequently in subjects who received rosuvastatin when compared to placebo (Table 28).

Table 35 Urine dipstick protein and blood—Subjects with shifts from none or trace at baseline to ++ or greater post-baseline (ITT population)

	Rosuvastatin 20 mg (N=8901)		Placebo (N=8901)	
	N	n (%)	N	n (%)
Urine protein				
Increase at any time	8031	290 (3.6)	8065	236 (2.9)
Persistent[a]	7803	19 (0.2)	7816	17 (0.2)
Urine blood				
Increase at any time	8150	415 (5.1)	8149	339 (4.2)
Persistent[a]	7921	38 (0.5)	7890	28 (0.4)

[a] Persistent is defined as subjectw with a change from none or trace at baseline to ++ or greater at the last 2 post-baseline visits.

Finally, the change from baseline to final visit in mean eGFR was similar in the rosuvastatin and placebo groups (Table 36).

Table 36 Change from baseline to final visit in eGFR (ITT population)

EGFR	RSV 20 mg (N=8901)	Placebo (N=8901)
Baseline		
N	8897	8898
Mean (SD)	75.4 (17.5)	75.4 (17.3)
Median	73.3	73.6
Change from baseline to final visit		
N	7448	7407
Mean (SD)	–7.23 (12.4)	–7.72 (12.2)
Median	–7.13	–7.27

eGFR Estimated glomerular filtration rate; ITT Intent-to-Treat; RSV Rosuvastatin; SD Standard deviation.

6.8 Safety in special groups and situations

6.8.1 Effect of sex

JUPITER enrolled 11001 men and 6801 women (61.8% and 38.2% of the cohort, respectively). The overall frequency of AEs was similar for men and women in the rosuvastatin (78.9% and 77.3%, respectively) and placebo groups (78.8% and 75.6%,

respectively), and the AE profile was similar across the 4 subgroups. The most common AEs for male subjects receiving rosuvastatin were back pain (7.7%), nasopharyngitis (7.7%), and myalgia (7.5%). The most common AEs for male subjects receiving placebo were hypertension (8.2%) upper respiratory tract infection (7.6%) and nasopharyngitis (7.6%). The most common AEs for female subjects receiving rosuvastatin were urinary tract infection (15.1%), bronchitis (8.1%), and myalgia (7.8%), whereas the most common AEs for female subjects receiving placebo were urinary tract infection (15.5%), bronchitis (8.6%) and upper respiratory tract infection (7.6%).

These findings indicate that, compared with placebo, rosuvastatin was well-tolerated by both males and females in the JUPITER study.

6.8.2 Effect of age

JUPITER subjects' age ranged between 49 and 97 years; mean age 66 years (Table 7). AEs were more frequent among older subjects in both treatment groups, however, the overall frequency of AEs was similar for subjects aged >65 years in the rosuvastatin and placebo groups (80.6% and 79.4%, respectively). The most common AEs for subjects ≤65 years old receiving rosuvastatin were nasopharyngitis (7.6%), back pain (7.3%), and myalgia (6.9%), and for those receiving placebo were nasopharyngitis (7.7%), upper respiratory tract infection (7.4%) and hypertension (7.4%). The most common AEs for subjects >65 years old receiving rosuvastatin were urinary tract infection (11.5%), myalgia (8.2%) and bronchitis (8.1%), while the most common AEs for subjects ≥65 years old receiving placebo were urinary tract infection (12.1%), hypertension (8.2%) and bronchitis (7.8%).

JUPITER included 5695 subjects ≥70 years of age at randomization (2878 rosuvastatin, 2817 placebo). Mean age of that subgroup was 75 years; 48.5% were males and 51.5% were females. The overall frequency of AEs was similar in the rosuvastatin and placebo groups (81.1% vs 80.1%, respectively). The frequency of AEs leading to death (2.6% vs 3.4%) was slightly lower in the rosuvastatin group than in placebo group. SAEs occurred with a similar frequency in the 2 groups (21.4% vs 20.7%).

Compared to placebo, rosuvastatin was well-tolerated by subjects <65 and ≥65 years of age, and also by subjects ≥70 years of age in the JUPITER study.

6.8.3 Adverse events with very low cholesterol levels (LDL <50mg/dL)

An additional descriptive analysis of treatment-emergent AEs is presented for subjects who had an LDL-C <50 mg/dL at any point during the study (Table 37). Rates of musculoskeletal AEs, particularly myalgia, were higher with rosuvastatin than placebo, but were similar among rosuvastatin-allocated subjects who did or did not attain LDL-C<50 mg/dL. Rates of cancer and neuropsychiatric AEs were not higher among patients treated with rosuvastatin who attained LDL-C <50 mg/dL compared to those with LDL-C >50 mg/dL or placebo.

Table 37 Numbers and percentages of treatment-emergent adverse events by treatment group and attained LDL-C <50 mg/dL at any visit for the rosuvastatin group

	Rosuvastatin		Placebo
	LDL-C <50 mg/dL at any visit		
System Organ Class	**No (N=4000)**	**Yes (N=4154)**	**(N=8150)**
Preferred term	**n (%)**	**n (%)**	**n (%)**
Any adverse event	3126 (78.2)	3424 (82.4)	6509 (79.9)
Musculoskeletal/connective tissue disorders	1489 (37.2)	1691 (40.7)	2930 (36.0)
Myalgia	317 (7.9)	326 (7.8)	559 (6.9)
Muscular weakness	43 (1.1)	30 (0.7)	61 (0.8)
Rhabdomyolysis/myopathy/ myositis	3 (0.08)	7 (0.2)	9 (0.1)
Nervous system disorders	628 (15.7)	720 (17.3)	1431 (17.6)
Peripheral neuropathy	18 (0.5)	20 (0.5)	40 (0.5)
Memory impairment	21 (0.5)	12 (0.3)	33 (0.4)
Renal and urinary disorders	344 (8.6)	439 (10.6)	782 (9.6)
Haematuria	86 (2.2)	123 (3.0)	175 (2.1)
Proteinuria	55 (1.4)	73 (1.8)	111 (1.4)
Renal failure	28 (0.7)	39 (0.9)	70 (0.9)
Neoplasms benign, malignant and unspecified	113 (2.8)	131 (3.2)	269 (3.3)
Psychiatric disorders	307 (7.7)	296 (7.1)	619 (7.6)
Depression	103 (2.6)	83 (2.0)	217 (2.7)
Anxiety	66 (1.7)	65 (1.6)	158 (1.9)

Memory impairment includes preferred terms memory impairment, dementia, dementia Alzheimer's type, cognitive disorder. Peripheral neuropathy includes preferred terms neuropathy peripheral, polyneuropathy, demyelinating polyneuropathy, myelopathy, neuromyopathy, peripheral sensory neuropathy. Proteinuria includes preferred terms proteinuria, microalbuminuria, nephrotic syndrome. Renal failure includes preferred terms renal failure, renal failure chronic, renal failure acute, renal impairment, azotaemia, anuria, oliguria, nephritis, glomerulonephritis, nephropathy. Depression includes preferred terms depression, depressed mood, major depression, suicidal ideation, completed suicide, suicide attempt, depression suicidal, depressive symptom. Anxiety includes preferred terms anxiety, nervousness, generalized anxiety disorder.

6.9 Investigator-reported diabetes mellitus

One of the secondary efficacy objectives of the JUPITER trial was to investigate whether rosuvastatin reduced the incidence of diabetes. The hypothesis of a preventative effect of statins was initially raised by the findings in a retrospective analysis of the West of Scotland Coronary Prevention Study (WOSCOPS) (Freeman et al 2001), which reported a 30% reduction (HR 0.70; 95% CI 0.50-0.99; p=0.042) in incident diabetes among subjects who received pravastatin versus placebo. The WOSCOPS observation was based on a post-hoc analysis of data, as diabetes was not a protocol-specified endpoint in the study. The WOSCOPS analysis defined diabetes as a documented significant rise in serum glucose levels

(>36 mg/dL) that exceeded 126 mg/dL on 2 occasions or use of anti-diabetes medications. After the initiation of the JUPITER study, several statin studies reported results that did not support the hypothesis of a preventative effect of statins on development of diabetes and raised the possible association of statin treatment with reported diabetes. In JUPITER, an increased frequency of investigator reported diabetes was observed with rosuvastatin compared to placebo (rosuvastatin: 2.8%, placebo: 2.3%, HR 1.27, 95% CI 1.05-1.03, p=0.015, Figure 8).

6.9.1 Definition of diabetes and data collection

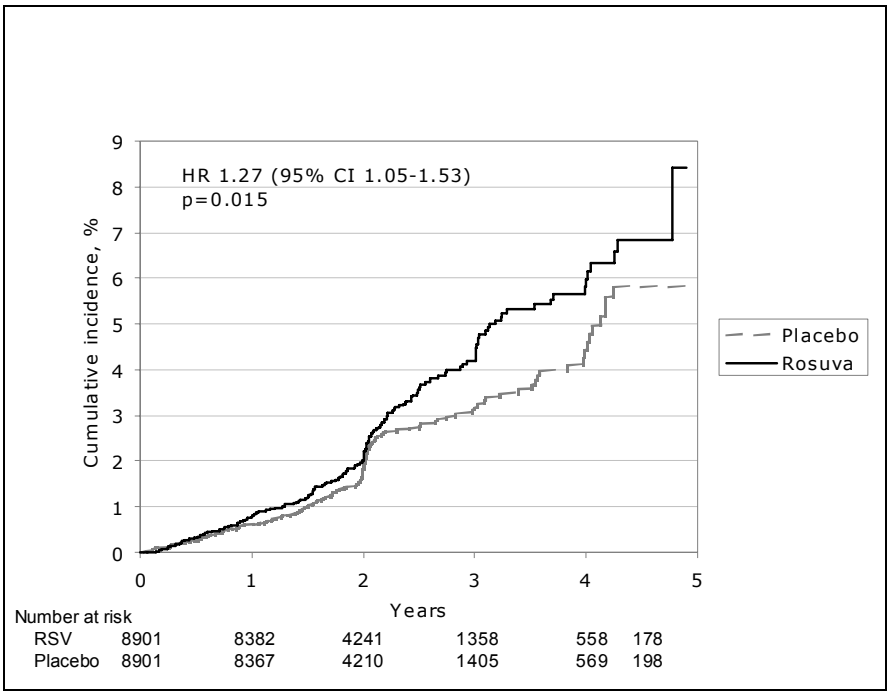
In the JUPITER study, investigators were to report diabetes among study subjects who developed any of the following criteria, which are based on the American Diabetes Association definition of diabetes (ADA 2008): new use of insulin or an oral hypoglycemic agent, a positive oral glucose tolerance test (glucose ≥200 mg/dL at 2 hours), repeated fasting glucose level above 126 mg/dL, or a random glucose level over 200 mg/dL with symptoms of polyuria, polydipsia, or unexplained weight loss.

Information relevant to this endpoint was collected on a separate case report form (CRF) every 3 months during the period of follow-up.

Diabetes was not an adjudicated endpoint; the investigator-reported diabetes endpoint did not require central laboratory documentation of repeated elevations of fasting glucose, a positive glucose tolerance test, or a random glucose level of 200 mg/dL or greater. However, a fasting glucose and Hb_{A1c} level were obtained on a single occasion prior to randomization and at year 2 and annually thereafter following randomization. Fasting glucose and Hb_{A1c} levels were also measured at each subject's final visit in the study.

In the JUPITER study, investigators reported diabetes in 251 (2.8%) rosuvastatin-treated subjects and 205 (2.3%) placebo subjects (HR 1.27; 95% CI 1.05-1.53; p=0.015) based on analysis of all randomized study subjects in the ITT population, using information from the JUPITER diabetes CRF. A Kaplan-Meier plot of time to investigator-reported diabetes is shown in Figure 8. The analysis included information obtained up to and including all subjects' final visits in the study, even if this visit occurred after the 30 March 2008 cut-off date that was used for analysis of the primary endpoint data. As seen in Figure 8, there appeared to be a period (at year 2) where the frequency of investigator-reported diabetes increased in both the rosuvastatin and the placebo group. This corresponded with the time that the first post-randomization fasting glucose measurement was reported from the central laboratory.

Figure 8 **Kaplan Meier plot of time to investigator-reported diabetes (ITT population)**



The results of the analysis conducted by AstraZeneca differ slightly from the results presented in published JUPITER manuscript (Ridker et al 2008, Appendix C). AstraZeneca's analysis was based on the ITT analysis of all randomized study subjects and only included subjects with investigator reported diabetes based on the JUPITER case report form that was used for the purpose of reporting this secondary endpoint. The academic investigators' analysis excluded some subjects who were felt to have diabetes at entry and included some cases where diabetes was reported as an adverse event but not reported on the JUPITER diabetes case report form. Both analyses showed similar results and are presented in Table 38.

Table 38 **Number and percent frequency of investigator-reported diabetes in the JUPITER study**

	RSV (N=8901)	Placebo (N=8901)	p value
AstraZeneca analysis	251 (2.8%)	205 (2.3%)	0.015
JUPITER manuscript[a]	270 (3.0%)	216 (2.4%)	0.01

AE Adverse event; ND Not determined; RSV Rosuvastatin.
[a] Ridker et al 2008.

6.9.2 Use of anti-diabetic medication in JUPITER

Concomitant anti-diabetes medication data are provided as separate tables for medication use at baseline (Table 39) or post-baseline (Table 40). In these tables, each subject is counted no more than once in each row. Note that "no anti-diabetic drugs" includes subjects reporting no use of anti-diabetic medication after the date of investigator-reported diabetes. As observed in these tables, concomitant anti-diabetes medication use was similar in the 2 treatment groups. These data are presented here to show that any objective measures of diabetes (fasting glucose and Hb_{A1c}) were not confounded by an imbalance in concomitant use of antidiabetic medications in the rosuvastatin compared to the placebo group.

Table 39 Number and percentage of subjects taking anti-diabetic medication at baseline (ITT population)

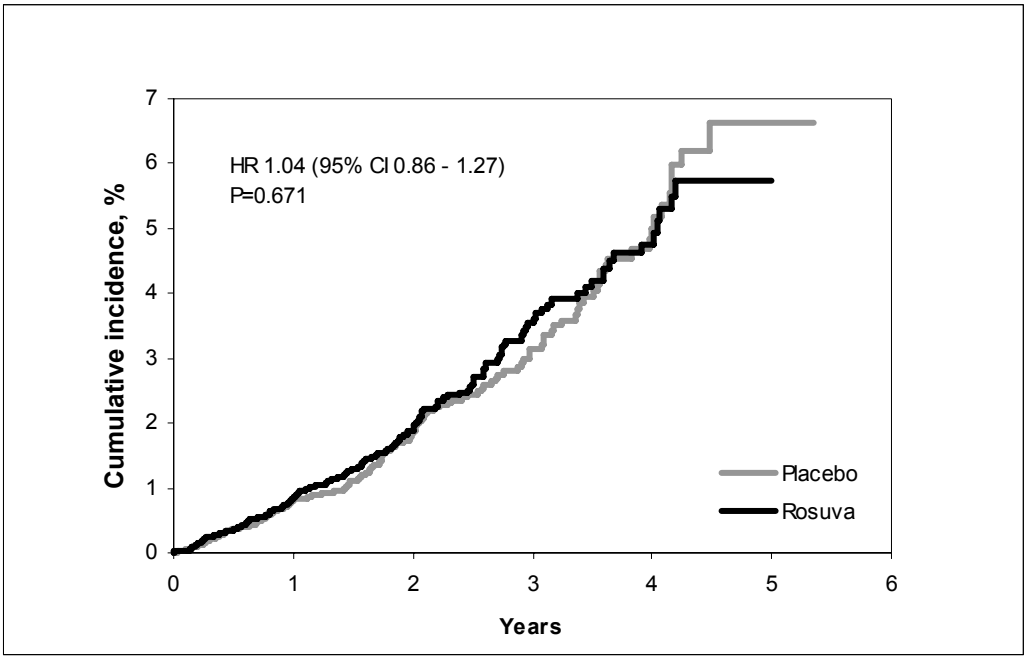
Category	Medication category	Rosuvastatin 20 mg (N=8901) n (%)	Placebo (N=8901) n (%)
Diabetic drugs	Any anti-diabetic medications	9 (0.1)	12 (0.1)
	Metformin only	7 (0.1)	8 (0.1)
	Sulfonylurea only	0	2 (0.02)
	Metformin + Sulfonylurea	1 (0.01)	0
	Other Antidiabetic	1 (0.01)	2 (0.02)

Table 40 Number and percentage of subjects taking anti-diabetic medication post-baseline (ITT population)

Category	Medication category	Rosuvastatin 20 mg (N=8901) n (%)	Placebo (N=8901) n (%)
Diabetic drugs	Any anti-diabetic medications	202 (2.3)	194 (2.2)
	Metformin only	124 (1.4)	136 (1.5)
	Sulfonylurea only	21 (0.2)	8 (0.1)
	Metformin + Sulfonylurea	6 (0.1)	7 (0.1)
	Insulin only	16 (0.2)	15 (0.2)
	Insulin + Metformin + Sulfonylurea	2 (0.02)	3 (0.03)
	Other Antidiabetic	33 (0.4)	25 (0.3)
No antidiabetic drugs	No antidiabetic drug treatment following investigator-reported diabetes	76 (0.9)	59 (0.7)

To further investigate the occurrence of diabetes in the JUPITER study, a post-hoc analysis of time to first use of anti-diabetic medication was performed. This analysis (Figure 9) includes subjects with or without investigator-reported diabetes and was based on post-baseline medication use (Table 40).

Figure 9 Kaplan Meier plot of time to use of anti-diabetic medication



There was no statistically significant difference in the use of antidiabetic medication (HR 1.04; 95% CI 0.86-1.27; p=0.671).

6.9.3 Fasting glucose levels

Since investigator-reported diabetes was not an adjudicated endpoint, AstraZeneca evaluated the objective measurements relevant to glucose control (fasting glucose and Hb_{A1c}).

Changes in mean fasting glucose levels were similar in rosuvastatin and placebo groups based on central laboratory measurements. As seen in Table 41, mean fasting glucose rose during follow-up in both groups and the magnitude of change was similar in the 2 groups. The magnitude of change in fasting glucose did not appear to increase with longer periods of follow-up.

Table 41 Fasting glucose levels at baseline and during follow-up (ITT population)

	Rosuvastatin 20 mg		Placebo		
	N	Mean value (SD)	N	Mean value (SD)	p value[a]
Fasting glucose, mg/dL					
Baseline	8875	94.7 (11.5)	8878	95.0 (11.8)	
Year 2	3520	100.3 (17.9)	3502	99.9 (18.0)	
Year 3	1198	100.4 (19.3)	1140	99.3 (15.9)	
Year 4	440	99.1 (15.3)	414	97.5 (15.5)	
Final	7124	98.1 (19.7)	7002	97.8 (18.9)	
Change in fasting glucose, mg/dL					
Baseline to Year 2	3515	4.7 (16.0)	3499	3.9 (16.2)	0.057
Baseline to Year 3	1197	4.4 (17.0)	1140	3.3 (14.2)	0.097
Baseline to Year 4	440	2.4 (13.1)	414	1.6 (14.1)	0.423
Baseline to Final	7104	3.4 (18.3)	6985	2.9 (17.6)	0.078

ITT Intent-to-treat; SD Standard deviation.
[a] p values for treatment group difference determined by t test for glucose and Hb_{A1c}.

Table 42 summarizes the number and percentage of subjects with increases in fasting glucose from baseline to ≥126 mg/dL at any time during the study. The number of subjects with such a shift was higher in the rosuvastatin treatment group than in the placebo group, but the difference was not statistically significant (p=0.19).

Table 42 Increases in glucose from baseline to a level ≥126 mg/dL at any time

	Rosuvastatin 20 mg	Placebo	p value
Number of subjects	7642	7611	
Number of subjects with shifts	594	548	
Percent (%) of subjects with shifts	7.8%	7.2%	0.19

6.9.4 Hb_{A1C} levels

Hb_{A1c} levels also rose in both treatment groups during the period of follow up. Mean Hb_{A1c} increased by 0.30% in the rosuvastatin group and by 0.22% in the placebo group (baseline compared to final visit). The magnitude of change in Hb_{A1c} did not increase during longer periods of follow-up (Table 43).

Table 43 Hb_{A1c} levels at baseline and during follow-up (ITT population)

	Rosuvastatin 20 mg		Placebo		
	N	Mean value (SD)	N	Mean value (SD)	p value[a]
Hb_{A1c}, %					
Baseline	8856	5.7 (0.42)	8853	5.7 (0.45)	
Year 2	3514	5.9 (0.48)	3497	5.8 (0.47)	
Year 3	1195	5.9 (0.46)	1134	5.8 (0.42)	
Year 4	439	5.9 (0.49)	409	5.9 (0.43)	
Final	7136	6.0 (0.50)	7054	6.0 (0.49)	<0.0001
Change in $Hb_{A1c,}$ %					
Baseline to Year 2	3506	0.29 (0.34)	3480	0.19 (0.33)	<0.0001
Baseline to Year 3	1191	0.29 (0.33)	1131	0.19 (0.29)	<0.0001
Baseline to Year 4	438	0.31 (0.34)	406	0.21 (0.33)	<0.0001
Baseline to Final	7115	0.30 (0.35)	7013	0.22 (0.40)	<0.0001

NOTE: The central laboratory reported Hb_{A1c} values to 1 decimal place, eg, 5.7%.
Hb_{A1c} Glycosylated hemoglobin; ITT Intent-to-treat; SD Standard deviation.
[a] p values for treatment group difference determined by t test for glucose and Hb_{A1c}.

Table 44 shows the results of a post-hoc analysis of the number and percentage of subjects with an increase in Hb_{A1c} from <7% to ≥7% in the rosuvastatin treatment group. This analysis was based on a single baseline and any single measurement during the period of treatment.

Table 44 Increases in Hb_{A1c} from baseline to a level ≥7.0% at any time during the JUPITER study

	Rosuvastatin 20 mg	Placebo	p value
Any increase			
Number of subjects	7624	7588	
Number of subjects with shifts	243	173	
Percent (%) of subjects with shifts	3.2%	2.3%	<0.001
Baseline Hb_{A1c}			
<6.0%			
Number of subjects	5882	5780	
Number of subjects with shifts	47	31	
Percent (%) of subjects with shifts	0.8%	0.5%	0.08
6.0-6.9%			
Number of subjects	1742	1808	
Number of subjects with shifts	196	142	
Percent (%) of subjects with shifts	11.3%	7.9%	0.006

There were 243 (3.2%) of subjects in the rosuvastatin group and 173 (2.3%) in the placebo group who had an increase in Hb_{A1c} to ≥7%. The difference in the percentage of subjects in the rosuvastatin and placebo groups who had a baseline Hb_{A1c} <6% was not statistically significant. However, there was a higher percentage of subjects with a baseline Hb_{A1c} of 6.0 to 6.9% who had an increase in HbA1c to a level ≥7%.

Other relevant clinical findings

For the entire population of JUPITER study subjects, there was a greater weight gain during the period of follow-up in the rosuvastatin group when compared to placebo group (mean change 0.44 kg rosuvastatin versus 0.15 kg placebo); however, bodyweight was only measured at baseline and the final visit. Diet and physical activity were not recorded during the study, and weight was not recorded at the time when investigators reported diabetes. The underlying cause of these changes is uncertain; the 2 groups were treated differently with respect to lipid-lowering therapy and it is possible that there were differences in diet, exercise, or other relevant lifestyle factors. There were no reports of diabetic ketoacidosis, hyperglycemic non-ketotic coma or other complications of severe hyperglycemia.

A post-hoc analysis was performed to assess the frequency of investigator reported diabetes among subsets of the JUPITER study population according to baseline glucose or body mass index. Results of this analysis are summarized in Table 45.

Table 45 Key characteristics of subjects with investigator-reported diabetes

	Rosuvastatin			Placebo		
	n and % subjects with investigator-reported diabetes who had characteristic at baseline					
	N	n	(%)	N	n	(%)
Impaired fasting glucose						
No	6120	59	(1.0)	6061	48	(0.8)
Yes	2755	192	(7.0)	2817	156	(5.5)
Obesity						
No	5535	80	(1.4)	5547	75	(1.4)
Yes	3339	171	(5.1)	3336	129	(3.9)
Obese with impaired fasting glucose	1320	136	(10.3)	1334	106	(7.9)

Note: Impaired fasting glucose is a glucose level of 100 to 125 mg/dL.

Pre-specified subgroup analyses included assessment of the primary endpoint among study subjects with impaired fasting glucose at baseline. This subset of the JUPITER study population had a statistically significant reduction in the risk of sustaining a major cardiovascular event if allocated to rosuvastatin treatment (HR 0.66, 95% CI 0.47-0.93). There was also evidence of a significant treatment benefit among other subsets of the

JUPITER study population who are known to be at risk for development of diabetes (patients who were obese or had the metabolic syndrome, Table 11).

6.9.5 Summary of diabetes findings in the JUPITER study

Key observations regarding investigator-reported diabetes in JUPITER are as follows:

- There was an increase in investigator-reported diabetes with rosuvastatin (2.8% of subjects) versus placebo (2.3% of subjects).
- There were no differences in mean fasting glucose levels between the 2 treatment groups but there was approximately a 0.1% increase in mean Hb_{A1c} with rosuvastatin compared to placebo.
- There were no apparent differences in the use of anti-diabetic medication in the 2 treatment groups.
- Rosuvastatin reduced major cardiovascular events in JUPITER subjects who were at increased risk of developing diabetes, ie, had a baseline fasting glucose ≥100 mg/dL.

6.10 Review of diabetes in the rosuvastatin development program

As noted previously, elevated glucose is included as a laboratory abnormality in the current US PI for CRESTOR. The reported adverse event of "blood glucose increased" among hyperlipidemic patients who received rosuvastatin 5 to 40 mg (28/10786 or 0.3%) was higher compared to placebo (0/483) in a pooled analysis of controlled trials. However, no difference in the mean of the maximum increase in fasting glucose (measured in a central laboratory) or the percentage of patients who had an increase in glucose to a level above the normal range was observed in this analysis.

Following the observation of an increase in investigator-reported diabetes in the JUPITER study, AstraZeneca reviewed data obtained during the rosuvastatin development program that are relevant to glucose disorders. Analyses of clinical trial and post-marketing safety data were also explored.

6.10.1 Preclinical information

Preclinical data were reviewed for signals relating rosuvastatin to insulin metabolism. Early studies reported no relevant preclinical data that would suggest an adverse effect of rosuvastatin on glucose metabolism. No increases or decreases in blood glucose were observed in studies of mice, rats, dogs or monkeys. Neither was there any pancreatic pathology.

6.10.2 Insulin sensitivity

In an active-controlled study of rosuvastatin versus gemfibrozil conducted in insulin-resistant patients with combined dyslipidemia (AstraZeneca Clinical Study 50; G Reaven MD,

Principal Investigator), rosuvastatin did not alter insulin-mediated glucose uptake (Lamendola et al 2005). The results from this study are summarized in Table 46.

Table 46 Glucose and insulin during modified insulin suppression test

	Rosuvastatin 40 mg (N=20)	Gemfibrozil 600 mg BID (N=19)
Glucose (mmol/hr)		
Baseline	47.4	47.6
Final	48.5	50.2
LS mean % change (95% CI)	1.61 (-2.44—5.67)	3.61 (-0.44—7.66)
Insulin (mU/L/hr)		
Baseline	233.7	209.2
Final	273.6	204.3
LS mean % change (95% CI)	12.78 (-2.80—28.36)	13.30 (-2.28—28.88)

Table based on AstraZeneca Study 50 (12-week, open-label study), reported in Lamendola et al 2005.

6.10.3 Homeostasis model assessment (HOMA) study in metabolic syndrome patients

AstraZeneca study D3560C00069 was a multicenter study conducted in nondiabetic, nonatherosclerotic patients with metabolic syndrome. A secondary objective was to assess rosuvastatin's effect on glucose metabolism and insulin resistance. In this study, there was also no significant difference in the HOMA index with rosuvastatin compared to placebo (Table 47, p=0.44).

Table 47 Changes in HOMA index (insulin in µU/mL x glucose in mmol/L/22.5)

	Baseline	Week 6	p value
Placebo (N=78)	2.9 (2.54)	3.0 (2.34)	0.44
Rosuvastatin 10 mg (N=160)	3.2 (2.54)	3.3 (2.80)	

HOMA Homeostasis model assessment.

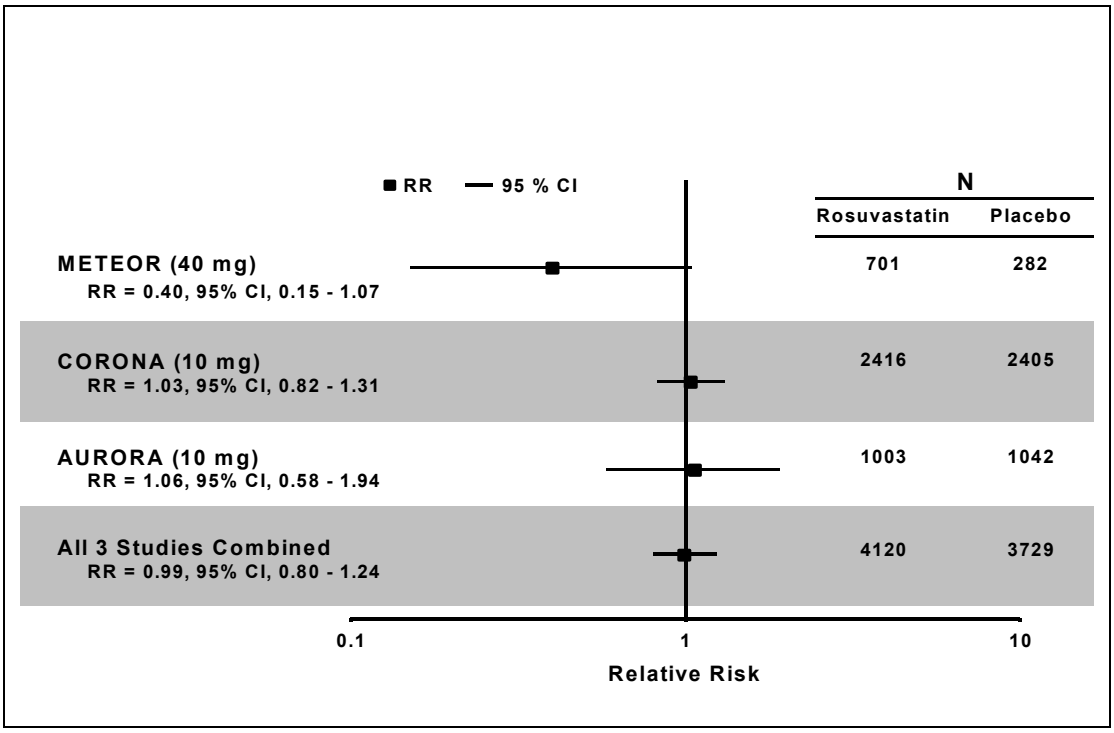
Thus review of rosuvastatin data provide no proven mechanism for statin-induced pancreatic beta cell pathology or insulin resistance.

6.10.4 Diabetes in prior long-term, placebo controlled studies of rosuvastatin treatment

In addition to the JUPITER study, there were 3 other long-term, placebo-controlled studies conducted by AstraZeneca: METEOR, CORONA, and AURORA. AE databases from these 3 studies were reviewed to identify possible glucose-related adverse events for the MedDRA hyperglycaemia/new onset diabetes SMQ list of preferred terms (see Appendix B). Data were combined across the 3 studies using the Maentel-Haenszel approach to estimate the overall

relative risk and 95% CI, stratified by study. This approach allows for differing exposure times between groups and studies. Using this method, the overall event rates derived for drug and control are fully consistent with the overall Maentel-Haenszel relative risk estimate in that the ratio of event rates exactly equals the relative risk. Figure 10 provides a summary of the analysis of data obtained in the METEOR, CORONA and AURORA studies and from a combined analysis of data from these 3 long-term placebo-controlled studies.

Figure 10 Forest plot displaying individual study data for METEOR, CORONA, and AURORA together with the overall Mantel Haenszel relative risk (RR) estimate and 95% CI



Applying the same analytic approach to the JUPITER study, that is, identifying possible glucose-related AEs from the MedDRA hyperglycemia/new onset diabetes SMQ list of Preferred terms (Appendix B), the Mantel-Haenszel relative risk estimate for the JUPITER study was 1.22 (95% CI 1.06-1.40). When the JUPITER study was included with METEOR, AURORA and CORONA, the Maentel-Haenszel relative risk estimate is 1.15 (95% CI 1.02-1.29). However, the frequency of glucose-related findings was higher in the JUPITER study than in prior studies, likely because of the inclusion of the investigator-reported diabetes secondary endpoint.

6.10.5 Diabetes in other rosuvastatin clinical studies (the All Controlled/Uncontrolled Trials Pool)

The rosuvastatin clinical development program included a variety of controlled trials and provided the opportunity for study subjects who completed these studies to receive open-label

rosuvastatin treatment in a long-term extension trial. A pooled analysis of data obtained from nondiabetic subjects in these trials assessed the relationship between rosuvastatin dose and the frequency of glucose-related adverse events using the same SMQ-derived list of Preferred terms (see Appendix B). As seen in Table 48, there was no evidence of a relationship between rosuvastatin dose and the frequency of glucose-related adverse events.

Table 48 Number and percentage of nondiabetic subjects with treatment-emergent potentially glucose-related adverse events during the treatment phase for All Controlled/Uncontrolled trial pool

	Rosuvastatin treatment group			
	5 mg (N=1158)	10 mg (N=8193)	20 mg (N=4806)	40 mg (N=4504)
MedDRA Preferred term	n (%)	n (%)	n (%)	n (%)
Any glucose-related AE	17 (1.5)	112 (1.4)	46 (1.0)	59 (1.3)
Diabetes mellitus	9 (0.8)	44 (0.5)	23 (0.5)	25 (0.6)
Blood glucose increased	4 (0.3)	33 (0.4)	13 (0.3)	12 (0.3)
Hyperglycaemia	0	17 (0.2)	4 (0.1)	4 (0.1)
Glycosuria	1 (0.1)	8 (0.1)	4 (0.1)	8 (0.2)
Glucose tolerance impaired	1 (0.1)	7 (0.1)	2 (0.04)	6 (0.1)
Thirst	2 (0.2)	3 (0.04)	3 (0.1)	2 (0.04)
Urine ketone body present	0	7 (0.1)	0	2 (0.04)
Glucose urine present	0	1 (0.01)	1 (0.02)	3 (0.1)
Polyuria	1 (0.1)	1 (0.01)	1 (0.02)	1 (0.02)
Glycosylated haemoglobin increased	0	1 (0.01)	1 (0.02)	0
Diabetes mellitus inadequate control	1 (0.1)	1 (0.01)	0	0
Insulin resistance	0	1 (0.01)	0	1 (0.02)
Diabetic ketoacidosis	0	0	1 (0.02)	0
Impaired fasting glucose	0	1 (0.01)	0	0
Polydipsia	0	0	1 (0.02)	0

AE, adverse event; MedDRA: Medical Dictionary for Regulatory Activities.
Note: Subjects may have had more than 1 exposure to rosuvastatin or a particular rosuvastatin dose. The first occurrence of a treatment-emergent adverse event MedDRA preferred term is counted in the SOC and MedDRA term under the column which represents the dose at the onset of the adverse event.

6.10.6 FDA-AERS database analysis

AstraZeneca evaluated the FDA Adverse Event Reporting System (AERS) database for potential signals, to further investigate the higher rate of investigator-reported diabetes among subjects assigned to rosuvastatin in JUPITER.

Reports through the first quarter of 2009 (1Q09) were analyzed for potential signals using the Empirica Signal 7.0 data mining tool. All currently marketed statins (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, simvastatin, and rosuvastatin) and the MedDRA hyperglycemia/new onset diabetes SMQ terms were included (see Appendix B).

Two data mining runs were performed: 1 for reports where a statin was considered a suspect medication and 1 for reports where a statin was considered either a suspect or concomitant medication. A standard tool was considered for identifying a potential safety signal, as reflected by a higher than expected number of reports (EB05 score ≥1.8). No potential safety signal was identified for rosuvastatin within any of the diabetes-related Preferred Terms or with terms relevant to complications of diabetes such as diabetic retinopathy, nephropathy or neuropathy in either data mining run. Tables summarizing these reports are presented in Appendix E.

6.10.7 Summary of diabetes findings

An increased frequency of investigator-reported diabetes and an increase in Hb_{A1c} levels (0.08%) were observed in the rosuvastatin compared to the placebo group in the JUPITER study. There was no apparent difference in the use of antidiabetic medication and no difference in mean fasting glucose in the rosuvastatin compared to the placebo group. Most of the excess in investigator-reported diabetes cases in the rosuvastatin compared to placebo group was in subjects with prediabetes (fasting glucose ≥100 mg/dL at entry). Rosuvastatin preclinical and clinical data did not identify a causative mechanism for the association observed in JUPITER. Diabetes-related AEs were not increased in other large placebo-controlled studies with rosuvastatin and there was no evidence of a dose-response relationship based on analyses of data obtained with rosuvastatin in prior clinical studies across its approved dose range. Finally, there was no evidence of a diabetes signal based upon post-marketing data using an adverse event reporting database.

6.11 Conclusions on safety in the JUPITER study

The numbers of subjects with treatment-emergent AEs, AEs leading to death, SAEs, and discontinuations due to AEs were similar in the 2 treatment groups. The overall AE profile by SOC was similar in the 2 treatment groups (Table 23). The frequency of treatment-emergent AEs leading to death was 1.6% in the rosuvastatin treatment group and 2.0% in the placebo group (Table 25).

Muscle-related AEs: Myalgia was reported more frequently with rosuvastatin (7.6% vs 6.6% with placebo). Myositis was reported by 9 (0.1%) rosuvastatin and 8 (0.1%) placebo subjects. Myopathy was reported for 1 subject (placebo) and rhabdomyolysis for 1 subject (rosuvastatin). The latter occurred after study closure and was due to laboratory-confirmed viral influenza with subsequent trauma. The reported AE of rhabdomyolysis was not considered to be related to study medication based on the investigator's assessment. Overall, the findings with respect to musculoskeletal AEs and individual clinically important central laboratory findings were consistent with the known safety profile of rosuvastatin.

Renal-related AEs: Hematuria and proteinuria were the most commonly reported renal AEs with a small excess among subjects assigned to rosuvastatin. AEs suggestive of renal impairment, persistent proteinuria or hematuria, and elevations of serum creatinine >100% over baseline were uncommon and reported with similar frequency in the 2 treatment groups.

Overall, the findings with respect to renal AEs and individual clinically important central laboratory findings were consistent with the known safety profile of rosuvastatin.

Hepatic AEs: Elevations of ALT>3xULN on 2 consecutive occasions occurred in 0.3% of rosuvastatin and 0.2% of placebo subjects, but there were no cases of rosuvastatin induced liver injury. The findings with respect to hepatic AEs and individual clinically important changes in ALT are consistent with the known safety profile of rosuvastatin.

Glucose-related AEs: There was approximately a 0.1% increase in Hb_{A1c} and an increased frequency of investigator-reported diabetes (2.8% vs 2.3% for placebo) in the JUPITER study but not in previous studies of rosuvastatin treatment. Elevated glucose is included as a laboratory abnormality in the current US PI for CRESTOR.

Neuropsychiatric disorders/cognitive function: There was no difference in the percentage of subjects with reported AEs related to cognitive function with rosuvastatin compared to placebo in the JUPITER study.

Cancer-related AEs: There was no evidence of an increase in cancer-related AEs in the rosuvastatin compared to the placebo group.

7. BENEFIT/RISK ASSESSMENT

Coronary heart disease caused about 1 of every 5 deaths in the US in 2005. In 2009, an estimated 785000 Americans will have a new coronary attack, and about 470000 will have a recurrent attack.

Statins are highly-effective cholesterol-lowering agents that have been proven to reduce cardiovascular events in numerous clinical studies. Current guidelines recommend statin use among patients with hypercholesterolemia, cardiovascular disease, or with multiple coronary heart disease risk factors (such as older age, cigarette smoking, hypertension, low levels of HDL-C, or a family history of premature coronary heart disease) (Expert Panel (NCEP) 2001, Graham et al 2007). However, at least half of all future cardiovascular events occur in individuals with "normal" cholesterol levels who are not recommended for cholesterol-lowering treatment based on current guidelines (Sachdeva et al 2009, Ridker et al 2002). The JUPITER study demonstrated that a significant reduction in major cardiovascular events can be achieved with rosuvastatin in a subject population that currently does not meet current guidelines for cholesterol-lowering treatment.

7.1 Summary of benefits

The JUPITER study demonstrated a 44% reduction in risk of having a major cardiovascular event with rosuvastatin (HR 0.56, 95% CI 0.46-0.69; $p<0.001$). Statistically significant reductions in the primary endpoint with rosuvastatin were observed in a wide range of subgroups regardless of sex, age, ethnicity, geographic region, hypertension, family history of premature coronary disease, prediabetes, smoking status, or baseline lipoprotein or hsCRP

levels and across the spectrum of cardiovascular risk (Table 11 and Table 18) included in the study.

Further, in the JUPITER study, rosuvastatin reduced total mortality by 20% (HR 0.80, 95% CI 0.67-0.97; p=0.021).

7.2 Summary of risks

Rosuvastatin has a well-studied tolerability profile from analysis of an integrated database of 33 studies including 16876 patients who received rosuvastatin 5 to 40 mg, representing 25670 patient-years of continuous exposure. The types and frequencies of AEs reported with rosuvastatin were similar to those observed with comparator statins (Shepherd et al 2007).

The JUPITER study assessed the tolerability of long-term treatment with rosuvastatin 20 mg once daily. Findings were consistent with the known safety profile of rosuvastatin, based on controlled clinical trials data and postmarketing experience, as reflected in the US PI for CRESTOR. There was an approximately 0.1% greater increase in Hb_{A1c} in the rosuvastatin compared to the placebo group and a higher percentage of subjects with investigator-reported diabetes (2.8% versus 2.3%). This occurred primarily in subjects with known risk factors for development of diabetes (impaired fasting glucose, obesity, or both). Elevated glucose is listed as an Adverse Reaction in the current US PI for CRESTOR.

7.3 Benefit/Risk evaluation

JUPITER confirms the benefits of effective statin therapy for cardiovascular event reduction and adds to data from previous statin studies. As expected based on results of previous statin studies:

- there was a similar relative reduction in the risk of major cardiovascular events with rosuvastatin among various subjects of the study population (see Table 19)
- thus, as expected, there was a greater absolute reduction of risk among subjects with a higher baseline level of risk (see Table 19).

In the JUPITER study, the benefits of treatment with rosuvastatin (reduction in the risk of major cardiovascular events and total mortality) outweighed the risks. There were 110 fewer subjects who experienced a major cardiovascular event (primary endpoint event), 49 fewer subjects who died, and a total of 135 fewer rosuvastatin-treated subjects who died or experienced a major nonfatal cardiovascular event during approximately 17000 patient-years of treatment. There was an approximate 0.1% increase in Hb_{A1c} and 46 more subjects with reported diabetes in the rosuvastatin compared to the placebo group. JUPITER study subjects who were considered by investigators to have developed diabetes were subjects with known risk factors for development of diabetes (impaired fasting glucose, obesity, or both of these diabetes risk factors). These subsets of the population who are known to be at risk for development of diabetes derived statistically significant and clinically relevant reductions in the risk of sustaining major cardiovascular events.

A numerical summary of the key benefits versus risks that were observed in the JUPITER study is presented in Table 49.

Table 49 Summary of benefits versus risks during 17000 subject-years of rosuvastatin treatment in the JUPITER study

Benefits	Risks
• 110 fewer subjects with a major cardiovascular event (cardiovascular death, myocardial infarction, stroke, unstable angina, or arterial revascularization) • 49 fewer deaths • 135 fewer subjects who died or experienced a nonfatal major cardiovascular event	• 0.1% increase in $Hb_{A1c,}$ 46 more investigator-reported diabetes cases

7.4 Conclusion

JUPITER was a placebo-controlled, clinical endpoint study designed to evaluate the long-term safety and cardiovascular risk-reducing efficacy of rosuvastatin treatment. As a group, the study population had an "intermediate" level of coronary heart disease risk based on Framingham criteria. Although most of the JUPITER study subjects had multiple risk factors for cardiovascular disease, they were not recommended for cholesterol-lowering treatment based on NCEP ATP III guidelines (Expert Panel (NCEP) 2001).

In the JUPITER study, rosuvastatin 20 mg once daily reduced the primary endpoint, a composite of cardiovascular death, nonfatal stroke, nonfatal myocardial infarction, unstable angina, or arterial revascularization, by 44% compared to placebo ($p<0.001$), and reduced total mortality by 20% ($p=0.021$). The safety profile of rosuvastatin was consistent with its known safety profile and the US PI for CRESTOR.

AstraZeneca is therefore seeking approval for use of rosuvastatin to reduce the risk of major cardiovascular events in patients at increased cardiovascular risk on the basis of the results of the JUPITER study.

8. LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse event
AERS	Adverse event reporting database
AHA	American Heart Association
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
ApoB	Apolipoprotein B
ATP III	Adult Treatment Panel III
CDC	Center for Disease Control
CEC	Clinical Events Committee
CHD	Coronary heart disease
CI	Confidence interval
cIMT	Carotid intimal-medial thickness
CK	Creatine kinase
CRF	Case report form
CRP	C-reactive protein
CSP	Clinical study protocol
CSR	Clinical study report
DAE	Premature discontinuation from the study due to an adverse event.
DCRI	Duke Clinical Research Institute
eGFR	Estimated glomerular filtration rate
FDA	Food and Drug Administration
FSG	Fasting serum glucose
Hb_{A1c}	Glycosylated hemoglobin
HDL-C	High-density lipoprotein cholesterol
HR	Hazard ratio
hsCRP	High sensitivity assay hsCRP
IDMB	Independent Data Monitoring Board
ITT	Intention-to-treat
JUPITER	Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin
LDL-C	Low-density lipoprotein cholesterol

Abbreviation or special term	Explanation
MCE	Major cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
Metabolic syndrome	Subjects had metabolic syndrome if they had 3 or more of the following 5 factors (Grundy et al 2005): 1) Waist circumference >40 in (men) or >35 in (women), 2) TG ≥150 mg/dL, 3) HDL-C <40 mg/dL (men) or <50 mg/dL (women), 4) Diastolic blood pressure ≥85 mmHg or systolic blood pressure ≥130 mmHg; or taking prescribed medication for hypertension, 5) Fasting blood glucose ≥100 mg/dL
MI	Myocardial Infarction
NCEP	National Cholesterol Education Program
NYHA	New York Heart Association
OAE	Other significant adverse event (ie, significant AEs, other than SAEs and DAEs, which are of particular clinical importance in this development program).
PI	Prescribing information
PT	Preferred term
RR	Relative risks
RRR	Relative risk reduction
RSV	Rosuvastatin
SAE	Serious adverse event
SAP	Statistical analysis plan
SMQ	Standardized MedDRA query(ies)
SOC	System organ class
TC	Total cholesterol
TG	Triglycerides
ULN	Upper limit of normal
US	United States

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Appendix A

Clinical Study Protocol (CSP) synopsis

CSP Study Plan (Table of assessments)

CSP pages for Inclusion and Exclusion criteria

PROTOCOL SYNOPSIS

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

Sponsor

AstraZeneca Pharmaceuticals LP, 1800 Concord Pike, Wilmington, DE 19850-5437

Investigator

Paul M Ridker, MD, MPH, FACC

Director, Center for Cardiovascular Disease Prevention

Brigham and Women's Hospital

Harvard Medical School

900 Commonwealth Avenue East

Boston, MA 02215

Study center(s) and number of subjects planned

This study will be conducted in approximately 15,000 male and female randomized subjects potentially recruited from the following areas:

United States – approximately 8,000 subjects, approximately 800 centers

Canada - approximately 2,000 subjects, approximately 150 centers

Belgium – approximately 400 subjects, approximately 100 centers

Israel – approximately 200 subjects, approximately 15 centers

Estonia – approximately 100 subjects, approximately 15 centers

Latin America – approximately 3,000 subjects, approximately 200 centers

Denmark – approximately 1,000 subjects, approximately 10 centers

Germany/Switzerland – approximately 1,000 subjects, approximately 40 centers

Netherlands – approximately 3,000 subjects, approximately 30 centers

Norway – approximately 400 subjects, approximately 60 centers

Poland – approximately 1,000 subjects, approximately 100 centers

Russia – approximately 1,000 subjects, approximately 100 centers

United Kingdom – approximately 3,000 subjects, approximately 40 centers

South Africa – approximately 1,000 subjects, approximately 50 centers

Study period		**Phase of development**
Estimated date of first subject enrolled	February 2003	III
Estimated date of last subject completed	August 2010[a]	

[a]The revised date is subject to change based upon the rate of endpoint occurrences.

Objectives

Primary objective:

The primary objective of the study is to investigate whether long-term treatment with rosuvastatin 20 mg compared with placebo will 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 LDL-C (<130 mg/dL [3.36 mmol/L]) who are at high vascular risk on the basis of an enhanced inflammatory response, as determined by elevated levels of CRP (≥2.0 mg/L).

Secondary objectives:

The secondary objectives of the study are 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 reduces the incidence of diabetes mellitus, venous thromboembolic events, and the incidence of bone fractures.

Study design

This is a randomized, double-blind, placebo-controlled, multicenter, Phase III study.

Target subject population

This study will recruit men aged 50 years and older and women aged 60 years and older, who have no prior history of MI, unstable angina, stroke or arterial revascularization and who, on initial screening, are found to have LDL-C levels <130 mg/dL (3.36 mmol/L) and CRP levels ≥2.0 mg/L.

Investigational product, dosage and mode of administration

Rosuvastatin 20 mg and placebo to match rosuvastatin 20 mg, administered once daily, in oral tablet form, as directed by the study physician.

Comparator, dosage and mode of administration

No active comparator will be used.

Duration of treatment

After a 4-week run-in period, subjects meeting the study inclusion criteria and having none of the exclusion criteria will be allocated to receive either rosuvastatin 20 mg/day or matching placebo until at least 520 primary endpoints have occurred.

Endpoints

Primary Endpoint:

The primary endpoint of the study will consist of the first occurrence of a major cardiovascular event after randomization; it will be cardiovascular death, stroke, myocardial infarction, unstable angina, or arterial revascularization.

Secondary Endpoints:

The secondary endpoints of the study will be the occurrence of:

(1) total mortality

(2) noncardiovascular mortality

(3) discontinuation of blinded study medication due to adverse effects

(4) development of diabetes mellitus

(5) development of venous thromboembolic events (deep vein thrombosis or pulmonary embolism)

(6) bone fractures

Statistical methods

A total of 15,000 subjects should be randomized to detect, with 90% power, a relative risk reduction as small as 25%. This assumes 3.5 year mean follow-up, a placebo event rate of 1.50 events per 100 patient-years-at-risk, and an annual 5% drop out/in rate. The study is scheduled to end when at least 520 primary endpoints have occurred. Planned interim analyses will be reviewed by the Independent Data Monitoring Board (IDMB). Statistical analysis of the primary endpoint will be based on the proportional hazards model using the Intention to Treat (ITT) population.

Table 4 Study Plan

Visit Number	1	2	3	4	5	TC[d]	6	TC[d]	7	TC[d]	8	TC[d]	9	TC[d]	10[e]	F
Week No.	-6	-4	0	13	26	39	52	65	78	91	104	117	130	143	156[e]	182
Visit Window		Within 17d of V1	±3d	±9d	±9d		±10d		±10d		±10d		±10d		±10d	Within final 6mo
	Screen Visit 1	Screen Visit 2	Rand Visit	Safety Visit	6 Mo Visit	9 Mo Contact	12 Mo Visit	15 Mo Contact	18 Mo Visit	21 Mo Contact	24 Mo Visit	27 Mo Contact	30 Mo Visit	33 Mo Contact	36 Mo Visit[e]	Close Out
Eligibility Questionnaire	√	√	√													
Informed Consent[f]	√	√														
Physical Exam		√														√
Waist Circumference		√														√
Screening Medical History		√														
Fasting Lipid Panel	√						√				√				√	√
C-reactive Protein[a]	√	√		√			√				√				√	√
ALT		√		√	√		√		√		√		√		√	√
CK		√														√
TSH		√														
Serum Creatinine		√					√									√
Apo A-1/Apo B-100		√					√									√
Fasting Serum Glucose		√									√				√	√
HbA_{1c}		√									√				√	√
Hematology		√														√
Whole blood reserve sample (for plasma storage and optional buffy coat)[g]		√														
Plasma storage sample[h]							√									
Urinalysis		√		√	√		√		√		√		√		√	√

Table 4 Study Plan

Visit Number	1	2	3	4	5	TC[d]	6	TC[d]	7	TC[d]	8	TC[d]	9	TC[d]	10[e]	F
Week No.	-6	-4	0	13	26	39	52	65	78	91	104	117	130	143	156[e]	182
Visit Window		Within 17d of V1	±3d	±9d	±9d		±10d		±10d		±10d		±10d		±10d	Within final 6mo
	Screen Visit 1	Screen Visit 2	Rand Visit	Safety Visit	6 Mo Visit	9 Mo Contact	12 Mo Visit	15 Mo Contact	18 Mo Visit	21 Mo Contact	24 Mo Visit	27 Mo Contact	30 Mo Visit	33 Mo Contact	36 Mo Visit[e]	Close Out
Drug		P[b]	P/R[c]	P/R[c]	P/R[c]		P/R[c]		P/R[c]		P/R[c]		P/R[c]		P/R[c]	
Endpt & DM Assessment		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Prior/Concomitant Meds		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Adverse Event Assessment		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Compliance Check[i]			√	√	√	√	√	√	√	√	√	√	√	√	√	√

[a]C-reactive protein (CRP) to be measured at Visit 1 must be ≥2.0 mg/L
[b]All potential participants to receive single-blind placebo therapy during 4 week compliance run-in.
[c]P = placebo, R = rosuvastatin
[d]TC represents a telephone contact.
[e]Until the study closes (at least 520 primary endpoints have occurred), subjects who have completed Visit 10, who have either not had a study endpoint, or have had an endpoint and continue to be followed, will be asked to return at six-month intervals to repeat the assessments conducted at Visit 9 and Visit 10, alternating until the final visit. If these additional visits are required, they will be numbered Visit 10.1, 10.2, etc. At the odd-numbered visits (10.1, 10.3, etc.), the assessments listed for Visit 9 should be performed, and at the even-numbered visits (10.2, 10.4, etc.), the assessments listed for Visit 10 should be performed. All randomized subjects will continue to be contacted by the site mid-way between these additional visits regarding their well-being, study medication administration, study participation, and to confirm their address has not changed.
[f]Informed Consent should include genetic addendum, if applicable.
[g]The whole blood reserve sample is optional for sites in Europe, Middle East, Latin America, and Africa. In the U.S. and Canada, the whole blood reserve sample is not optional; however, the buffy coat will be discarded if the subject does not consent to participate in the genetic portion of the study.
[h]Plasma storage sample is optional for sites in Europe, Middle East, Latin America, and Africa.
[i]At visits, pills will be counted; at phone calls, study drug administration will be verified.

3.2 Rationale for study design, doses and control groups

This study is designed to evaluate the ability of long term therapy with rosuvastatin 20 mg daily, compared with placebo, to reduce the risk of first ever acute cardiovascular events among apparently healthy men and women with low to normal levels of LDL-C and elevated levels of CRP. The targeted subject population is chosen based on the fact that almost half of all future vascular events occur among apparently healthy individuals with normal levels of LDL-C and, at the same time, high levels of C-reactive protein (a marker of low grade systemic inflammation which is a strong predictor of vascular risk among apparently healthy men and women, even in the absence of hyperlipidemia) (Ridker et al 2001). Therefore, very large numbers of patients are at substantial risk for future vascular disease and might well benefit from prophylactic statin therapy. The 20 mg dose was selected as it was anticipated that this dose should achieve greater than a 50% reduction in LDL-C in this study (data on file) while maintaining a very favorable safety profile (Shepherd et al 2001). The marked reduction in LDL-C that is expected to accompany treatment with rosuvastatin should enhance the ability to demonstrate a cardiovascular risk reduction response to therapy in the study (Pedersen et al 1998). Safety of long-term therapy with rosuvastatin will be monitored carefully throughout the course of the study through comparisons of total mortality, noncardiovascular mortality, and adverse events.

In addition, the unique structure of this study, in which enrollment is based upon the presence of an elevated CRP level, will also allow for prospective testing to show whether or not rosuvastatin therapy reduces incident diabetes mellitus among primary prevention subjects at risk for first cardiovascular events.

3.3 Selection of study population

3.3.1 Study selection record

The investigator(s) must keep a record of subjects who were considered for randomization in the study but who were not randomized. The reason that these subjects were not randomized should also be recorded on the Screen Fail CRF.

3.3.2 Inclusion criteria

For inclusion in the study subjects must fulfill all of the following criteria:

1. Written informed consent to participate in the study (See Appendix B)
2. Men aged 50 years and over; women aged 60 years and over
3. Fasting LDL-C value <130 mg/dL (3.36 mmol/L) at Screening Visit 1
4. CRP value ≥2.0 mg/L at Screening Visit 1
5. TG <500 mg/dL (5.65 mmol/L) at Screening Visit 1

3.3.3 Exclusion criteria

Any of the following is regarded as a criterion for exclusion from the study:

1. Treatment with any HMG-CoA reductase inhibitors or other lipid lowering therapies including fibric acid derivatives (fibrates), niacin (>50 mg per day), and bile acid sequestrants within 6 weeks of Screening Visit 1

2. History of serious hypersensitivity (including myopathy) reactions to other HMG-CoA reductase inhibitors

3. Prior history of cardiovascular or cerebrovascular events such as MI, unstable angina, prior arterial revascularization, or stroke, or CHD risk equivalent as defined by NCEP ATP III

4. Current use of postmenopausal oral hormone replacement therapy (HRT)

5. Current treatment with cyclosporin, tacrolimus, azathioprine, or other immunosuppressants including chronic use of oral glucocorticoids (See Appendix I)

6. Active liver disease or hepatic dysfunction or elevations of ALT >2 x ULN at Screening Visit 2

7. Baseline elevations of CK >3 x ULN at Screening Visit 2

8. Serum creatinine >2.0 mg/dL (177 umol/L) at Screening Visit 2

9. Diabetes mellitus, as defined by FSG >126 mg/dL (7.0 mmol/L) at Screening Visit 2 or by the use of insulin and/or an oral hypoglycemic agent

10. Uncontrolled hypertension, defined as systolic blood pressure >190 mmHg or a diastolic blood pressure >100 mmHg at Screening Visit 2.

11. History of malignancy within the past 5 years, with the exception of basal cell or squamous cell carcinoma of the skin (women with a history of cervical dysplasia should be excluded unless 3 consecutive normal cervical smears, Papanicolaou (Pap) smears, have been recorded subsequently before entry)

12. Uncontrolled hypothyroidism defined as a thyroid stimulating hormone (TSH) >1.5 x ULN at Screening Visit 2 or subjects whose thyroid replacement therapy was initiated or modified within the last 3 months.

13. Chronic inflammatory condition such as severe arthritis, lupus, or inflammatory bowel disease

14. History of alcohol or drug abuse within the past 1 year

15. Participation in another investigational drug study <30 days before enrollment or according to the participants local ethics committee requirements where a longer period is stipulated

16. Prior participation in this study

17. Serious or unstable medical or psychological conditions that, in the opinion of the investigator, would compromise the subject's safety or successful participation in the study

NOTE: The exclusion of women using postmenopausal oral HRT is based upon several factors. Most importantly, several studies indicate that use of oral HRT increases CRP levels (Ridker et al 1999, Cushman et al 1999), yet the pathophysiologic consequences of this effect on vascular risk are uncertain, particularly as these agents also interact with lipid metabolism. Thus, women taking oral HRT at baseline will not be eligible for study enrollment.

3.3.4 Discontinuation of subjects from treatment or assessment

3.3.4.1 Criteria for discontinuation

Subjects may be discontinued from study medication at any time, at the discretion of the investigator(s). It is essential that every randomized subject be followed for the duration of the study, including those that have been discontinued from study medication. Subjects who have been discontinued from study medication will complete their scheduled office visits, or may be contacted via phone by the site for the purpose of documenting endpoints. Specific reasons for discontinuing a subject from study medication are:

1. Withdrawal of informed consent

2. If, at any time, the subject's CK measures >10 x ULN and is accompanied by unexplained muscle pain, tenderness or weakness

3. If persistent ALT levels >3 x ULN on two occasions at least 48 hours apart are demonstrated

4. If there is deterioration in the subject's condition which, in the opinion of the investigator, warrants study medication withdrawal

5. If there is the occurrence of an adverse event which, in the opinion of the investigator, warrants study medication withdrawal

6. At the investigator's discretion

3.3.4.2 Voluntary discontinuation by a subject

Subjects who request to discontinue from the study should always be asked about the reason(s) for their discontinuation and about the presence of any endpoints or adverse events. If possible, they should be seen and assessed by an investigator(s). Adverse events should be

Appendix B: MedDRA terms used in database search for glucose disorder adverse events

The search of database for diabetes-related adverse events used all of the SMQ terms in the narrow list (pages 2-5) and the highlighted terms in the broad list (pages 6-8).

SMQ Name	Preferred Term	System Organ Class	High Level Group Term	High Level Term	PT Code
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Abnormal loss of weight	Metabolism and nutrition disorders	Appetite and general nutritional disorders	General nutritional disorders NEC	10000159
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Abnormal weight gain	Metabolism and nutrition disorders	Appetite and general nutritional disorders	General nutritional disorders NEC	10000188
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Acidosis	Metabolism and nutrition disorders	Acid-base disorders	Mixed acid-base disorders	10000486
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Altered state of consciousness	Nervous system disorders	Neurological disorders NEC	Disturbances in consciousness NEC	10001854
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Blood cholesterol increased	Investigations	Lipid analyses	Cholesterol analyses	10005425
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Blood glucose abnormal	Investigations	Metabolic, nutritional and blood gas investigations	Carbohydrate tolerance analyses (incl diabetes)	10005554
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Blood insulin abnormal	Investigations	Endocrine investigations (incl sex hormones)	Gastrointestinal, pancreatic and APUD hormone analyses	10005606
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Blood insulin decreased	Investigations	Endocrine investigations (incl sex hormones)	Gastrointestinal, pancreatic and APUD hormone analyses	10005613
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Blood lactic acid increased	Investigations	Metabolic, nutritional and blood gas investigations	Blood gas and acid base analyses	10005635
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Blood osmolarity increased	Investigations	Water, electrolyte and mineral investigations	Water and electrolyte analyses NEC	10005697
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Blood triglycerides increased	Investigations	Lipid analyses	Triglyceride analyses	10005839
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Body mass index decreased	Investigations	Physical examination topics	Physical examination procedures	10005895
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Body mass index increased	Investigations	Physical examination topics	Physical examination procedures	10005897

Hyperglycaemia/new onset diabetes mellitus (SMQ)	Coma	Nervous system disorders	Neurological disorders NEC	Coma states	10010071
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Dehydration	Metabolism and nutrition disorders	Electrolyte and fluid balance conditions	Total fluid volume decreased	10012174
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Depressed level of consciousness	Nervous system disorders	Neurological disorders NEC	Disturbances in consciousness NEC	10012373
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Glucose tolerance decreased	Investigations	Metabolic, nutritional and blood gas investigations	Carbohydrate tolerance analyses (incl diabetes)	10018428
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Glucose tolerance test abnormal	Investigations	Metabolic, nutritional and blood gas investigations	Carbohydrate tolerance analyses (incl diabetes)	10018433
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Hunger	General disorders and administration site conditions	General system disorders NEC	Feelings and sensations NEC	10020466
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Hypercholesterolaemia	Metabolism and nutrition disorders	Lipid metabolism disorders	Elevated cholesterol	10020603
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Hyperlactacidaemia	Metabolism and nutrition disorders	Acid-base disorders	Metabolic acidoses (excl diabetic acidoses)	10020660
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Hyperosmolar state	Metabolism and nutrition disorders	Electrolyte and fluid balance conditions	Electrolyte imbalance NEC	10020697
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Hyperphagia	Metabolism and nutrition disorders	Appetite and general nutritional disorders	Appetite disorders	10020710
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Hypertriglyceridaemia	Metabolism and nutrition disorders	Lipid metabolism disorders	Elevated triglycerides	10020869
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Hypoglycaemia	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Hypoglycaemic conditions NEC	10020993
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Increased appetite	Metabolism and nutrition disorders	Appetite and general nutritional disorders	Appetite disorders	10021654

Hyperglycaemia/new onset diabetes mellitus (SMQ)	Increased insulin requirement	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Diabetes mellitus (incl subtypes)	10021664
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Insulin autoimmune syndrome	Immune system disorders	Autoimmune disorders	Endocrine autoimmune disorders	10022472
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Insulin tolerance test abnormal	Investigations	Endocrine investigations (incl sex hormones)	Gastrointestinal, pancreatic and APUD hormone analyses	10022494
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Lactic acidosis	Metabolism and nutrition disorders	Acid-base disorders	Metabolic acidoses (excl diabetic acidoses)	10023676
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Lipids increased	Investigations	Lipid analyses	Lipoprotein and lipid tests NEC	10024592
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Loss of consciousness	Nervous system disorders	Neurological disorders NEC	Disturbances in consciousness NEC	10024855
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Metabolic acidosis	Metabolism and nutrition disorders	Acid-base disorders	Metabolic acidoses (excl diabetic acidoses)	10027417
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Obesity	Metabolism and nutrition disorders	Appetite and general nutritional disorders	General nutritional disorders NEC	10029883
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Overweight	Metabolism and nutrition disorders	Appetite and general nutritional disorders	General nutritional disorders NEC	10033307
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Polydipsia	Metabolism and nutrition disorders	Electrolyte and fluid balance conditions	Fluid intake increased	10036067
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Polyuria	Renal and urinary disorders	Urinary tract signs and symptoms	Urinary tract signs and symptoms NEC	10036142
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Thirst	General disorders and administration site conditions	General system disorders NEC	Feelings and sensations NEC	10043458
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Unresponsive to stimuli	Nervous system disorders	Neurological disorders NEC	Neurological signs and symptoms NEC	10045555

Hyperglycaemia/new onset diabetes mellitus (SMQ)	Weight decreased	Investigations	Physical examination topics	Physical examination procedures	10047895
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Weight increased	Investigations	Physical examination topics	Physical examination procedures	10047899
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Underweight	Metabolism and nutrition disorders	Appetite and general nutritional disorders	General nutritional disorders NEC	10048828
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Blood glucose fluctuation	Investigations	Metabolic, nutritional and blood gas investigations	Carbohydrate tolerance analyses (incl diabetes)	10049803
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Impaired insulin secretion	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Hyperglycaemic conditions NEC	10052341
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Hyperlipidaemia	Metabolism and nutrition disorders	Lipid metabolism disorders	Hyperlipidaemias NEC	10062060
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Central obesity	Metabolism and nutrition disorders	Appetite and general nutritional disorders	General nutritional disorders NEC	10065941

SMQ Name	Preferred Term	System Organ Class	High Level Group Term	High Level Term	PT Code
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Blood glucose increased	Investigations	Metabolic, nutritional and blood gas investigations	Carbohydrate tolerance analyses (incl diabetes)	10005557
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Diabetes complicating pregnancy	Pregnancy, puerperium and perinatal conditions	Maternal complications of pregnancy	Pregnancy complicated by maternal disorders	10012596
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Diabetes mellitus	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Diabetes mellitus (incl subtypes)	10012601
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Diabetes mellitus inadequate control	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Diabetes mellitus (incl subtypes)	10012607
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Diabetes with hyperosmolarity	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Diabetes mellitus (incl subtypes)	10012631
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Diabetic coma	Nervous system disorders	Neurological disorders NEC	Coma states	10012650
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Diabetic hyperglycaemic coma	Nervous system disorders	Neurological disorders NEC	Coma states	10012668
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Diabetic hyperosmolar coma	Nervous system disorders	Neurological disorders NEC	Coma states	10012669
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Diabetic ketoacidosis	Metabolism and nutrition disorders	Diabetic complications	Diabetic complications NEC	10012671
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Diabetic ketoacidotic hyperglycaemic coma	Nervous system disorders	Neurological disorders NEC	Coma states	10012672
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Fructosamine increased	Investigations	Metabolic, nutritional and blood gas investigations	Carbohydrate tolerance analyses (incl diabetes)	10017395
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Gestational diabetes	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Diabetes mellitus (incl subtypes)	10018209

Hyperglycaemia/new onset diabetes mellitus (SMQ)	Glucose tolerance impaired	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Hyperglycaemic conditions NEC	10018429
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Glucose tolerance impaired in pregnancy	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Hyperglycaemic conditions NEC	10018430
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Glycosuria	Renal and urinary disorders	Urinary tract signs and symptoms	Urinary abnormalities	10018473
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Glycosuria during pregnancy	Renal and urinary disorders	Urinary tract signs and symptoms	Urinary abnormalities	10018475
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Glucose urine present	Investigations	Renal and urinary tract investigations and urinalyses	Urinalysis NEC	10018478
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Glycosylated haemoglobin increased	Investigations	Metabolic, nutritional and blood gas investigations	Carbohydrate tolerance analyses (incl diabetes)	10018484
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Hyperglycaemia	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Hyperglycaemic conditions NEC	10020635
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Insulin resistance	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Hyperglycaemic conditions NEC	10022489
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Insulin resistance syndrome	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Hyperglycaemic conditions NEC	10022490
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Insulin resistant diabetes	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Diabetes mellitus (incl subtypes)	10022491
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Ketoacidosis	Metabolism and nutrition disorders	Acid-base disorders	Metabolic acidoses (excl diabetic acidoses)	10023379
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Ketonuria	Renal and urinary disorders	Urinary tract signs and symptoms	Urinary abnormalities	10023388
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Ketosis	Metabolism and nutrition disorders	Acid-base disorders	Metabolic acidoses (excl diabetic acidoses)	10023391

Hyperglycaemia/new onset diabetes mellitus (SMQ)	Neonatal diabetes mellitus	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Diabetes mellitus (incl subtypes)	10028933
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Pancreatogenous diabetes	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Diabetes mellitus (incl subtypes)	10033660
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Metabolic syndrome	Metabolism and nutrition disorders	Metabolism disorders NEC	Metabolic disorders NEC	10052066
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Insulin-requiring type 2 diabetes mellitus	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Diabetes mellitus (incl subtypes)	10053247
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Impaired fasting glucose	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Hyperglycaemic conditions NEC	10056997
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Urine ketone body present	Investigations	Metabolic, nutritional and blood gas investigations	Metabolism tests NEC	10057597
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Hyperglycaemic hyperosmolar nonketotic syndrome	Metabolism and nutrition disorders	Diabetic complications	Diabetic complications neurological	10063554
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Blood 1,5-anhydroglucitol decreased	Investigations	Metabolic, nutritional and blood gas investigations	Carbohydrate tolerance analyses (incl diabetes)	10065367
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Latent autoimmune diabetes in adults	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Diabetes mellitus (incl subtypes)	10066389
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Type 1 diabetes mellitus	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Diabetes mellitus (incl subtypes)	10067584
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Type 2 diabetes mellitus	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Diabetes mellitus (incl subtypes)	10067585

Appendix C:

Ridker et al 2008: 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

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Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein

Paul M Ridker, M.D., Eleanor Danielson, M.I.A., Francisco A.H. Fonseca, M.D., Jacques Genest, M.D., Antonio M. Gotto, Jr., M.D., John J.P. Kastelein, M.D., Wolfgang Koenig, M.D., Peter Libby, M.D., Alberto J. Lorenzatti, M.D., Jean G. MacFadyen, B.A., Børge G. Nordestgaard, M.D., James Shepherd, M.D., James T. Willerson, M.D., and Robert J. Glynn, Sc.D., for the JUPITER Study Group*

ABSTRACT

BACKGROUND

Increased levels of the inflammatory biomarker high-sensitivity C-reactive protein predict cardiovascular events. Since statins lower levels of high-sensitivity C-reactive protein as well as cholesterol, we hypothesized that people with elevated high-sensitivity C-reactive protein levels but without hyperlipidemia might benefit from statin treatment.

METHODS

We randomly assigned 17,802 apparently healthy men and women with low-density lipoprotein (LDL) cholesterol levels of less than 130 mg per deciliter (3.4 mmol per liter) and high-sensitivity C-reactive protein levels of 2.0 mg per liter or higher to rosuvastatin, 20 mg daily, or placebo and followed them for the occurrence of the combined primary end point of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes.

RESULTS

The trial was stopped after a median follow-up of 1.9 years (maximum, 5.0). Rosuvastatin reduced LDL cholesterol levels by 50% and high-sensitivity C-reactive protein levels by 37%. The rates of the primary end point were 0.77 and 1.36 per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (hazard ratio for rosuvastatin, 0.56; 95% confidence interval [CI], 0.46 to 0.69; P<0.00001), with corresponding rates of 0.17 and 0.37 for myocardial infarction (hazard ratio, 0.46; 95% CI, 0.30 to 0.70; P=0.0002), 0.18 and 0.34 for stroke (hazard ratio, 0.52; 95% CI, 0.34 to 0.79; P=0.002), 0.41 and 0.77 for revascularization or unstable angina (hazard ratio, 0.53; 95% CI, 0.40 to 0.70; P<0.00001), 0.45 and 0.85 for the combined end point of myocardial infarction, stroke, or death from cardiovascular causes (hazard ratio, 0.53; 95% CI, 0.40 to 0.69; P<0.00001), and 1.00 and 1.25 for death from any cause (hazard ratio, 0.80; 95% CI, 0.67 to 0.97; P=0.02). Consistent effects were observed in all subgroups evaluated. The rosuvastatin group did not have a significant increase in myopathy or cancer but did have a higher incidence of physician-reported diabetes.

CONCLUSIONS

In this trial of apparently healthy persons without hyperlipidemia but with elevated high-sensitivity C-reactive protein levels, rosuvastatin significantly reduced the incidence of major cardiovascular events. (ClinicalTrials.gov number, NCT00239681.)

From the Center for Cardiovascular Disease Prevention (P.M.R., E.D., J.G.M., R.J.G.) and Division of Cardiovascular Medicine (P.M.R., P.L.), Brigham and Women's Hospital, Harvard Medical School, Boston; Universidade Federal de São Paulo, São Paulo (F.A.H.F.); McGill University Health Center, Montreal (J.G.); Weill Cornell Medical College of Cornell University, New York (A.M.G.); Department of Vascular Medicine, Academic Medical Center, University of Amsterdam, Amsterdam (J.J.P.K.); University of Ulm Medical Center, Ulm, Germany (W.K.); Hospital Cordoba, Cordoba, Argentina (A.J.L.); Herlev Hospital, Copenhagen University Hospital, Herlev, Denmark (B.G.N.); University of Glasgow, Glasgow, Scotland (J.S.); and St. Luke's Episcopal Hospital–Texas Heart Institute, Houston (J.T.W.). Address reprint requests to Dr. Ridker at the Center for Cardiovascular Disease Prevention, Brigham and Women's Hospital, Boston, MA 02215, or at pridker@partners.org.

*Members of the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study group are listed in the Appendix and in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

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Current treatment algorithms for the prevention of myocardial infarction, stroke, and death from cardiovascular causes recommend statin therapy for patients with established vascular disease, diabetes, and overt hyperlipidemia.[1,2] However, half of all myocardial infarctions and strokes occur among apparently healthy men and women with levels of low-density lipoprotein (LDL) cholesterol that are below currently recommended thresholds for treatment.

Measurement of high-sensitivity C-reactive protein, an inflammatory biomarker that independently predicts future vascular events, improves global classification of risk, regardless of the LDL cholesterol level.[3-9] We have previously shown that statin therapy reduces high-sensitivity C-reactive protein levels[10,11] and that among healthy persons,[12] patients with stable coronary disease,[13] and those with the acute coronary syndrome,[14-16] the magnitude of the benefit associated with statin therapy correlates in part with the achieved high-sensitivity C-reactive protein level. To date, however, no prospective outcome trial has directly addressed the question of whether apparently healthy persons with levels of LDL cholesterol below current treatment thresholds but with elevated levels of high-sensitivity C-reactive protein might benefit from statin therapy. The primary objective of the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) was to investigate whether treatment with rosuvastatin, 20 mg daily, as compared with placebo, would decrease the rate of first major cardiovascular events.

METHODS

TRIAL DESIGN

JUPITER was a randomized, double-blind, placebo-controlled, multicenter trial conducted at 1315 sites in 26 countries (see the Supplementary Appendix, available with the full text of this article at www.nejm.org). The trial protocol was designed and written by the study chair and approved by the local institutional review board at each participating center. The trial data were analyzed by the academic study statistician and the academic programmer. The academic authors vouch for the accuracy and completeness of the data and the analyses.

The trial was financially supported by AstraZeneca. The sponsor collected the trial data and monitored the study sites but played no role in the conduct of the analyses or drafting of the manuscript and had no access to the unblinded trial data until after the manuscript was submitted for publication.

STUDY POPULATION

As described in detail elsewhere,[17,18] men 50 years of age or older and women 60 years of age or older were eligible for the trial if they did not have a history of cardiovascular disease and if, at the initial screening visit, they had an LDL cholesterol level of less than 130 mg per deciliter (3.4 mmol per liter) and a high-sensitivity C-reactive protein level of 2.0 mg per liter or more. Other requirements for inclusion were a willingness to participate for the duration of the trial, provision of written informed consent, and a triglyceride level of less than 500 mg per deciliter (5.6 mmol per liter).

Exclusion criteria were previous or current use of lipid-lowering therapy, current use of postmenopausal hormone-replacement therapy, evidence of hepatic dysfunction (an alanine aminotransferase level that was more than twice the upper limit of the normal range), a creatine kinase level that was more than three times the upper limit of the normal range, a creatinine level that was higher than 2.0 mg per deciliter (176.8 μmol per liter), diabetes, uncontrolled hypertension (systolic blood pressure >190 mm Hg or diastolic blood pressure >100 mm Hg), cancer within 5 years before enrollment (with the exception of basal-cell or squamous-cell carcinoma of the skin), uncontrolled hypothyroidism (a thyroid-stimulating hormone level that was more than 1.5 times the upper limit of the normal range), and a recent history of alcohol or drug abuse or another medical condition that might compromise safety or the successful completion of the study. Because a core scientific hypothesis of the trial concerned the role of underlying low-grade inflammation as evidenced by elevated high-sensitivity C-reactive protein levels, patients with inflammatory conditions such as severe arthritis, lupus, or inflammatory bowel disease were excluded, as were patients taking immunosuppressant agents such as cyclosporine, tacrolimus, azathioprine, or long-term oral glucocorticoids.

All potentially eligible subjects underwent a 4-week run-in phase during which they received placebo. The purpose of this phase was to identify a group of willing and eligible participants who demonstrated good compliance (defined as the taking of more than 80% of all study tablets) dur-

ing that interval. Only subjects who successfully completed the run-in phase were enrolled.

TRIAL PROTOCOL

Eligible subjects were randomly assigned in a 1:1 ratio to receive either rosuvastatin, 20 mg daily, or matching placebo. Randomization was performed with the use of an interactive voice-response system and was stratified according to center.

Follow-up visits were scheduled to occur at 13 weeks and then 6, 12, 18, 24, 30, 36, 42, 48, 54, and 60 months after randomization. A closeout visit occurred after study termination. Follow-up assessments included laboratory evaluations, pill counts, and structured interviews assessing outcomes and potential adverse events. Measurements of lipid levels, high-sensitivity C-reactive protein levels, hepatic and renal function, blood glucose levels, and glycated hemoglobin values were performed in a central laboratory. Personnel at each site also contacted their participants midway between scheduled visits to evaluate their well-being and to maintain study participation.

END POINTS

The primary outcome was the occurrence of a first major cardiovascular event, defined as nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, an arterial revascularization procedure, or confirmed death from cardiovascular causes. Secondary end points included the components of the primary end point considered individually — arterial revascularization or hospitalization for unstable angina, myocardial infarction, stroke, or death from cardiovascular causes — and death from any cause.

All reported primary end points that occurred through March 30, 2008, were adjudicated on the basis of standardized criteria by an independent end-point committee unaware of the randomized treatment assignments. Only deaths classified as clearly due to cardiovascular or cerebrovascular causes by the end-point committee were included in the analysis of the primary end point. For the end point of death from any cause, all deaths were included, regardless of whether data were available to confirm the cause of death.

STATISTICAL ANALYSIS

JUPITER was an event-driven trial designed to continue until 520 confirmed primary end points had been documented, to provide a statistical power of 90% to detect a 25% reduction in the rate of the primary end point, with a two-sided significance level of 0.05. Pretrial estimates of the duration of follow-up and number of participants were based on event rates in earlier prevention trials[19,20] and were modified to take into account plans to include low-risk groups, including women.

The trial's prespecified monitoring plan called for two interim efficacy analyses with O'Brien–Fleming stopping boundaries determined by means of the Lan–DeMets approach. The stopping boundary was crossed at the first prespecified efficacy evaluation, and on March 29, 2008, the independent data and safety monitoring board voted to recommend termination of the trial. This recommendation took into account the size and precision of the observed treatment benefit, as well as effects on the rates of death and other secondary end points being monitored and on major subgroups. Although the trial ended on March 30, 2008, when the steering committee formally accepted this recommendation, we continued the adverse-event reporting in a blinded manner for each study participant until the date he or she appeared for a formal closeout visit and discontinued therapy.

All primary analyses were performed on an intention-to-treat basis. Study participation was considered to be complete for any individual participant at the time he or she had an occurrence of the primary end point, had informed consent withdrawn, was unable to be followed further because the study site closed, or had been followed through at least March 30, 2008. The exposure time was calculated as the time between randomization and the first major cardiovascular event, the date of death, the date of the last study visit, the date of withdrawal or loss to follow-up, or March 30, 2008, whichever came first.

Cox proportional-hazards models were used to calculate hazard ratios and 95% confidence intervals for the comparison of event rates in the two study groups. Prespecified subgroup analyses were performed according to the presence or absence of major cardiovascular risk factors.

RESULTS

Between February 4, 2003, and December 15, 2006, a total of 89,890 people were screened for enrollment. Of these, 72,088 were ineligible, including 37,611 (52.2%) with LDL cholesterol levels of 130 mg per deciliter or more and an additional 25,993 (36.1%) with high-sensitivity C-reactive protein lev-

Table 1. Baseline Characteristics of the Trial Participants, According to Study Group.*

Characteristic	Rosuvastatin (N = 8901)	Placebo (N = 8901)
Age — yr		
Median	66.0	66.0
Interquartile range	60.0–71.0	60.0–71.0
Female sex — no. (%)	3426 (38.5)	3375 (37.9)
Race or ethnic group — no. (%)†		
White	6358 (71.4)	6325 (71.1)
Black	1100 (12.4)	1124 (12.6)
Hispanic	1121 (12.6)	1140 (12.8)
Other or unknown	322 (3.6)	312 (3.5)
Body-mass index‡		
Median	28.3	28.4
Interquartile range	25.3–32.0	25.3–32.0
Blood pressure — mm Hg		
Systolic		
Median	134	134
Interquartile range	124–145	124–145
Diastolic		
Median	80	80
Interquartile range	75–87	75–87
Current smoker — no. (%)	1400 (15.7)	1420 (16.0)
Family history of premature CHD — no. (%)§	997 (11.2)	1048 (11.8)
Metabolic syndrome — no. (%)¶	3652 (41.0)	3723 (41.8)
Aspirin use — no. (%)	1481 (16.6)	1477 (16.6)
High-sensitivity C-reactive protein — mg/liter‖		
Median	4.2	4.3
Interquartile range	2.8–7.1	2.8–7.2
LDL cholesterol — mg/dl		
Median	108	108
Interquartile range	94–119	94–119
HDL cholesterol — mg/dl		
Median	49	49
Interquartile range	40–60	40–60
Triglycerides — mg/dl		
Median	118	118
Interquartile range	85–169	86–169
Total cholesterol — mg/dl		
Median	186	185
Interquartile range	168–200	169–199
Glucose — mg/dl		
Median	94	94
Interquartile range	87–102	88–102

Table 1. (Continued.)

Characteristic	Rosuvastatin (N=8901)	Placebo (N=8901)
Glycated hemoglobin — %		
Median	5.7	5.7
Interquartile range	5.4–5.9	5.5–5.9
Glomerular filtration rate — ml/min/1.73 m^2 of body-surface area		
Median	73.3	73.6
Interquartile range	64.6–83.7	64.6–84.1

* To convert values for low-density lipoprotein (LDL), high-density lipoprotein (HDL), and total cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. To convert values for glucose to millimoles per liter, multiply by 0.05551.
† Race or ethnic group was self-reported.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ A family history of premature coronary heart disease (CHD) was defined as diagnosis of the disease in a male first-degree relative before the age of 55 years or in a female first-degree relative before the age of 65 years.
¶ The metabolic syndrome was defined according to consensus criteria of the American Heart Association and the National Heart, Lung, and Blood Institute.[21]
‖ Values for high-sensitivity C-reactive protein are expressed as the average of the values obtained at two screening visits.

els of less than 2.0 mg per liter. Other reasons for exclusion are presented in Figure 1 in the Supplementary Appendix. A total of 17,802 people were randomly assigned to a study group.

BASELINE CHARACTERISTICS

By design, the study population was diverse; 6801 of the 17,802 participants were women (38.2%) and 4485 (25.2%) were black or Hispanic (Table 1). Aspirin was used by 16.6% of participants, and 41.4% had the metabolic syndrome.[21] In both the rosuvastatin and placebo groups, the median LDL cholesterol level was 108 mg per deciliter (2.8 mmol per liter), the high-density lipoprotein (HDL) cholesterol level was 49 mg per deciliter (1.3 mmol per liter), and the triglyceride level was 118 mg per deciliter (1.3 mmol per liter); the high-sensitivity C-reactive protein level was 4.2 and 4.3 mg per liter in the rosuvastatin and placebo groups, respectively.

COMPLIANCE AND EFFECTS OF ROSUVASTATIN ON LIPIDS AND HIGH-SENSITIVITY C-REACTIVE PROTEIN

At the time the study was terminated, 75% of participants were taking their study pills. Among those assigned to rosuvastatin, the median LDL cholesterol level at 12 months was 55 mg per deciliter (1.4 mmol per liter) (interquartile range, 44 to 72 [1.1 to 1.9]), and the median high-sensitivity C-reactive protein level was 2.2 mg per liter (interquartile range, 1.2 to 4.4) (Table 2). At the 12-month visit, the rosuvastatin group, as compared with the placebo group, had a 50% lower median LDL cholesterol level (mean difference, 47 mg per deciliter [1.2 mmol per liter]), a 37% lower median high-sensitivity C-reactive protein level, and a 17% lower median triglyceride level ($P<0.001$ for all three comparisons). These effects persisted throughout the study period. At 12 months, the median HDL cholesterol level was 4% higher in the rosuvastatin group than in the placebo group ($P<0.001$), but this effect was not present at the time of study completion ($P=0.34$).

END POINTS

At the time of study termination (median follow-up, 1.9 years; maximal follow-up, 5.0 years), 142 first major cardiovascular events had occurred in the rosuvastatin group, as compared with 251 in the placebo group (Table 3). The rates of the primary end point were 0.77 and 1.36 per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (hazard ratio for rosuvastatin, 0.56; 95% confidence interval [CI], 0.46 to 0.69; $P<0.00001$) (Table 3 and Fig. 1). In a test for interaction between the study-group assignment and follow-up time, there was no significant violation of the proportional-hazards assumption.

On the basis of Kaplan–Meier estimates (Fig. 1), the number of patients who would need to be treated with rosuvastatin for 2 years to prevent the occurrence of one primary end point is 95, and

Table 2. Lipid and High-Sensitivity C-Reactive Protein Levels during the Follow-up Period, According to Study Group.*

Level	12 Mo		24 Mo		36 Mo		48 Mo	
	Rosuvastatin	Placebo	Rosuvastatin	Placebo	Rosuvastatin	Placebo	Rosuvastatin	Placebo
High-sensitivity C-reactive protein (mg/liter)								
Median	2.2	3.5	2.2	3.5	2.0	3.5	1.8	3.3
Interquartile range	1.2–4.4	2.0–6.2	1.2–4.3	2.0–6.1	1.1–3.9	1.8–6.0	1.1–3.7	1.7–6.1
LDL cholesterol (mg/dl)								
Median	55	110	54	108	53	106	55	109
Interquartile range	44–72	94–125	42–69	93–123	42–69	90–121	44–70	94–124
HDL cholesterol (mg/dl)								
Median	52	50	52	50	50	49	50	50
Interquartile range	43–64	41–61	44–65	42–61	41–62	40–59	41–61	42–60
Triglycerides (mg/dl)								
Median	99	119	99	116	106	123	99	118
Interquartile range	74–137	87–167	73–134	83–165	77–148	90–173	74–140	87–164

* P<0.001 for all between-group comparisons except for high-density lipoprotein (HDL) cholesterol at 36 months (P=0.003) and at 48 months (P=0.34). The mean difference in low-density lipoprotein (LDL) cholesterol levels between the two groups at 12 months was 47 mg per deciliter (1.2 mmol per liter). To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129.

the number needed to treat for 4 years is 31. If 4-year risks are projected over an average 5-year treatment period, as has been commonly done in previous statin trials according to the method of Altman and Andersen,[22] the number needed to treat to prevent the occurrence of one primary end point is 25.

Rosuvastatin was also associated with significant reductions in rates of the individual components of the primary trial end point. For the end point of fatal or nonfatal myocardial infarction, event rates were 0.17 and 0.37 per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (hazard ratio for rosuvastatin, 0.46; 95% CI, 0.30 to 0.70; P=0.0002). The corresponding rates were 0.18 and 0.34 for fatal or nonfatal stroke (hazard ratio, 0.52; 95% CI, 0.34 to 0.79; P=0.002), 0.41 and 0.77 for arterial revascularization or unstable angina (hazard ratio, 0.53; 95% CI, 0.40 to 0.70; P<0.00001), and 0.45 and 0.85 for the combined end point of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes (hazard ratio, 0.53; 95% CI, 0.40 to 0.69; P<0.00001).

In addition, the rates of death from any cause were 1.00 and 1.25 per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (hazard ratio for the rosuvastatin group, 0.80; 95% CI, 0.67 to 0.97; P=0.02) (Table 3 and Fig. 1). In analyses limited to deaths for which the date of death was known with certainty, there was a similar reduction in the hazard ratio associated with rosuvastatin (0.81; 95% CI, 0.67 to 0.98; P=0.03).

SUBGROUP ANALYSES

For the primary end point, there was no evidence of heterogeneity in the results for any subgroup evaluated. Relative hazard reductions in the rosuvastatin group were similar for women (46%) and men (42%) and were observed in every subgroup evaluated, including subgroups according to age, race or ethnic group, region of origin, status with regard to traditional risk factors, and Framingham risk score (Fig. 2). Groups typically assumed to be at very low risk also benefited. For participants who had elevated levels of high-sensitivity C-reactive protein but who were nonsmokers, were not overweight (had a body-mass index [the weight in kilograms divided by the square of the height in meters] ≤25), did not have the metabolic syndrome, had a calculated Framingham risk score of 10% or less, or had an LDL cholesterol level of 100 mg per deciliter (2.6 mmol per

Table 3. Outcomes According to Study Group.

End Point	Rosuvastatin (N=8901)		Placebo (N=8901)		Hazard Ratio (95% CI)	P Value
	No. of Patients	Rate per 100 person-yr	No. of Patients	Rate per 100 person-yr		
Primary end point	142	0.77	251	1.36	0.56 (0.46–0.69)	<0.00001
Nonfatal myocardial infarction	22	0.12	62	0.33	0.35 (0.22–0.58)	<0.00001
Any myocardial infarction	31	0.17	68	0.37	0.46 (0.30–0.70)	0.0002
Nonfatal stroke	30	0.16	58	0.31	0.52 (0.33–0.80)	0.003
Any stroke	33	0.18	64	0.34	0.52 (0.34–0.79)	0.002
Arterial revascularization	71	0.38	131	0.71	0.54 (0.41–0.72)	<0.0001
Hospitalization for unstable angina	16	0.09	27	0.14	0.59 (0.32–1.10)	0.09
Arterial revascularization or hospitalization for unstable angina	76	0.41	143	0.77	0.53 (0.40–0.70)	<0.00001
Myocardial infarction, stroke, or confirmed death from cardiovascular causes	83	0.45	157	0.85	0.53 (0.40–0.69)	<0.00001
Death from any cause						
Death on known date	190	0.96	235	1.19	0.81 (0.67–0.98)	0.03
Any death	198	1.00	247	1.25	0.80 (0.67-0.97)	0.02

liter) or lower, the observed relative reductions in the hazard ratio associated with rosuvastatin for the primary end point were similar to those in higher-risk groups. For subjects with elevated high-sensitivity C-reactive protein levels but no other major risk factor other than increased age, the benefit of rosuvastatin was similar to that for higher-risk subjects (hazard ratio, 0.63; 95% CI, 0.44 to 0.92; P=0.01).

ADVERSE EVENTS

Total numbers of reported serious adverse events were similar in the rosuvastatin and placebo groups (1352 and 1377, respectively; P=0.60) (Table 4). Nineteen myopathic events were reported (in 10 subjects receiving rosuvastatin and 9 receiving placebo, P=0.82). After closure of the trial, one nonfatal case of rhabdomyolysis was reported in a 90-year-old participant with febrile influenza, pneumonia, and trauma-induced myopathy who was in the rosuvastatin group (listed in Table 4).

There were no significant differences between the two study groups with regard to muscle weakness, newly diagnosed cancer, or disorders of the hematologic, gastrointestinal, hepatic, or renal systems. With regard to direct measures of safety, rates of elevation of the alanine aminotransferase level to more than three times the upper limit of the normal range were similar in the two groups. Median glomerular filtration rates at 12 months were 66.8 and 66.6 ml per minute per 1.73 m^2 of body-surface area in the rosuvastatin and placebo groups, respectively (P=0.02). Protocol-specified measurements showed no significant differences between the study groups during the follow-up period with respect to the fasting blood glucose level (98 mg per deciliter [5.4 mmol per liter] in both groups, P=0.12) or newly diagnosed glycosuria (in 36 subjects in the rosuvastatin group and 32 in the placebo group, P=0.64); there was a minimal difference in the median glycated hemoglobin value (5.9% and 5.8%, respectively; P=0.001). Nevertheless, physician-reported diabetes was more frequent in the rosuvastatin group (270 reports of diabetes, vs. 216 in the placebo group; P=0.01); these events were not adjudicated by the end-point committee. In contrast to the findings in a previous study of high-dose statin therapy,[23] we found no significant between-group difference in the number of subjects with intracranial hemorrhage (six in the rosuvastatin group and nine in the placebo group, P=0.44).

DISCUSSION

In this randomized trial of apparently healthy men and women with elevated levels of high-sensitivity C-reactive protein, rosuvastatin significantly re-

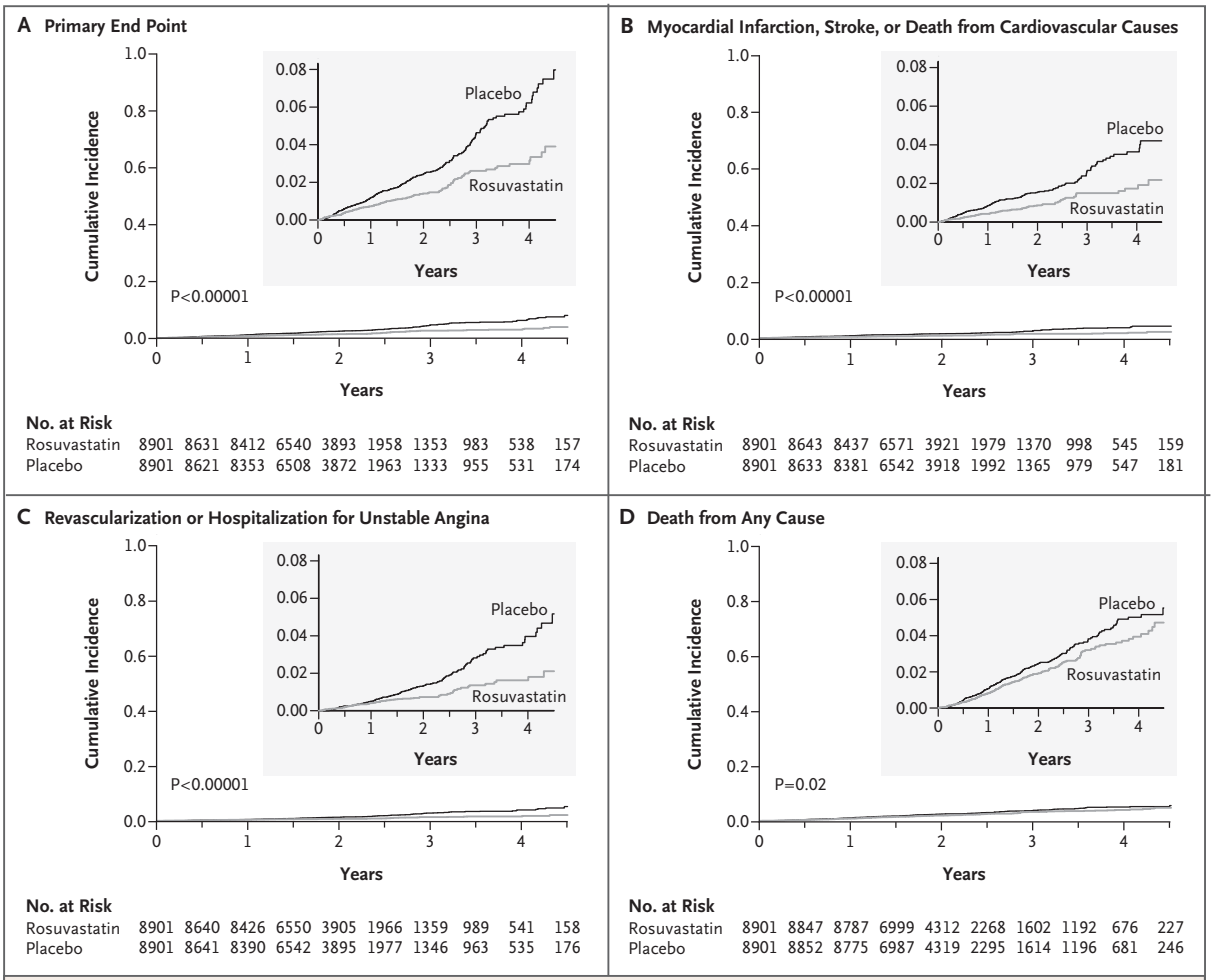

Figure 1. Cumulative Incidence of Cardiovascular Events According to Study Group.

Panel A shows the cumulative incidence of the primary end point (nonfatal myocardial infarction, nonfatal stroke, arterial revascularization, hospitalization for unstable angina, or confirmed death from cardiovascular causes). The hazard ratio for rosuvastatin, as compared with placebo, was 0.56 (95% confidence interval [CI], 0.46 to 0.69; P<0.00001). Panel B shows the cumulative incidence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes, for which the hazard ratio in the rosuvastatin group was 0.53 (95% CI, 0.40 to 0.69; P<0.00001). Panel C shows the cumulative incidence of arterial revascularization or hospitalization for unstable angina, for which the hazard ratio in the rosuvastatin group was 0.53 (95% CI, 0.40 to 0.70; P<0.00001). Panel D shows the cumulative incidence of death from any cause, for which the hazard ratio in the rosuvastatin group was 0.80 (95% CI, 0.67 to 0.97; P=0.02). In each panel, the inset shows the same data on an enlarged y axis and on a condensed x axis.

duced the incidence of major cardiovascular events, despite the fact that nearly all study participants had lipid levels at baseline that were well below the threshold for treatment according to current prevention guidelines. Rosuvastatin also significantly reduced the incidence of death from any cause. These effects were consistent in all subgroups evaluated, including subgroups customarily considered to be at low risk, such as people with Framingham risk scores of 10% or less, those with LDL cholesterol levels of 100 mg per deciliter or less, those without the metabolic syndrome, and those with elevated levels of high-sensitivity C-reactive protein but no other major risk factor. The trial also showed robust reductions in cardiovascular events with statin therapy in women and black and Hispanic populations for which data on primary prevention are limited.

Previous statin trials (most of which used LDL cholesterol level criteria for enrollment) have gen-

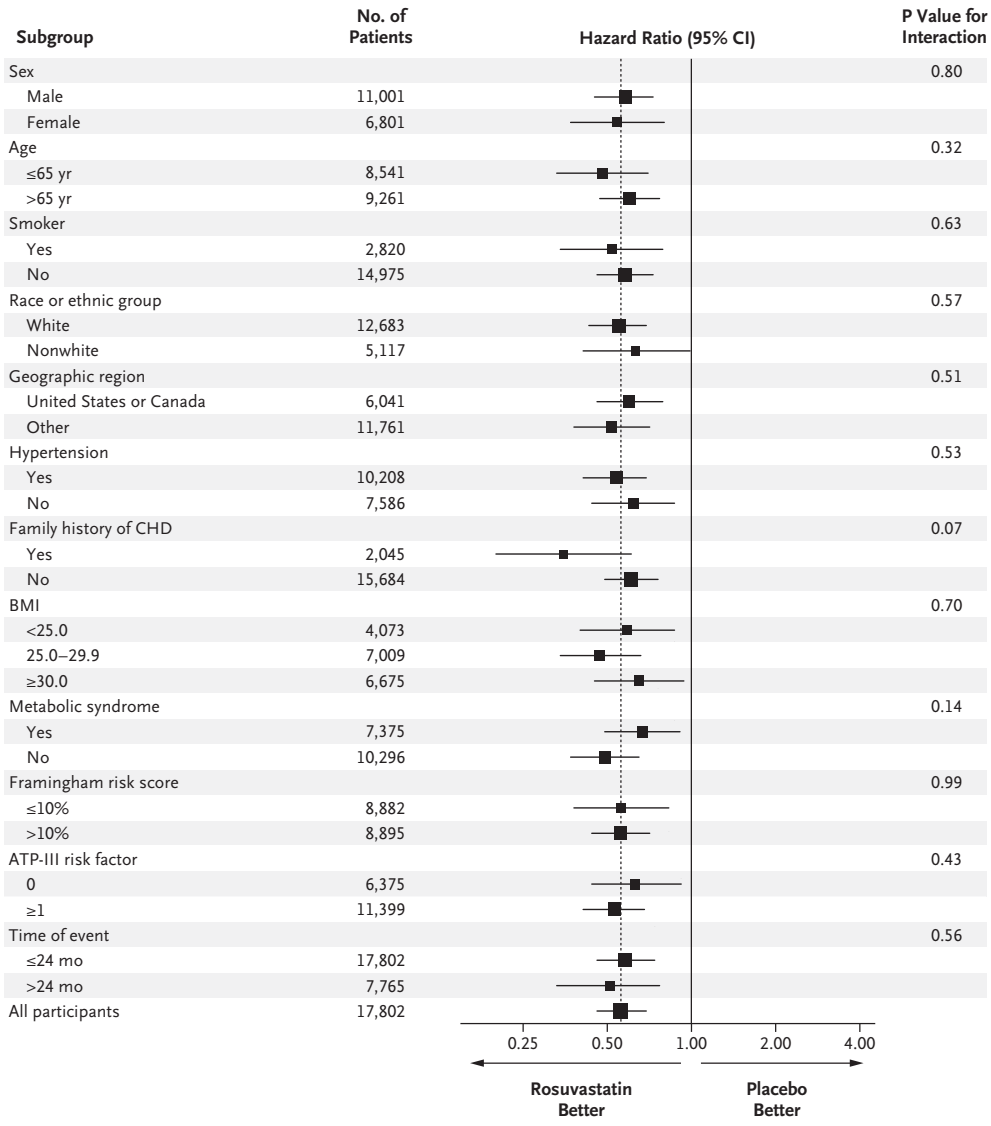

Figure 2. Effects of Rosuvastatin on the Primary End Point, According to Baseline Characteristics.

The primary end point was the combination of nonfatal myocardial infarction, nonfatal stroke, arterial revascularization, hospitalization for unstable angina, or confirmed death from cardiovascular causes. The relative hazard ratios for rosuvastatin as compared with placebo are shown, with the size of each black square proportionate to the number of participants who had an occurrence of the primary end point in the subgroup; the horizontal lines indicate 95% confidence intervals. The dashed vertical line indicates the overall relative risk reduction for the complete trial cohort. Also shown are the P values for the test of an interaction between the primary end point and the categories within each subgroup. For the ordinal variables, interaction tests considered a trend across the subgroup categories with integer scores applied to these categories. Data were missing for some participants in some subgroups. The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. CHD denotes coronary heart disease. The metabolic syndrome was defined according to 2005 consensus criteria of the American Heart Association and the National Heart, Lung, and Blood Institute.[21] ATP-III risk factors refer to major risk factors, other than increased age, according to the Adult Treatment Panel III of the National Cholesterol Education Program. Race or ethnic group was self-reported.

Table 4. Monitored Adverse Events, Measured Laboratory Values, and Other Reported Events of Interest during the Follow-up Period.*

Event	Rosuvastatin (N=8901)	Placebo (N=8901)	P Value
Monitored adverse events			
Any serious adverse event — no. (%)	1352 (15.2)	1377 (15.5)	0.60
Muscular weakness, stiffness, or pain — no. (%)	1421 (16.0)	1375 (15.4)	0.34
Myopathy — no. (%)	10 (0.1)	9 (0.1)	0.82
Rhabdomyolysis — no. (%)†	1 (<0.1)	0	—
Newly diagnosed cancer — no. (%)	298 (3.4)	314 (3.5)	0.51
Death from cancer — no. (%)	35 (0.4)	58 (0.7)	0.02
Gastrointestinal disorder — no. (%)	1753 (19.7)	1711 (19.2)	0.43
Renal disorder — no. (%)	535 (6.0)	480 (5.4)	0.08
Bleeding — no. (%)	258 (2.9)	275 (3.1)	0.45
Hepatic disorder — no. (%)	216 (2.4)	186 (2.1)	0.13
Laboratory values‡			
Creatinine, >100% increase from baseline — no. (%)	16 (0.2)	10 (0.1)	0.24
Glomerular filtration rate at 12 mo — ml/min/1.73 m^2			0.02
Median	66.8	66.6	
Interquartile range	59.1–76.5	58.8–76.2	
Alanine aminotransferase >3× ULN on consecutive visits — no. (%)	23 (0.3)	17 (0.2)	0.34
Glycated hemoglobin at 24 mo — %			0.001
Median	5.9	5.8	
Interquartile range	5.7–6.1	5.6–6.1	
Fasting glucose at 24 mo — mg/dl			0.12
Median	98	98	
Interquartile range	91–107	90–106	
>Trace of glucose in urine at 12 mo — no. (%)	36 (0.5)	32 (0.4)	0.64
Other events			
Newly diagnosed diabetes (physician-reported) — no. (%)	270 (3.0)	216 (2.4)	0.01
Hemorrhagic stroke — no. (%)	6 (0.1)	9 (0.1)	0.44

* Data were missing for some patients for some events.
† The single case of rhabdomyolysis occurred after closure of the trial.
‡ To convert values for creatinine to micromoles per liter, multiply by 88.4. To convert values for glucose to millimoles per liter, multiply by 0.05551. ULN denotes upper limit of the normal range.

erally reported a 20% reduction in vascular risk for each 1 mmol per liter (38.7 mg per deciliter) of absolute reduction in the LDL cholesterol level,[24,25] an effect that would have predicted a proportionate reduction in the number of events in our study of approximately 25%. However, the reduction in the hazard seen in our trial, in which enrollment was based on elevated high-sensitivity C-reactive protein levels rather than on elevated LDL cholesterol levels, was almost twice this magnitude and revealed a greater relative benefit than that found in most previous statin trials (see Fig. 2 in the Supplementary Appendix).

In this trial, myopathy, hepatic injury, and cancer did not occur more frequently with rosuvastatin than with placebo, despite the fact that LDL cholesterol levels below 55 mg per deciliter were achieved in half the participants receiving rosuvastatin (and LDL cholesterol levels below 44 mg per deciliter in 25%). Since the median follow-up of subjects was 1.9 years, we cannot rule out the possibility that the rate of adverse events might

increase in this population during longer courses of therapy. However, no such increase was detected in an analysis of participants who continued to receive treatment for 4 or more years.

We did detect a small but significant increase in the rate of physician-reported diabetes with rosuvastatin, as well as a small, though significant, increase in the median value of glycated hemoglobin. Increases in glucose and glycated hemoglobin levels, the incidence of newly diagnosed diabetes, and worsening glycemic control have been reported in previous trials of pravastatin, simvastatin, and atorvastatin.[26,27] However, systematic protocol-specified measurements showed no significant difference between our two study groups in fasting blood glucose levels or glycosuria during the follow-up period. Therefore, although the increase in the rate of physician-reported diabetes in the rosuvastatin group could reflect the play of chance, further study is needed before any causative effect can be established or refuted. Physicians' reports of diabetes were not adjudicated by the end-point committee, and careful evaluation of participants' records will be needed to better understand this possible effect.

Potential limitations of our study merit consideration. First, we did not include people with low levels of high-sensitivity C-reactive protein in our trial, since our hypothesis-generating analysis of high-sensitivity C-reactive protein in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)[12] showed extremely low event rates and no evidence that statin therapy lowered vascular risk among persons who had neither hyperlipidemia nor elevated high-sensitivity C-reactive protein levels. Thus, a trial of statin therapy involving people with both low cholesterol and low high-sensitivity C-reactive protein levels would have been not only infeasible in terms of statistical power and sample size but also highly unlikely to show a benefit.

Second, since the trial was stopped early by the independent data and safety monitoring board after a median follow-up of less than 2 years, the effect of longer-term therapy should be considered. We verified that the assumption of proportional hazards was not violated during the follow-up period, and we found a robust benefit of rosuvastatin in analyses restricted to events occurring more than 2 years after randomization. These findings, as well as the demonstration that rates of hospitalization and arterial revascularization were reduced by 47% within a 2-year period, suggest that the strategy tested could be cost-effective. The strategy also could reduce the demand for imaging tests in asymptomatic populations. On the other hand, our trial evaluated the use of rosuvastatin for the prevention of first cardiovascular events; therefore, the absolute event rates are lower than would be expected among patients with a history of vascular disease, a fact that should be taken into account in considering whether the use of statin therapy among those with low LDL cholesterol levels but elevated high-sensitivity C-reactive protein levels would be cost-effective if applied widely.

With regard to the inflammatory hypothesis of atherothrombosis, our trial involved an agent that is highly effective at reducing levels of both cholesterol and high-sensitivity C-reactive protein. In previous work, achieving low levels of both LDL cholesterol and high-sensitivity C-reactive protein appears to have contributed to the clinical benefit of statin therapy.[12-16] Given the recognition that atherothrombosis is in some respects a disorder of innate immunity,[28] we hope the data presented here spur the further development of targeted antiinflammatory drugs as potential vascular therapeutic agents and lead to innovative trials that can directly address whether the inhibition of inflammation by agents other than statins can reduce rates of vascular events.[29]

In conclusion, in this randomized trial of apparently healthy men and women who did not have hyperlipidemia but did have elevated levels of high-sensitivity C-reactive protein, the rates of a first major cardiovascular event and death from any cause were significantly reduced among the participants who received rosuvastatin as compared with those who received placebo.

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APPENDIX

Committee and board members for JUPITER were as follows: **Steering Committee** — P.M. Ridker (principal investigator and trial chair), F.A.H. Fonseca, J. Genest, A.M. Gotto, Jr., J.J.P. Kastelein, W. Koenig, P. Libby, A.J. Lorenzatti, B.G. Nordestgaard, J. Shepherd, J.T. Willerson; **Clinical Coordinating Center** — P.M. Ridker (chair), E. Danielson, R.J. Glynn, J.G. MacFadyen, S. Mora (Brigham and Women's Hospital, Boston); **Study Statistician** — R.J. Glynn; **Independent Data and Safety Monitoring Board** — R. Collins (chair), K. Bailey, B. Gersh, G. Lamas, S. Smith, D. Vaughan; **Clinical End Point Committee —** K. Mahaffey (chair), P. Brown, D. Montgomery, M. Wilson, F. Wood (Duke University, Durham NC). The site investigators are listed in the Supplementary Appendix.

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Appendix D: Clinical Study Protocol Appendix H, Management of Increased Creatine Kinase (CK)

AstraZeneca

Clinical Study Protocol: Appendix H	
Study Code	4522US/0011
Version No.	2.0
Appendix Date	15 January, 2003

Appendix H

Management of Increased Creatine Kinase (CK)

MANAGEMENT OF INCREASED CREATINE KINASE (CK)

- Subjects should be advised to promptly report unexplained muscle pain or weakness
- Myopathy is defined as muscle aches or weakness in conjunction with increases in CK > 10 x ULN, should be recorded as an adverse event
- Should markedly elevated CK levels occur or myopathy diagnosed or suspected, trial therapy should be discontinued
- Trial therapy should be temporarily withheld or discontinued in any subject with an acute, serious condition suggestive of myopathy, or if a condition predisposing to the development of renal failure secondary to rhabdomyolysis (eg. Sepsis, hypotension, major surgery, trauma, severe metabolic, endocrine or electrolyte disorders, or uncontrolled seizures) is present

Appendix E: FDA AERS database tables for glucose disorder AEs and microvascular complications of diabetes

LIST OF TABLES

Table 1 FDA AERS database through 1Q2009: Statins and glucose disorder AEs ("Suspect Medication Only" vs "Suspect or Concomitant Medication")

MedDRA PT Statins	n (Suspect)	EB05 (Suspect)	n (Suspect or concomitant)	EB05 (Suspect or concomitant)
Diabetes mellitus				
Lovastatin	76	2.239	133	1.513
Atorvastatin	394	1.716	890	1.435
Pravastatin	51	0.872	183	1.055
Simvastatin	81	0.625	442	1.026
Fluvastatin	11	0.459	59	1.161
Rosuvastatin	41	0.371	89	0.604
Pitavastatin	0	NA	4	0.716
Type 2 diabetes mellitus				
Atorvastatin	57	1.433	233	1.991
Simvastatin	26	1.024	135	1.6
Pravastatin	6	0.429	45	1.361
Rosuvastatin	13	0.373	33	0.789
Fluvastatin	2	0.247	7	0.576
Lovastatin	1	0.146	22	1.58
Pitavastatin	0	NA	0	NA
Diabetes mellitus inadequate control				
Atorvastatin	75	0.964	360	1.904
Simvastatin	34	0.713	217	1.594
Rosuvastatin	18	0.627	38	1.105
Pravastatin	14	0.572	75	1.225
Pitavastatin	1	0.302	5	1.525
Fluvastatin	1	0.061	15	0.727
Lovastatin	0	NA	22	1.016
Glucose tolerance impaired				
Atorvastatin	28	2.619	63	2.162
Simvastatin	5	0.522	21	0.889
Fluvastatin	1	0.219	1	0.281
Rosuvastatin	2	0.149	4	0.343
Pravastatin	1	0.134	7	0.637
Pitavastatin	0	NA	0	NA
Lovastatin	0	NA	2	0.394
Glycosylated haemoglobin increased				
Atorvastatin	65	2.136	216	2.329
Pravastatin	10	0.945	59	2.158

Table 1 FDA AERS database through 1Q2009: Statins and glucose disorder AEs ("Suspect Medication Only" vs "Suspect or Concomitant Medication")

MedDRA PT Statins	n (Suspect)	EB05 (Suspect)	n (Suspect or concomitant)	EB05 (Suspect or concomitant)
Fluvastatin	5	0.893	16	1.617
Simvastatin	12	0.487	119	1.69
Rosuvastatin	11	0.391	30	0.894
Lovastatin	0	NA	15	1.202
Pitavastatin	0	NA	2	0.643

PT Preferred term.

NOTE: EB05 is the lower boundary of the 90% CI for the Empiric Bayesian Geometric Mean (EBGM). The EBGM, as calculated using the Multi item Gamma Poisson Shrinker (MGPS), is the adjusted ratio of the observed number of reports for a drug event pair to the expected number of reports for that pair. An EB05 score ≥1.8 was considered the threshold for identifying a potential safety signal, as reflected by a higher than expected number of reports. Only Preferred Terms for which there was at least 1 drug-event combination with an EB05 ≥1.8 (in either data mining run) are shown.

Table 2 FDA AERS database through 1Q2009: Statins and microvascular complications of diabetes ("Suspect Medication Only" vs "Suspect or Concomitant Medication")

MedDRA Preferred Term Statins	n (Suspect)	EB05 (Suspect)	n (Suspect or concomitant)	EB05 (Suspect or concomitant)
Diabetic Nephropathy				
Atorvastatin	17	1.953	46	2.241
Simvastatin	9	1.323	31	1.877
Rosuvastatin	4	0.611	6	0.843
Pravastatin	2	0.36	19	2.333
Lovastatin	0	NA	4	0.842
Fluvastatin	0	NA	3	0.706
Pitavastatin	0	NA	2	0.764
Diabetic Neuropathy				
Atorvastatin	21	2.221	88	2.381
Simvastatin	10	0.942	46	1.612
Lovastatin	2	0.527	7	1.087
Fluvastatin	2	0.452	7	1.224
Pravastatin	2	0.253	21	1.63
Rosuvastatin	0	NA	6	0.468
Pitavastatin	0	NA	2	0.741
Diabetic Retinopathy				
Fluvastatin	2	0.457	5	0.895
Atorvastatin	5	0.26	53	1.499
Lovastatin	1	0.236	8	1.37
Simvastatin	2	0.138	32	1.239
Pravastatin	1	0.11	13	1.026
Rosuvastatin	0	NA	2	0.192
Pitavastatin	0	NA	0	NA

PT Preferred term.

NOTE: EB05 is the lower boundary of the 90% CI for the Empiric Bayesian Geometric Mean (EBGM). The EBGM, as calculated using the Multi item Gamma Poisson Shrinker (MGPS), is the adjusted ratio of the observed number of reports for a drug event pair to the expected number of reports for that pair. An EB05 score ≥1.8 was considered the threshold for identifying a potential safety signal, as reflected by a higher than expected number of reports.