CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-366/S-016

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	S 16
Priority or Standard	Standard
Submit Date(s)	8 April 2009
Received Date(s)	8 April 2009
PDUFA Goal Date	8 February 2010
Division/Office	DMEP/OND
Reviewer Name(s)	Mary Dunne Roberts, MD
Review Completion Date	5 February 2010
Established Name	Rosuvastatin calcium
(Proposed) Trade Name	CRESTOR
Therapeutic Class	Statin
Applicant	AstraZeneca
Formulation(s)	Tablet
Dosing Regimen	10 to 40 mg
Indication(s)	Prevention of cardiovascular events
Intended Population(s)	Persons with increased risk of atherosclerotic cardiovascular disease

Template Version: March 6, 2009

Table of Contents

1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT 11

1.1 Recommendation on Regulatory Action 11
1.2 Risk Benefit Assessment 11
1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies . 12
1.4 Recommendations for Postmarket Requirements and Commitments 12

2 INTRODUCTION AND REGULATORY BACKGROUND 12

ROSUVASTATIN EFFICACY TRIALS OF CLINICAL OUTCOMES PRIOR TO JUPITER SUBMISSION 17

2.1 Product Information 19
2.2 Tables of Currently Available Treatments for Proposed Indications 20
2.3 Availability of Proposed Active Ingredient in the United States 23
2.4 Important Safety Issues With Consideration to Related Drugs 23
2.5 Summary of Presubmission Regulatory Activity Related to Submission 23
2.6 Other Relevant Background Information 24

3 ETHICS AND GOOD CLINICAL PRACTICES 24

3.1 Submission Quality and Integrity 24
3.2 Compliance with Good Clinical Practices 25
3.3 Financial Disclosures 27

4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES 28

4.1 Chemistry Manufacturing and Controls 28
4.2 Clinical Microbiology 28
4.3 Preclinical Pharmacology/Toxicology 28
4.4 Clinical Pharmacology 28
4.4.1 Mechanism of Action 28
4.4.2 Pharmacodynamics 28
4.4.3 Pharmacokinetics 28

5 SOURCES OF CLINICAL DATA 29

5.1 Tables of Studies/Clinical Trials 29
5.2 Review Strategy 29
5.3 Discussion of Individual Studies/Clinical Trials 30
5.3.1 Objectives and outcome measures 30
5.3.2 Statistical and Analytical Plans 31
5.3.3 Study design 32
5.3.4 Amendments and Post Hoc Changes 34

6 REVIEW OF EFFICACY 36

6.1 Indication 37
6.1.1 Methods 37
6.1.2 Demographics and other subject characteristics 40
6.1.3 Subject Disposition 45
6.1.4 Analysis of Primary Endpoint(s) 50
6.1.4.1 Breakdown of Events within the primary endpoint 52
6.1.4.2 Summary of primary endpoint 53
6.1.5 Analysis of Secondary Endpoints(s) 54
6.1.5.1 Time to death (total mortality) 54
6.1.5.2 Time to noncardiovascular death 54
6.1.5.3 Time to discontinuation of blinded study medication due to adverse events 55
6.1.5.4 Time to development of (investigator-reported) diabetes mellitus 55
6.1.5.5 Time to development of venous thromboembolic events 56
6.1.5.6 Time to bone fractures 56
6.1.6 Other Endpoints 57
6.1.6.1 Lipoprotein and hsCRP levels 57
6.1.7 Subpopulations 61
6.1.7.1 Prespecified subgroup analyses 61
6.1.7.2 Post-hoc exploratory subgroup analyses 62
6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations 63
6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects 64
6.1.10 Additional Efficacy Issues/Analyses 64

7 REVIEW OF SAFETY 64

7.1 Methods 66
7.1.1 Studies/Clinical Trials Used to Evaluate Safety 66
7.1.2 Categorization of Adverse Events 69
7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence 70
7.2 Adequacy of Safety Assessments 70
7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations 70
7.2.2 Explorations for Dose Response 71
7.2.3 Special Animal and/or In Vitro Testing 71
7.2.4 Routine Clinical Testing 71
7.2.5 Metabolic, Clearance, and Interaction Workup 71
7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class 71
7.3 Major Safety Results 71
7.3.1 Deaths 71
7.3.1.1 Fatal TEAEs in the cardiac and nervous system SOC 75
7.3.1.2 Fatal TEAEs in the General disorder SOC 79
7.3.1.3 Fatal TEAEs in Gastrointestinal SOC 85
7.3.2 Nonfatal Serious Adverse Events 90

7.3.3 Dropouts and/or Discontinuations 94
7.3.3.2 Withdrawal of study participation due to adverse event 95
7.3.4 Significant Adverse Events 96
7.3.4.1 Hepatic adverse events 96
7.3.4.2 Hepatic biochemistry 98
7.3.4.3 Skeletal muscle adverse events 99
7.3.4.4 Skeletal muscle biochemistry 100
7.3.4.5 Renal adverse events 101
7.3.4.6 Renal biochemistry 103
7.3.4.7 Renal function 104
7.3.4.8 Neuropsychiatric adverse events 105
7.3.5 Submission Specific Primary Safety Concerns 120
7.4 Supportive Safety Results 120
7.4.1 Common Adverse Events 120
7.4.2 Laboratory Findings 122
7.4.3 Vital Signs 124
7.4.4 Electrocardiograms (ECGs) 124
7.4.5 Special Safety Studies/Clinical Trials 124
7.4.6 Immunogenicity 124
7.5 Other Safety Explorations 124
7.5.1 Dose Dependency for Adverse Events 124
7.5.2 Time Dependency for Adverse Events 124
7.5.3 Drug-Demographic Interactions 125
7.5.3.1 Effect of gender 125
7.5.3.2 Effect of age 125
7.5.3.3 Effect of ethnicity 125
7.5.3.4 Effect of LDL <50 mg/dL 126
7.5.4 Drug-Disease Interactions 126
7.5.4.1 Effect of hypertension at baseline 126
7.5.4.2 Effect of renal impairment (<60 ml/min/1.73 m^2) 126
7.5.5 Drug-Drug Interactions 126
7.5.5.1 Vitamin K antagonist anticoagulants 126
7.5.5.2 Gemfibrozil 126
7.5.5.3 Cyclosporine 127
7.5.5.4 Lopinavir/Ritonavir 127
7.6 Additional Safety Evaluations 127
7.6.1 Human Carcinogenicity 127
7.6.1.1 Fatal events due to cancer 127
7.6.3 Pediatrics and Assessment of Effects on Growth 133
7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound 133
7.7 Additional Submissions / Safety Issues 133

8 POSTMARKET EXPERIENCE 133

8.1 Update of regulatory actions taken for safety reasons 133

8.2 Patient exposure 133
8.3 Hepatic events 133
8.4 Musculoskeletal events 134
8.4.1 Rhabdomyolysis 134
8.4.2 Myopathy, myositis, and CK increase 136
8.5 Renal events 137

9 APPENDICES 139

9.1 Literature Review/References 142
9.2 Labeling Recommendations 142
9.3 Advisory Committee Meeting 153

Table of Tables

Table 1: NCEP 2004 Update of ATP-III goals and cutpoints for treatment 14
Table 2: Percent change from baseline across the dose range of rosuvastatin, atorvastatin, pravastatin, and simvastatin-STELLAR trial 17
Table 3: Cardiovascular primary and secondary prevention indications in statin labels20
Table 4: JUPITER trial centers closed due to noncompliance with GCP standards..... 25
Table 5: JUPITER trial centers inspected and results of inspection by DSI 26
Table 6: JUPITER clinical investigators receiving significant payments from applicant 27
Table 7: Description of and key objectives in the rosuvastatin clinical efficacy study for the primary prevention of cardiovascular events..... 29
Table 8: Demographic and baseline characteristics (ITT population)..... 41
Table 9: JUPITER: Major cardiovascular NCEP-ATP III risk factors at baseline (ITT population) 43
Table 10: JUPITER: Number of cardiovascular risk factors at baseline unadjusted for HDL-c ≥ 60 mg/dL (ITT population)..... 43
Table 11: JUPITER: Number of cardiovascular risk factors at baseline adjusted for HDL-C ≥ 60 mg/dL 43
Table 12: JUPITER: Baseline lipoprotein and hsCRP levels (ITT population)..... 44
Table 13: Concomitant diabetic/cardiovascular medications at baseline (ITT population) 45
Table 14: Number of study centers and subjects randomized by country 45
Table 15: Number of subjects withdrawing participation from JUPITER (ITT population) 48
Table 16: Number of subjects withdrawing participation from JUPITER (U.S. vs. Rest of World) 48
Table 17: Reason for discontinuing study medication (ITT population)..... 49
Table 18: Number and frequency of study medication discontinuations for pre-specified reasons in JUPITER protocol..... 49
Table 19: Summary of analysis for primary composite endpoint[a]..... 50
Table 20: FDA analysis of number needed to treat (NNT) 51
Table 21: Number of events[a] by treatment group for the composite primary endpoint (ITT population)..... 52
Table 22: Number of first events by treatment group for each individual cardiovascular endpoint (ITT population) [a] 52
Table 23: Other cardiovascular efficacy endpoints (ITT population) 53
Table 24: Number of events by treatment group time to death (total mortality) with and without external vital status data (ITT population)..... 54
Table 25: Summary and time to development of noncardiovascular death 55
Table 26: Summary and time to development of (investigator-reported) diabetes mellitus..... 56
Table 27: Summary and time to development of venous thromboembolic event[a]..... 56
Table 28: JUPITER: Summary and time to development of bone fractures 56

Table 29: Summary of lipoproteins and hsCRP values throughout study (ITT population) 58
Table 30: Summary of changes in lipoproteins and hsCRP after 1 year of study treatment and at final visit (ITT population) 60
Table 31: Time to primary composite endpoint among prespecified subgroups 61
Table 32: Time to primary composite endpoint among post-hoc subgroups 63
Table 33: Simulation of primary endpoint accounting for subject withdrawal 64
Table 34: Clinical trials used to evaluate safety 66
Table 35: Categorization of adverse events (verbatim term compared to preferred term) 69
Table 36: JUPITER drug exposure 70
Table 37: Subjects with treatment emergent AE leading to death (ITT population) 72
Table 38: Fatal treatment emergent AEs in the cardiac and nervous system SOC not adjudicated as cardiovascular death 75
Table 39: Description of subjects with fatal TEAE listed in the cardiac or nervous system SOC that was not adjudicated as cardiovascular death 76
Table 40: Description of subjects with fatal TEAE listed by preferred term as death that was not adjudicated as an efficacy endpoint 79
Table 41: Description of subjects with fatal TEAEs in Gastrointestinal SOC in JUPITER 86
Table 42: Fatal treatment-emergent adverse events in the Gastrointestinal disorders SOC: AURORA trial 90
Table 43: JUPITER: Nonfatal treatment-emergent SAEs (ITT population) 91
Table 44: Nonfatal GI treatment emergent SAE by preferred terms occurring in rosuvastatin treatment group 91
Table 45: Nonfatal Psychiatric disorders SAEs by preferred term 93
Table 46: Reasons for discontinuing study medication (ITT population)[a] 94
Table 47: Number and frequency of subjects with TEAE leading to discontinuation of study medication (ITT population) 94
Table 48: Number and frequency of subjects with TEAE leading to study withdrawal (ITT population) 95
Table 49: JUPITER: Number and percentage of subjects with hepatic-related adverse events reported ant any time during the randomized treatment phase, by SOC and preferred term (ITT population)[a] 96
Table 50: JUPITER: Number (%) of subjects with elevations of ALT in the randomized treatment phase (ITT population) 99
Table 51: JUPITER: Number and percentage of subjects with muscle-related adverse events reported during the randomized treatment phase, by SOC and preferred term (ITT population)[a] 100
Table 52: JUPITER: Subjects with CK >10xULN (1200 U/L) in randomized treatment phase (ITT population) 101
Table 53: JUPITER: Number and percentage of subjects with renal-related adverse events reported during the randomized treatment phase, by SOC and preferred term (ITT population) 102

Table 54: Serum creatinine elevations increased >100% 103
Table 55: JUPITER: Urine dipstick protein and blood at Baseline and Final visit..... 103
Table 56: Incidence and persistence of proteinuria and hematuria by urine dipstick . 104
Table 57: JUPITER: Number and percentage of subjects with selected nervous system and psychiatric disorders adverse events reported during the randomized treatment phase, by SOC and preferred term (ITT population)..... 105
Table 58: JUPITER: Description of rosuvastatin-treated subjects experiencing AE of confusional state 107
Table 59: JUPITER: Summary and time to development of (investigator-reported) diabetes mellitus (without 30 March 2008 cutoff)..... 110
Table 60: JUPITER: Summary of criteria for investigator-reported diabetes (without 30 March 2008 cutoff) (ITT population)..... 111
Table 61: Summary and time to diabetes or death (any cause) ITT population 112
Table 62: Baseline characteristics of subjects with and without investigator-reported diabetes 113
Table 63: JUPITER: Prespecified subgroup analysis of number of MCE in subjects with impaired fasting glucose at baseline (ITT population) 113
Table 64: JUPITER: Change in weight from baseline in those with and without development of diabetes..... 114
Table 65: JUPITER: Fasting glucose and HBA1c levels at baseline and during follow-up (ITT population)..... 114
Table 66: Subjects developing diabetes using HbA1c >6.5% (ITT population)..... 115
Table 67: Subjects developing diabetes using FSG ≥ 126 mg/dL at least once (ITT population) 115
Table 68: Subjects developing diabetes using HbA1c >6.5% or FSG ≥ 126 mg/dL at least once (ITT population) 115
Table 69: Fasting glucose levels at baseline and final visit, METEOR and JUPITER trials (Safety and ITT population, respectively) 116
Table 70: Number and frequencies of treatment-emergent diabetes-related adverse events during the treatment phase in METEOR, CORONA, AURORA, and JUPITER trials 116
Table 71: Corrected results of Mantel Haenszel analysis of diabetes-related adverse events for rosuvastatin placebo-controlled trials 118
Table 72: Applicant data-mining of AERS database for diabetes-related terms..... 119
Table 73: JUPITER: Overview of frequency of treatment-emergent adverse event categories (ITT population) 121
Table 74: JUPITER: The most common treatment-emergent adverse events occurring with a frequency of ≥ 2%..... 121
Table 75: Mean decrease in platelet count in JUPITER and recent clinical trials from baseline 122
Table 76: Listing of JUPITER subjects with platelet count <50x10^9/L 123
Table 77: JUPITER: Time to discontinuation of study medication due to an adverse event (ITT population)..... 124

Table 78: Number and percentage of subjects with TEAE leading to death in the Neoplasm SOC (ITT population) 128
Table 79: Number and percentage of subjects with treatment-emergent SAE in the Neoplasm SOC (ITT population) 129
Table 80: Cumulative spontaneous reporting rates of hepatic events group by preferred term and dose 134
Table 81: Rhabdomyolysis: periodic spontaneous reporting rates for reports meeting ACC/AHA/NHLBI criteria in PSUR #12 versus PSUR #11 135
Table 82: Cumulative global reporting rates by dose for sponatneous reports of rhabdomyolysis meeting ACC/AHA/NHLBI criteria 136
Table 83: Cumulative global reporting rates for myopathy, myositis, and CK increase by dose 136
Table 84: Periodic and cumulative spontaneous reporting rates by dose for renal failure 137
Table 85: Periodic and cumulative spontaneous reporting rates by dose for renal impairment 138

Table of Figures

Figure 1: Risk ratio for CHD associated with hsCRP level >3 versus <1 mg/L 15
Figure 2: Structural formula of rosuvastatin calcium 19
Figure 3: JUPITER study flow chart 33
Figure 4: Disposition of JUPITER study subjects 47
Figure 5: Kaplan Meier curve of time to primary composite endpoint 51
Figure 6: DCF for Subject 6050-0165 76
Figure 7: JUPITER: Kaplan-Meier curve of time to investigator-reported diabetes (without 30 March 2008 cutoff) (ITT population) 110
Figure 8: Kaplan-Meier plot of time to use of diabetic medication 112
Figure 9: Forest plot of METEOR, CORONA, AURORA, and JUPITER diabetes-related AE data* 118
Figure 10: Kaplan-Meier curve for discontinuations of study medication due to adverse events 125

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This clinical reviewer recommends new indications be granted for rosuvastatin for reduction in risk of myocardial infarction (MI), stroke, and arterial revascularizations. Evidence of risk reduction for cardiovascular death and hospitalizations for unstable angina did not achieve a level of statistical significance that warrants granting these indications. This clinical reviewer further recommends the indication for risk reduction of total mortality be denied based on weak statistical significance for an uncontrolled secondary endpoint and the absence of rigorous examination of noncardiovascular causes of death.

1.2 Risk Benefit Assessment

In the JUPITER trial of almost 18,000 adults with no clinically evident cardiovascular disease, a LDL-C of <130 mg/dL, high sensitivity C-reactive protein (hsCRP) ≥2 mg/L, and at least one major ATP-III risk factor, treatment with rosuvastatin resulted in a statistically significant 44% relative risk reduction and 1.2% absolute risk reduction in time to major cardiovascular events (MCE) defined as the composite of cardiovascular death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina, and revascularization compared to treatment with placebo. While the previous statement is true, examination of the individual components revealed that only nonfatal MI, nonfatal stroke, and revascularization procedures were significantly reduced in the rosuvastatin group compared to placebo. In addition, 8% of the JUPITER population with no traditional cardiovascular risk factors except age, after adjustment for HDL-C ≥60 mg/dL experienced no treatment benefit with rosuvastatin in a post hoc subgroup analysis. It is important, therefore when granting the treatment indication to exclude individuals that receive no benefit but assume the risks associated with rosuvastatin use.

The hepatic, musculoskeletal, and renal related adverse events were consistent with the known safety profile of rosuvastatin.

One safety issue identified was an imbalance in the adverse event "confusional state" against rosuvastatin. Published case reports have identified altered neurocognition, for example, memory impairment or confusion, in individuals taking statins. The agency has also received spontaneous reports from the public regarding statin use and memory loss or amnesia. Memory loss is an adverse event listed in most of the statin labels **including CRESTOR. The imbalance in "confusional state" was discussed before the** Endocrinologic and Metabolism Division Advisory Committee (EDMAC) who felt the finding in the JUPITER trial was unlikely to be an authentic safety signal, but recommended further study. A review of neurocognitive adverse events associated with

statin use is under review by the Office of Surveillance and Epidemiology (OSE). The **results of OSE's review may prompt statin drug class labeling for neurocognitive** adverse events.

The major safety issue identified in the JUPITER trial was the 27% increase in investigator-reported diabetes mellitus in the rosuvastatin-exposed subjects compared to placebo-exposed subjects. The majority of the subjects who developed diabetes had a diagnosis of impaired fasting glucose, metabolic syndrome, and were overweight at the beginning of the trial. It is well established that people with diabetes are at high risk for major cardiovascular events and are more likely to die due to a cardiovascular event. **An important finding which alleviates some of this reviewer's concern over the increase** in diabetes is the significant 34% reduction in major cardiovascular events observed in rosuvastatin-treated subjects with impaired fasting glucose at baseline.

It is important to emphasize that the JUPITER trial was not designed to answer questions regarding the validity of hsCRP as a surrogate marker for baseline cardiovascular risk as all JUPITER participants had elevated hsCRP levels, nor was JUPITER designed to determine therapeutic goals for hsCRP levels as statins concurrently lower LDL-C and hsCRP blood levels.

Overall, the results of the JUPITER trial extend the clinical benefits of rosuvastatin to a broader patient population than previously studied.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable

1.4 Recommendations for Postmarket Requirements and Commitments

Although a formal postmarketing requirement or commitment is not required of the applicant, the agency requests semi-annual monitoring for two years of the following three safety issues in the periodic safety update report:

1. Diabetes-related adverse events
2. Neurocognitive impairment events
3. Serious gastrointestinal events

2 Introduction and Regulatory Background

Prior to submission of this NDA efficacy supplement, there was no evidence of **rosuvastatin's association with risk reduction of cardiovascular disease outcomes. The** applicant now seeks such an efficacy claim based on the results of the JUPITER trial. This introductory section explains one of the algorithms for assessment of

cardiovascular disease event risk, describes the emerging risk factor of high sensitivity C-reactive protein (hsCRP) and recommendations for its use in risk assessment, and lastly the rationale and implications of the JUPITER trial.

In the United States, coronary heart disease (CHD) continues to be the leading cause of death among adults.[1] High levels of low-density lipoprotein cholesterol (LDL-C) have been identified as a major risk factor for CHD. It has also been established that the lowering of LDL-C levels conveys a significant reduction in the risk of major cardiovascular events in persons with and without established CHD. One way to effectively guide treatment prevention is assessment of risk based on the ATP-III guidelines of the National Cholesterol Education Program (NCEP) which sets goals for **optimal LDL-C levels based on an individual's calculated risk.**[2]

The ATP-III guidelines, updated in 2004[3], categorize adults into 3 risk categories: (1) established CHD and CHD risk equivalents, (2) two or more risk factors, and (3) zero to one risk factors. In individuals with at least two of the ATP-III major risk factors defined as age (≥ 45 years in men, ≥ 55 years in women), cigarette smoking, hypertension (blood pressure ≥ 140/90 mmHg or on antihypertensive medication), low HDL-C (<40 mg/dl), and family history of premature CHD further cate**gorization of an individual's** hard coronary heart disease (myocardial infarction and coronary death) 10-year risk is recommended. Ten-year risk is calculated using a subset of the Framingham risk factors which group individuals into 10-year risk levels of <10%, 10-20%, and >20%. Persons with diabetes mellitus or multiple risk factors and 10-year risk >20% are considered as having a CHD risk equivalent.

The NCEP 2004 update reduced the LDL-C threshold for drug therapy for high risk persons (CHD/CHD risk equivalent) to 100 mg/dL with the continued LDL-C goal of <100 mg/dL or the optional goal of < 70 mg/dL for very high risk individuals - recent heart attack, cardiovascular disease combined with either diabetes, severe or poorly controlled risk factors (such as continued smoking), or metabolic syndrome (Table 1).[4] In addition, for those defined as moderately high risk (2+ risk factors and 10-year risk of 10-20%), the LDL-C goal remained at < 130 mg/dL; however there were two modifications in the NCEP 2004 update:

1. A LDL-C goal of <100 mg/dL was considered a therapeutic option

---

1 Heron et al. Deaths: Final Data for 2006. National Vital Statistics Reports; Vol 57 No 14. Hyattsville, MD: National Center for Heatlh Statistics; 2009. Accessed at www.cdc.gov/nchs on October 15, 2009.
2 National Heart Lung and Blood Institute, Executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 2001; 285 (19): 2486-97.
3 Grundy et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. JACC 2004; 44: 720-32.
4 www.nhlbi.nih.gov/guidelines/cholesterol/upd-info_prof.htm. Accessed online October 27, 2009.

2. For individuals with LDL-C values of 100-129 mg/dL at baseline or on lifestyle therapy, initiation of a LDL-lowering therapy to achieve a LDL-C < 100 mg/dL was proposed as a reasonable treatment option.

Table 1: NCEP 2004 Update of ATP-III goals and cutpoints for treatment

Risk Category	LDL-C Goal	Initiate TLC	Consider Drug Therapy**
High risk: CHD* or CHD risk equivalents† (10-year risk >20%)	<100 mg/dL (optional goal: <70 mg/dL)‖	≥100 mg/dL#	≥100 mg/dL†† (<100 mg/dL: consider drug options)**
Moderately high risk: 2+ risk factors‡ (10-year risk 10% to 20%)§§	<130 mg/dL¶	≥130 mg/dL#	≥130 mg/dL (100–129 mg/dL; consider drug options)‡‡
Moderate risk: 2+ risk factors‡ (10-year risk <10%)§§	<130 mg/dL	≥130 mg/dL	≥160 mg/dL
Lower risk: 0–1 risk factor§	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160–189 mg/dL: LDL-lowering drug optional)

Source: Grundy et al.

Individuals eligible for enrollment in the JUPITER trial were not eligible for statin therapy according to the NCEP ATP-III 2001 guidelines. However, according to the NCEP 2004 update, 22% of JUPITER subjects could be treated with statins by qualifying as moderately high risk with a baseline LDL-C of 100 to 129 mg/dL.

Both the ATP-III guidelines and Framingham risk scores rely on conventional risk factors (hyperlipidemia, smoking, diabetes, hypertension) and do not include other emerging non-traditional risk factors such as high sensitivity CRP. Some data suggest over 50% of patients with CHD lack conventional risk factors.[5,6] Other contradictory data contend that 80 to 90% of patients with CHD do exhibit conventional risk factors.[7,8] In a recent report, 41.5% of people hospitalized with CHD with no history of previous atherosclerotic disease, CHD, or diabetes had LDL-C levels below100 mg/dL.[9] The debate regarding these potential at-risk individuals lacking conventional risk factors has fostered research into improving identification and risk assessment by non-traditional risk factors.

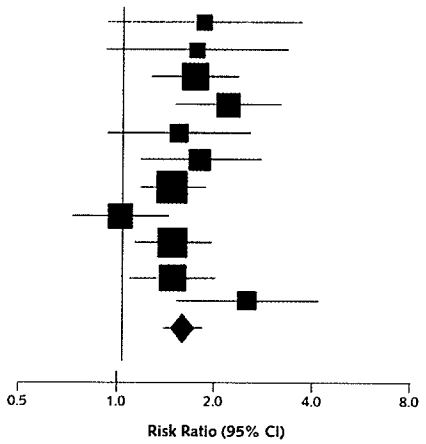
High sensitivity CRP is a non-specific biomarker of inflammation. Inflammation contributes to the plaque instability of atherosclerotic disease.[10] Epidemiologic data

5 Futterman et al. Fifty percent of patients with coronary artery disease do not have any of the conventional risk factors. Am J Crit Care 1998; 7:240-4.
6 Hennekens et al. Increasing burden of cardiovascular disease: current knowledge and future directions for research on risk factors. Circulation 1998; 97:1095-1102.
7 Greenland et al. Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. JAMA 2003; 290:891-897.
8 Khot et al. Prevalence of conventional risk factors in patients with coronary heart disease. JAMA 2003; 290:898-904.
9 Sachdeva et al. Lipid levels in patients hospitalized with coronary artery disease: an analysis of 136,905 hospitalizations in Get With The Guidelines. Am Heart J 2009; 157:111-7.e2.
10 Ross et al. Atherosclerosis-an inflammatory disease. NEJM 1999; 340:115-26.

demonstrate elevated hsCRP is associated with obesity,[11] conventional cardiovascular risk factors,[12] and increased risk of CHD.[13,14] In a recent meta-analysis for the U.S. Preventive Services Task Force (USPSTF), 10 studies determined by the USPSTF to be of good quality that adjusted for all Framingham risk factors demonstrated a relative risk for CHD of 1.58 (CI, 1.37 to 1.83) for high (>3 mg/L) versus low (<1 mg/dL) hsCRP (Figure 1).[15]

Figure 1: Risk ratio for CHD associated with hsCRP level >3 versus <1 mg/L

Study, Year (Reference)	Participants, n*	Risk Ratio (95% CI)
Good-quality studies		
Pradhan et al, 2002 (46)	560	1.83 (0.88–3.82)
Luc et al, 2003 (44)	772	1.75 (0.88–3.47)
Ballantyne et al, 2004 (52)	1348	1.72 (1.24–2.39)
Koenig et al, 2004 (33)	3435	2.21 (1.49–3.27)
Pai et al, 2004 (women) (45)	708	1.53 (0.89–2.62)
Pai et al, 2004 (men) (45)	794	1.79 (1.14–2.83)
Cushman et al, 2005 (56)	3971	1.45 (1.14–1.86)
St-Pierre et al, 2005 (42)	1982	0.98 (0.68–1.42)
Boekholdt et al, 2006 (55)	3272	1.46 (1.10–1.95)
Mora et al, 2006 (60)	27 742	1.46 (1.05–2.02)
Pischon et al, 2007 (61)	979	2.56 (1.51–4.35)
Combined		1.58 (1.37–1.83)



In 2002, neither the Centers for Disease Control and Prevention nor the American Heart Association endorsed global screening for hsCRP for cardiovascular risk assessment **but recommended the "optional use of hsCRP to identify patients without known** cardiovascular disease who may be at higher absolute risk than estimated by major risk factors.[16] Specifically, those patients at intermediate risk (10-year 10-20% CHD risk) in whom the physician may need additional information to guide considerations of further

11 Lemieux et al. Elevated C-reactive protein: another component of the atherothrombotic profile of abdominal obesity. Arterioscler Thromb Vasc Biol. 2001;21:961-7.
12 Miller et al. High attributable risk of elevated C-reactive protein level to conventional coronary heart disease risk factors; The Third National Health and Nutrition Examination Survey. Arch Intern Med 2005; 165:2063-8.
13 Cushman et al. C-reactive protein and the 10-year incidence of coronary heart disease in older men and women: the cardiovascular health study. Circulation 2005;112:25-31.
14 Pischon et al. Comparison of relative and attributable risk of myocardial infarction and stroke according to C-reactive protein and low-density lipoprotein cholesterol levels. Eur J Epidemiol 2007;22:429-38.
15 Buckley et al. C-reactive protein as a risk factor for coronary heart disease: a systematic review and meta-analysis for the U.S. Preventive Services Task Force. Ann Intern med 2009;151:483-95.
16 Pearson et al. Markers of inflammation and cardiovascular disease: application to clinical and public healthy practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003;107:499-511.

evaluation or therapy may benefit from measurement of hsCRP." Levels of hsCRP were assigned risk categories of low (<1 mg/L), average (1-3 mg/L), and high (>3 mg/L).

The AFCAPs/TexCAPs trial supported the identification and treatment of individuals at higher cardiovascular risk based on hsCRP. In this randomized, placebo-controlled primary prevention trial of 6605 people with normal to mildly elevated total cholesterol and LDL-C levels and without clinically evident atherosclerotic cardiovascular disease it was noted in a post-hoc evaluation, that subjects with a below median LDL-C (149 mg/dL) but above median hsCRP (1.6 mg/L) had similar placebo-event rates of coronary events as subjects with above median LDL-C values.[17] In addition, this subgroup when treated with lovastatin demonstrated a risk reduction similar to their high LDL-C counterparts.

Data from the National Health and Nutrition Examination Survey (NHANES) estimated the number of United States adults eligible for statin therapy according to JUPITER eligibility criteria.[18] Population estimates based on a sample number of cases and weighted to the civilian noninstitutionalized U.S. population calculated approximately 3.9 million men age ≥ 50 years and 2.6 million women ≥ 60 years have an LDL <130 mg/dL and hsCRP ≥ 2.0 mg/L. This group comprised 57% Whites, 15% Blacks, and 26% Hispanics. In a separate estimation including younger adults excluded from the JUPITER trial because of age, approximately 14.5 million men and 22.2 million women ≥ 20 years have LDL <130 mg/dL and hsCRP ≥ 2.0 mg/L. In addition, the authors estimated an additional 10 million older adults have lipid levels below their NCEP/ATP-III cutpoints for therapy who may become eligible to initiate statin therapy based on an elevated hsCRP ≥ 2.0 mg/L.

The regulatory background section which follows describes current CRESTOR **indications, previous clinical trials demonstrating rosuvastatin's effect on lipid** metabolism and efficacy in cardiovascular disease trials, and concludes with indications sought by the applicant based on the JUPITER trial.

CRESTOR® (rosuvastatin) is a member of the statin class of lipid-lowering compounds, which inhibits the rate-limiting enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase decreasing cholesterol synthesis. Currently, rosuvastatin is available in 5, 10, 20, and 40 mg tablets and is indicated for:

1. Patients with primary hyperlipidemia (heterozygous familial and non-familial) and mixed dyslipidemia (Fredrickson Type IIa and IIb) as an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, nonHDL-C, and TG levels and to increase HDL-C
2. Patients with hypertriglyceridemia (Fredrickson Type IV) as an adjunct to diet

17 Ridker et al. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. NEJM 2001;344:1959-65.
18 Michos et al. Prevalence of low Low-Density Lipoprotein cholesterol with elevated high sensitivity C-reactive protein in the U.S.: Implications of the JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) Study. JACC 2009;53:931-5.

3. Patients with primary dysbetalipoproteinemia (Type III hyperlipoproteinemia) as an adjunct to diet
4. Patients with homozygous familial hypercholesterolemia to reduce LDL-C, total-C, and ApoB
5. Slowing the progression of atherosclerosis as part of a treatment strategy to lower total-C and LDL-C as an adjunct to diet
6. Pediatric patients 10 to 17 years of age with heterozygous familial hypercholesterolemia (HeFH) to reduce elevated total-C, LDL-C, and Apo B after failing an adequate trial of diet therapy

Rosuvastatin has a higher potency when compared to other statins. The STELLAR trial compared rosuvastatin to other statins across their respective dose ranges and demonstrated a greater effect of rosuvastatin on lipids and lipoproteins (Table 2).[19]

Table 2: Percent change from baseline across the dose range of rosuvastatin, atorvastatin, pravastatin, and simvastatin-STELLAR trial

	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.

Rosuvastatin efficacy trials of clinical outcomes prior to JUPITER submission

METEOR was a randomized, double-blind, placebo-controlled trial of 984 subjects randomized in a 5:2 ratio into two parallel treatment arms over a period of 104 weeks. This study assessed the efficacy of rosuvastatin 40 mg in altering the natural history of carotid intimal-media thickness (cIMT) as compared to placebo. METEOR showed rosuvastatin 40 mg significantly slowed the progression of carotid atherosclerosis compared to placebo. The difference in the annualized rate of change in the mean maximum cIMT analyzed over all 12 carotid artery sites between rosuvastatin-treated patients and placebo-treated patients was -0.0145 mm/year (95% CI: -0.0196, -0.0093; $p<0.001$).

CORONA was a randomized, double-blind, placebo-controlled study evaluating the efficacy of rosuvastatin 10 mg on cardiovascular morbidity and mortality in 5011 patients with chronic symptomatic systolic heart failure (New York Heart Association

19 Jones et al. Comparison of efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR trial). Am J Cardiol 2003;92:152-60.

class [NYHA] II-IV) of ischemic etiology on top of standard heart failure treatment (angiotensin converting enzyme inhibitors/angiotensin receptor blockers/beta-blockers/diuretics). In this population, rosuvastatin 10 mg did not reduce the primary composite cardiovascular endpoint (cardiovascular death, MI, or stroke) or impact all-cause mortality.

GISSI-HF was a randomized, double-blind, placebo-controlled study in approximately 4500 patients with chronic symptomatic systolic heart failure (NYHA II-IV) receiving standard of care heart failure treatment; GISSI enrolled patients with heart failure of both ischemic and non-ischemic etiology. The trial was designed to evaluate whether the long-term treatment with rosuvastatin 10 mg was more effective than placebo in reducing all cause mortality or hospitalization for heart failure (co-primary endpoints). GISSI results corroborated CORONA, with rosuvastatin 10 mg showing no difference from placebo for either endpoint.

The **AURORA** trial was a randomized, double-blind, placebo-controlled trial, which evaluated the effects of rosuvastatin 10 mg versus placebo on survival and major cardiovascular events in patients with end-stage renal disease on chronic hemodialysis. The study included 2774 patients followed over 3.8 years. Rosuvastatin 10 mg had no significant effect on the composite primary endpoint of cardiovascular death, MI or stroke.

Indication sought based on JUPITER trial

This NDA supplement presents data from one pivotal efficacy trial, Study D3560L00030 (**JUPITER**: "**J**ustification for the **U**se of statins in **P**rimary prevention: an **I**ntervention **T**rial **E**valuating **Rosuvastatin**": **A randomized, double-blind, placebo controlled,** multicenter, phase 3 study of rosuvastatin 20 mg in the primary prevention of cardiovascular events among subjects with low levels of LDL-cholesterol and elevated **levels of C-reactive protein" to support an indication for:**

In adult patients with an increased risk of cardiovascular disease based on the presence of cardiovascular disease risk markers such as an elevated hsCRP level, age, hypertension, low HDL-C, smoking or a family history of premature coronary heart disease, CRESTOR is indicated to:

- ***reduce the risk of total mortality***
- ***reduce the risk of cardiovascular death***
- ***reduce the risk of stroke***
- ***reduce the risk of myocardial infarction***
- ***reduce the risk of arterial revascularization***
- ***reduce the risk of unstable angina***

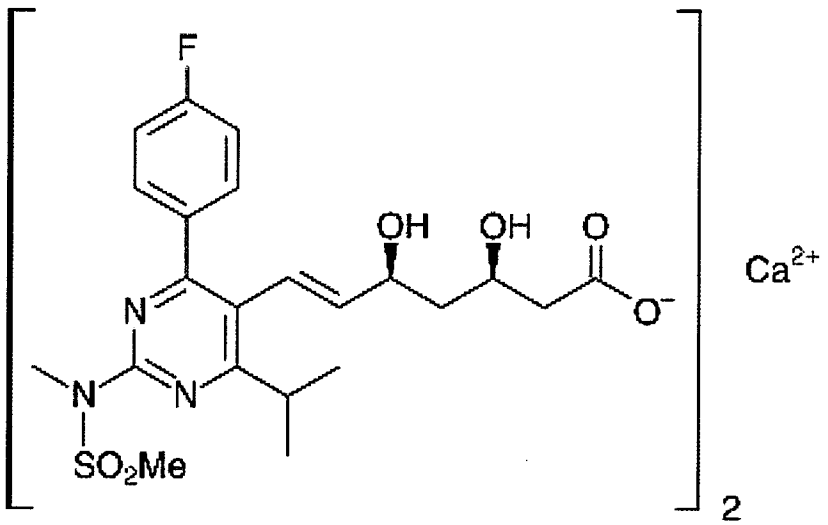
The indication was revised by the applicant on 21 December 2009 to:

In adult patients at (b) (4) risk of cardiovascular disease based on cardiovascular disease risk markers such as age, elevated hsCRP level, hypertension, low HDL-C, smoking or a family history of premature coronary heart disease, CRESTOR is indicated to reduce the risk of total mortality and major cardiovascular events: cardiovascular death, stroke, myocardial infarction, arterial revascularization, unstable angina.

2.1 Product Information

Rosuvastatin calcium is bis[(E)-7-[4-4(4-fluorophenyl)- 6-isopropyl-2-[methyl(methylsulfonyl)amino] pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt. The empirical formula for rosuvastatin calcium is $(C_{22}H_{27}FN_3O_6S)_2$ Ca. Its molecular weight is 1001.14. Its structural formula is:

Figure 2: Structural formula of rosuvastatin calcium



Source: CRESTOR label

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently five of the seven of the FDA-approved statins contain primary or secondary cardiovascular disease prevention indications in their labels. These are summarized in Table 3 along with CRESTOR's proposed indication.

Table 3: Cardiovascular primary and secondary prevention indications in statin labels

Statin	CV trials in label	Patient population studied	Duration of study	Clinical endpoints used	Date of indication approval	Indication in label
CRESTOR (Rosuvastatin)	**JUPITER**	**N=17802 (6765 women) LDL < 130 mg/dL (mean 104 mg/dL) CRP ≥ 2 mg/L (median 4.3 mg/L) +1 risk factor for CHD**	**Median 1.9 years of 20 mg or placebo**	**MCE (CV death, MI, stroke, unstable angina, or arterial revasc) (RRR 44%)**	**8 February 2010**	**(Proposed) Primary prevention CHD: *In adult patients with an increased risk of cardiovascular disease based on the presence of cardiovascular disease risk markers such as an elevated hsCRP level, age, hypertension, low HDL-C, smoking or a family history of premature coronary heart disease, CRESTOR is indicated to:* • *reduce the risk of total mortality* • *reduce the risk of cardiovascular death* • *reduce the risk of stroke* • *reduce the risk of myocardial infarction* • *reduce the risk of arterial revascularization* • *reduce the risk of unstable angina* Revised by Applicant on 21 December 2009 to: *In adult patients at moderate-to-high risk of cardiovascular disease based on cardiovascular disease risk markers such as age, elevated hsCRP level, hypertension, low HDL-C, smoking or a family history of premature coronary heart disease, CRESTOR is indicated to reduce the risk of total mortality and major cardiovascular events: cardiovascular death, stroke, myocardial infarction, arterial revascularization, unstable angina.***
PRAVACHOL (Pravastatin)	WOSCOPS (R, DB, PC)	N=6595 men 45-64 yo No previous MI LDL-C 156-254 mg/dL	Median 4.8 years of 40 mg or placebo	CHD death or nonfatal MI (RRR 31%)	2 July 1996	Primary prevention CHD: *In hypercholesterolemic patients without clinically evident coronary heart disease, PRAVACHOL is indicated to:* • *Reduce the risk of MI* • *Reduce the risk of undergoing myocardial revascularization procedures* • *Reduce the risk of CV mortality with no increase in death from non-CV causes*

Statin	CV trials in label	Patient population studied	Duration of study	Clinical endpoints used	Date of indication approval	Indication in label
	CARE (DB, PC)	N=4159 (3583 men, 576 women) h/o MI in previous 3-20 months Normal (<75th%ile) total cholesterol levels LDL-C 101-180 mg/dL (mean 139 mg/dl)	Mean 4.9 years of 40 mg or placebo	CHD death or nonfatal MI (RRR 24%)	27 March 1998	Secondary prevention CHD: *In patients with clinically evident coronary artery heart disease, PRAVACHOL is indicated to:* • *Reduce the risk of total mortality by reducing coronary death* • *Reduce the risk of MI* • *Reduce the risk of undergoing myocardial revascularization procedures* • *Reduce the risk of stroke and stroke/TIA*
	LIPID (R, DB, PC)	N=9014 (7498 men, 1516 women, 3514 ≥65 y, 782 DM) h/o MI or hospitalized for unstable angina in previous 3-36 months LDL-C 46-274 mg/dL (mean 150 mg/dL)	Median 5.9 years of 40 mg or placebo	CHD death (RRR 24%)	10 February 2000	
ZOCOR (Simvastatin)	4S (R, DB, MC, PC)	N=4444 (844 women) 35-71 yo	Median 5.4 years of 20-40 mg or placebo	1.Total mortality (RRR 30%) 2. CHD death, non-fatal acute MI (RRR 34%)	31 March 1998	Primary and Secondary prevention CHD: *In patients at high risk of coronary events because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease, ZOCOR is indicated to:* • *Reduce the risk of total mortality by reducing CHD deaths* • *Reduce the risk of non-fatal myocardial infarction and stroke* • *Reduce the need for coronary and non-coronary revascularization procedures*
	HPS (MC, DB, PC)	N=20536 (4107 women) 40-80 yo 51% LDL-C≤130 mg/dL Total-C ≥ 135 mg/dL Substantial 5-year risk of CV death	Mean 5 years of 40 mg or placebo	Mortality (RRR 13%) CHD death (RRR 18%)	16 April 2003	
MEVACOR (Lovastatin)	AFCAPS/TexCAPS (R, DB, PC)	N=6605 (997 women) Total-C 180-264 mg/dL LDL-C 130-190 mg/dL, HDL-C ≤ 45 mg/dL	Median 5.1 years of 20-40 mg or placebo	MCE (MI, unstable angina, sudden cardiac death) (RRR 37%)	11 March 1999	Primary prevention CHD: *In individuals without symptomatic cardiovascular disease, average to moderately elevated total-C and LDL-C, and below average HDL-C, MEVACOR is indicated to reduce the risk of:* • *MI* • *Unstable angina* • *Coronary revascularization procedures*
LESCOL/ LESCOL XL (Fluvastatin)	LIPS (R, MC, DB, PC)	N=1677 with CHD and PCI 18-80 yo 268 women LDL-C 42-243 mg/dL (mean 132 mg/dL)	Median 3.9 years 40 mg BID or placebo	MCE (CHD death, nonfatal MI, revascularization) (RRR 22%)	27 May 2003	Secondary prevention CHD: *In patients with coronary heart disease, Lescol and Lescol XL are indicated to reduce the risk of undergoing coronary revascularization procedures*

Statin	CV trials in label	Patient population studied	Duration of study	Clinical endpoints used	Date of indication approval	Indication in label
LIPITOR (Atorvastatin)	ASCOT-LLA (R, MC, DB, PC)	N=10305 hypertensive 40-80 yo No MI ≥ 3 CV risk factors	Median 3.3 years 10 mg or placebo	CHD death or nonfatal MI (RRR 36%)	30 July 2004	Primary prevention CHD: *In adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease, such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease, LIPITOR is indicated to:* • *Reduce the risk of MI* • *Reduce the risk of stroke* • *Reduce the risk for revascularization procedures and angina* *In patients with type 2 diabetes, and without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking, or hypertension, LIPITOR is indicated to:* • *Reduce the risk of MI* • *Reduce the risk of stroke*
	CARDS (R, MC, DB, PC)	N=2838 (908 women) 40-75 yo Type 2 diabetes No CVD LDL≤160 mg/dL (median LDL-C 120 mg/dL)	Median 3.9 years 10 mg or placebo	MCE (MI, acute CHD death, unstable angina, coronary revasc, stroke) (RRR 37%)	21 September 2005	
	TNT	N=10001 (1900 women) h/o CHD Achieved LDL-C <130 mg/dL after run-in period of 10 mg Lipitor	Median 4.9 years 80 mg vs 10 mg Lipitor	MCE (CHD death, nonfatal MI, resuscitated cardiac arrest, fatal and nonfatal stroke) (RRR 22%)	2 March 2007	Secondary prevention CHD: *In patients with clinically evident coronary heart disease, LIPITOR is indicated to:* • *Reduce the risk of non-fatal MI* • *Reduce the risk of fatal and non-fatal stroke* • *Reduce the risk for revascularization procedures* • *Reduce the risk of hospitalization for CHF* • *Reduce the risk of angina*
	IDEAL (R, OL, blinded endpoint)	N=8888 (1688 women) h/o CHD Mean LDL-C 121.5 mg/dL	Median 4.8 years 80 mg Lipitor vs 20-40 mg simva	MCE (fatal CHD, nonfatal MI and resuscitated cardiac arrest) NS (p=0.07)	2 March 2007	

2.3 Availability of Proposed Active Ingredient in the United States

Rosuvastatin was approved in the U.S. on 12 August 2003.

2.4 Important Safety Issues With Consideration to Related Drugs

The safety profile of the statin drug class is primarily characterized by its hepatic and musculoskeletal disorders. The safety profile of rosuvastatin is similar to other statins.

It is established that statin use is associated with an increase in liver transaminases in a small percentage of subjects and this was confirmed in the JUPITER trial.[20] The most common adverse events were abnormal hepatic-related laboratory levels and occurred with higher frequency in the rosuvastatin-treatment group (ALT >3x ULN and/or AST >3x ULN, 1.4%). For comparison, a similar percentage of ALT elevations were observed in simvastatin-exposed subjects in the Heart Protection Study (HPS) (ALT 2-4x ULN 1.35%).[21]

Moreover, in a report of controlled trials with rosuvastatin, 0.2% of ~10,000 rosuvastatin -exposed subjects experienced a clinically significant ALT elevation described as two consecutive ALT elevations >3x ULN. The frequency of transaminase elevation was similar to the AFCAPS/TexCAPS trial, where 0.6% of lovastatin-exposed subjects experienced a clinically significant ALT or AST elevation.[22,23]

Muscle-related adverse events have been consistently demonstrated with statin use and this was reflected in the JUPITER trial.[20] Muscle-related AEs occurred at a slightly higher incidence in the rosuvastatin-treatment group compared to the placebo group. Myalgia was the most commonly reported preferred term in the rosuvastatin and placebo groups. In JUPITER, two subjects experienced a CK>10x ULN on rosuvastatin versus one in placebo. For comparison, 0.1% simvastatin-treated subjects in HPS and 0.7% lovastatin-treated subjects in AFCAPS/TexCAPS experienced CK >10x ULN.[21, 23]

2.5 Summary of Presubmission Regulatory Activity Related to Submission

In developing the JUPITER trial for primary prevention of cardiovascular disease, AstraZeneca sought guidance from the agency by requesting a Special Protocol

---

20 Grundy et al. HMG-CoA reductase inhibitors for treatment of hypercholesterolemia. NEJM 1988; 319: 24-33.
21 MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomized placebo-controlled trial. Lancet 2002;360:7-22.
22 Shepherd et al. Safety of rosuvastatin: update on 16,876 rosuvastatin-treated patients in a multinational clinical trial program. Cardiology 2007;107:433-443.
23 Downs et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. JAMA 1998;279 (20):1615-22.

Assessment (SPA). The following changes were incorporated based on the agency's response to the SPA:

1. Changed triglyceride inclusion criterion from <600 mg/dL to <500 mg/dL.
2. **Added "or CHD risk equivalent" to exclusion criteria for prior cardiovascular** event.
3. Added venous thromboembolic events and bone fractures as secondary endpoints.
4. Added health economic evaluation.
5. Added urinalysis at follow up visits and creatinine and CK at final visit.

The following selected italicized comments by the agency were sent to the applicant for further guidance:

- **Regarding JUPITER's primary efficacy endpoint**

Assuming the results for the primary efficacy assessment favor drug treatment, the individual components (cardiovascular death, stroke, MI, unstable angina, or arterial revascularization procedures) would need to be evaluated as secondary or tertiary endpoints to determine their contribution to the overall efficacy findings.

- Regarding the use of hsCRP in JUPITER

While this study may identify a population of subjects with high CRP levels who would benefit from therapy with rosuvastatin, this does not identify CRP as a validated surrogate for risk of cardiovascular disease and a specific target of therapy. Several clinical studies have shown that a variety of statins are capable of lowering CRP levels but the clinical benefits of lowering CRP have not been established. It is unlikely that the results of JUPITER will support labeling for CRP as a goal of statin therapy.

2.6 Other Relevant Background Information

Not applicable

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

An audit conducted at three JUPITER trial centers (Centers 7153, 5001, 5006) assessed adherence to FDA regulatory requirements. In general, the trial conduct was appropriate and data collection reliable. The inspection uncovered a systemic clinical **conduct issue - failure to calculate a subject's Framingham risk score before enrollment.** A Framingham risk score of >20% is a CHD risk equivalent as defined by NCEP ATP III guidelines and disqualified subjects for enrollment per the JUPITER protocol. Approximately 9% of subjects were not excluded from participation due to this systemic

oversight. In an FDA analysis, exclusion of these subjects found no effect on the primary efficacy endpoint.

Please see the full Department of Scientific Investigations report by Dr. Susan Leibenhaut.

There were four JUPITER trial centers (3 in the U.S. and 1 in Venezuela) that were closed by the applicant due to noncompliance with Good Clinical Practice (GCP) standards (Table 4). All data obtained from subjects randomized at these sites were included in the analyses. Although in a letter data 31 January 2006, the subject data **from Site 1302 was deemed "unusable due to lack of physician oversight." Due to the** small number of subjects randomized from these four centers it is unlikely to affect the overall efficacy and safety results observed in the JUPITER trial.

Table 4: JUPITER trial centers closed due to noncompliance with GCP standards

Center number	Location	Principal investigator	Number of subjects randomized
2217	Hendersonville, TN USA	Anthony Dallas	3
1302	Westchester, PA USA	B. Steven Burke	31
1458	Alhambra, CA USA	Mohammed Saad	8
7231	Venezuela	Jose Beaujon Sierralta	43

3.2 Compliance with Good Clinical Practices

AstraZeneca conducted the JUPITER trial in compliance with GCP requirements. As certified in the submission, no debarred investigators were used in the conduct of this trial.

Re: **NDA 21-366**

CRESTOR® (rosuvastatin calcium) Tablets

Debarment Certification Statement

In response to the requirements of the Generic Drug Enforcement Act of 1992, I hereby certify on behalf of AstraZeneca Pharmaceuticals LP (AstraZeneca), that we did not use and will not use in connection with this Supplemental New Drug Application, the services of any person in any capacity debarred under section 306 (a) or (b).

Sincerely,

Anthony F. Rogers 3/25/09

Anthony F. Rogers, Vice President
Regulatory Affairs
AstraZeneca

JUPITER trial centers considered for inspection screened large numbers of subjects and reported major violations and deviations. The table below lists the centers inspected and results of the investigation by DSI.

Table 5: JUPITER trial centers inspected and results of inspection by DSI

Name of Clinical Investigator (CI) and Location	# of Subjects screened/ # of subjects enrolled	Inspection Dates	Final Classification
CI#1 Center 7153 Jose Luis Cervantes, MD Hospital Angeles del Pedregal Periferico Sur #3697-Suite 1050 Col. Heroes de Padierna Mexico City, CP 10700, Mexico	1252/280 subjects	September 7 to 11, 2009	VAI[a]
CI#2 Center 5001 Rex Sarimento, MD Synexus Midlands Birmingham Research Park Vincent Drive, Egbaston Birmingham, B15 2SQ United Kingdom	2443 subjects/322 subjects	September 21 to 25, 2009	VAI
CI#3 Center 5006 John S. Robinson Synexus Manchester Clinical Research Centre, William House Manchester Science Park, Lloyd St North Manchester M15 6SX, United Kingdom	1271 subjects/276 subjects	September 14 to 18, 2009	VAI

[a]VAI: Deviations from regulations
Source: Clinical Inspection Summary 19 November 2009

3.3 Financial Disclosures

The applicant indicated the following investigators received significant payments defined as a monetary value of greater than $25,000 from AstraZeneca.

Table 6: JUPITER clinical investigators receiving significant payments from applicant

Center number/Location	Clinical investigator	Number of subjects randomized	Financial information
	(b) (6)		Significant payments between $25,000-50,000 total as consultant for Crestor National Educators Network, speaker honoraria, and visiting professor
			Significant payments-education grant to institution to support fellowship training
			Significant payments-speaker honoraria
			Significant payments-research support for investigator initiated grant-$30,000 from AstraZeneca unrelated to this trial
			Significant payments-honoraria for CME speaking engagements
			Significant payments-honoraria and grants of about $85,000
			Equity interest - $97,000 USD
			Significant payments-support of research activities

Source: Response to FDA information request: Disclosure report submitted 11 May 2009

It is the opinion of this clinical reviewer that the small number of subjects randomized by financially compensated investigators did not compromise the integrity of the data.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The sponsor was granted a categorical exclusion from preparing an environmental assessment (EA) based on an expected environmental concentration of (b) (4) µg/L (ppb) **which is below the EA threshold of 1 ppb. Please see Dr. Janice Brown's review for** further information.

4.2 Clinical Microbiology

No new data were submitted

4.3 Preclinical Pharmacology/Toxicology

No new data were submitted

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Rosuvastatin is a member of the lipid-lowering statin drug class. Statins work by inhibiting the rate-limiting enzyme HMG-CoA reductase, thereby decreasing cholesterol synthesis and promoting a compensatory mechanism which increases LDL-C uptake by upregulating LDL-C receptor synthesis.

4.4.2 Pharmacodynamics

No new data were submitted

4.4.3 Pharmacokinetics

No new data were submitted

5 Sources of Clinical Data

This NDA supplement presents data from one pivotal efficacy study Study D3560L00030 **JUPITER**: "**J**ustification for the **U**se of statins in **P**rimary prevention: an **I**ntervention **T**rial **E**valuating **Rosuvastatin**".

5.1 Tables of Studies/Clinical Trials

Table 7: Description of and key objectives in the rosuvastatin clinical efficacy study for the primary prevention of cardiovascular events

Study and Location	Study design Dose Duration	Patient population	Key objectives
JUPITER 1316 sites in 26 countries	Randomized, double-blind, placebo-controlled Treatment: Rosuvastatin 20 mg QD Comparator: Placebo QD 1.9 years mean duration of treatment	Men (≥50 years), Women (≥60 years) without clinically evident cardiovascular disease, LDL <130 mg/dL, hsCRP ≥2 mg/L	Effect of rosuvastatin versus placebo on: Primary: • Rate of major cardiovascular events (combined endpoint of cardiovascular death, stroke, myocardial infarction, unstable angina, or arterial revascularization) Secondary: • total mortality, • noncardiovascular mortality • diabetes mellitus • venous thromboembolic events • bone fractures

5.2 Review Strategy

Only one trial was submitted in support of the clinical efficacy of rosuvastatin and primary prevention of major cardiovascular events. For the safety review, the primary focus was JUPITER data. Three long-term, placebo controlled trials with rosuvastatin, METEOR, CORONA, and AURORA, previously submitted or submitted during the course of this efficacy supplement review to the agency were reviewed for the specific safety issues of diabetes-related adverse events and deaths reported as due to gastrointestinal adverse events discovered within the JUPITER data.

5.3 Discussion of Individual Studies/Clinical Trials

Study D3560L00030 (4522US/0011): Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin: JUPITER. A randomized, double-blind, placebo-controlled, multicenter, phase 3 study of rosuvastatin (CRESTOR) 20 mg in the primary prevention of cardiovascular events among subjects with low levels of LDL-Cholesterol and elevated levels of C-Reactive Protein.

Study initiation date: 05 February 2003
Study completion date: 30 March 2008 terminated early by DMSB. Last subject completed 20 August 2008

5.3.1 Objectives and outcome measures

Primary objective:
JUPITER's primary objective was to investigate whether long-term treatment with rosuvastatin 20 mg compared with placebo would decrease the rate (based on time to first event after randomization) of major cardiovascular events (combined endpoint of cardiovascular death, nonfatal stroke, nonfatal myocardial infarction, hospitalization for unstable angina, or arterial revascularization) among older individuals (men ≥50 years, women ≥60 years) with low LDL-C (<130 mg/dL) who are at high vascular risk on the basis of an enhanced inflammatory response, as determined by elevated levels of high sensitivity CRP (≥ 2.0 mg/L).

Secondary objectives:
The secondary objectives of JUPITER were to investigate

- The safety of long-term treatment with rosuvastatin compared to placebo through comparisons of total mortality, noncardiovascular mortality, and adverse events
- Whether rosuvastatin reduces the incidence of diabetes mellitus, venous thromboembolic events, and bone fractures

Primary efficacy measures:
First occurrence of a major cardiovascular event after randomization defined as the composite of:

- Cardiovascular death
- Nonfatal stroke
- Nonfatal myocardial infarction
- Hospitalization for unstable angina
- Arterial revascularization

Secondary efficacy measures:
The secondary endpoints were the occurrence of:

- Total mortality
- Noncardiovascular mortality

- Discontinuation of blinded study medication due to adverse effects
- Development of investigator-reported diabetes mellitus
- Development of venous thromboembolic events (deep vein thrombosis or pulmonary embolism
- Bone fractures

Additional secondary variables which controlled for type 1 error in the statistical analysis plan included three composite outcomes:
- Cardiovascular/cerebrovascular (CV) death, nonfatal myocardial infarction or nonfatal stroke
- Fatal or nonfatal myocardial infarction
- Fatal or nonfatal stroke

Safety measures:
- Adverse events
- Physical examination
- Vital signs
- Clinical laboratory data: serum creatinine, creatinine kinase, hematology, alanine aminotransferase, and urinalysis

5.3.2 Statistical and Analytical Plans

The intent-to-treat principle was used in the primary analysis of primary and secondary variables. The applicant controlled for multiplicity for three secondary variables. The following variables were tested in sequential order after establishing statistical significance in the primary efficacy analysis, each at a 5% level of significance:

- CV death, non-fatal stroke or non-fatal MI
- Fatal or non-fatal MI
- Fatal or non-fatal stroke

Hazard ratios and 95% confidence intervals were calculated for event rates between the treatment groups using Cox proportional-hazard models.

The Independent Data Monitoring Board (IDMB) for JUPITER had prespecified interim analyses to occur after 37.5%, 75%, and 100% of primary events had occurred. A group sequential design was used to preserve the overall type 1 error probability of 0.05 (false positive efficacy result). The group sequential boundaries for the three scheduled analyses were 2.947, 2.411, and 2.011, which corresponded to nominal p-values of 0.003, 0.016, and 0.044, respectively. The study was to be terminated early if both the IDMB and steering committee agreed based on safety or efficacy data available at the time of their interim review. The first IDMB meeting recommended continuation of the study with an additional meeting in 6 months. The IDMB convened 6 months later on

29 March 2008 and reviewed unblinded safety and efficacy data. At that time, 328 primary endpoints had been confirmed. On the basis of their review, the IDMB recommended stopping the study early based on evidence of treatment benefit in the rosuvastatin group.

Analysis populations:

- Efficacy analysis set: All randomized subjects or the Intention to Treat (ITT) population
- Safety analysis set: All subjects who took at least one dose of study drug. For the **safety analysis, on treatment was defined as up to 30 days following the subject's** last dose. Safety information reported from the Safety population during the follow-**up period beyond the date of the last dose + 30 days was reported as either "off rosuvastatin" or "off placebo". Safety results from the screening period were** presented separately from results after randomization.

5.3.3 Study design

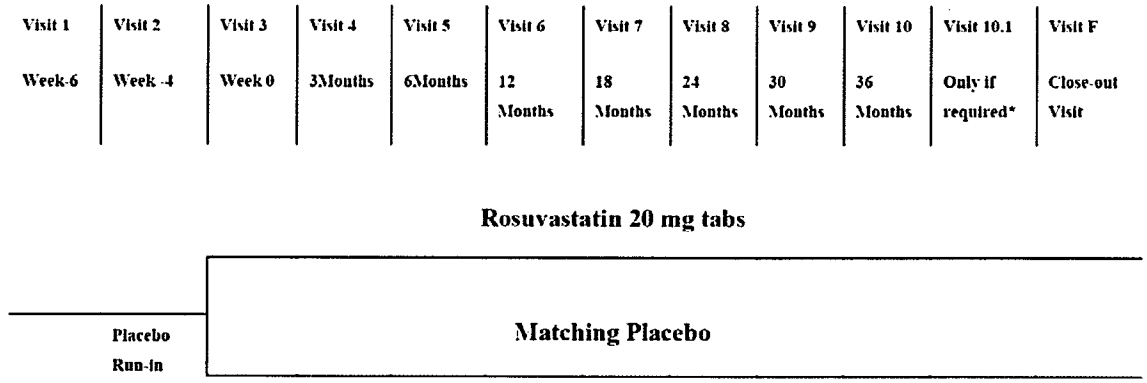
JUPITER was a randomized, double-blind, parallel-group, placebo-controlled, multicenter, phase 3 study comparing 20 mg of rosuvastatin in adult patients with low LDL-C and elevated hsCRP to placebo for the primary prevention of the cardiovascular events of cardiovascular death, nonfatal stroke, nonfatal myocardial infarction, hospitalization for unstable angina, or arterial revascularization. The original protocol planned to follow subjects for approximately 3.5 years to accrue the 520 clinical endpoints upon which the study was powered.

The study was composed of two screening visits, a four-week placebo run-in period, followed by a randomized treatment period (Figure 3). Initial screening for study eligibility could not occur within two weeks of a major viral or bacterial illness. High sensitivity CRP and lipid levels drawn at the initial screening visit determined eligibility for a second screening visit. A second hsCRP level was drawn two weeks after the initial screening visit at the second screening visit. Baseline hsCRP was considered the average of these two hsCRP values. A minimum of 10 study visits were planned. After randomization follow-up visits were scheduled at 13 weeks and then at 6-month intervals. Subjects who completed Visit 10 but had not reached a study endpoint were followed at 6-month intervals to repeat assessments done during Visit 9. Once the study closed, all subjects attended a final clinic visit.

Per the protocol with the occurrence of a subject's first cardiovascular event blinded study medication was discontinued, subjects continued scheduled follow-up **assessments and treatment was left to investigator's discretion. For subjects who** discontinued study medication this did not necessarily mean withdrawal from study participation. The reason for medication discontinuation was assessed, and subjects could continue scheduled follow-up assessments for adverse events and clinical

endpoints. Assessment of vital status was to be done on all randomized JUPITER subjects.

Figure 3: JUPITER study flow chart



* If required, Visit 10.1, 10.2, etc. will be done at 6-month intervals.

Randomization: Eligible patients were randomized in a 1:1 ratio to 20 mg rosuvastatin or placebo, stratified by center.

Inclusion criteria:

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

Exclusion criteria:

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 cyclosporine, tacrolimus, azathioprine, or other immunosuppresants including chronic use of oral glucocorticoids

6. Active liver disease or hepatic dysfunction or elevations of ALT>2x ULN at Screening Visit 2
7. Baseline elevations of CK>3x ULN at Screening Visit 2
8. Creatinine >2.0 mg/dL
9. Diabetes mellitus, defined by fasting serum glucose>126 mg/dL at Screening Visit 2 or by the use of insulin and/or 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 five 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, Pap smears, have been recorded subsequently before entry)
12. Uncontrolled hypothyroidism defined as a thyroid stimulating hormone (TSH)>1.5x 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

Per the applicant, the exclusion of women using postmenopausal oral HRT is based on studies that indicate oral HRT increase hsCRP levels. The pathophysiological consequences of this effect on vascular risk are uncertain, as these agents also interact with lipid metabolism.

5.3.4 Amendments and Post Hoc Changes

There were a total of four amendments and two administrative changes. Listed below are the significant changes from the four amendments.

Amendment 1 (15 January 2003):

- Changed triglyceride inclusion criterion from <600 mg/dL to <500 mg/dL
- Added "or CHD risk equivalent" to exclusion for prior cardiovascular event
- Added venous thromboembolic events and bone fractures as secondary endpoints
- Added health economic evaluation
- Added urinalysis at follow-up visits and creatinine and CK at final visit

Amendment 2 (29 April 2003)

- Expanded recruitment area to Canada (100 centers)
- Added exclusion criterion of serum creatinine >2.0 mg/dL at Screening Visit 2
- Clarified that subjects will be followed for 30 days after final visit for adverse event follow-up
- Colesevelam hydrochloride added to the list of Disallowed Concomitant Medications

Amendment 3 (21 October 2004)

- Expanded recruitment area outside of the United States and Canada to the following areas
    - Belgium – approximately 500 subjects, approximately 50 centers
    - Israel – approximately 200 subjects, approximately 15 centers
    - Estonia – approximately 100 subjects, approximately 15 centers
    - Latin America – approximately 3000 subjects, approximately 200 centers
    - Denmark – approximately 1000 subjects, approximately 100 centers
    - Germany – approximately 1000 subjects, approximately 100 centers
    - Italy – approximately 2000 subjects, approximately 200 centers
    - Netherlands – approximately 3000 subjects, approximately 20 centers
    - Norway – approximately 400 subjects, approximately 40 centers
    - United Kingdom – approximately 5000 subjects, approximately 200 centers
    - Lebanon – approximately 500 subjects, approximately 50 centers
    - Switzerland – approximately 300 subjects, approximately 30 centers
- Added that all randomized subjects will be contacted mid-way between their six-month visits regarding their study participation and have a final visit during the last 6 months of the study
- Discontinued study medication in subjects with ALT levels up >3x ULN on 2 consecutive measurements 48 hours apart
- Clarified that every randomized subject be followed for the duration of the study including subjects discontinued from study drug
- Discontinued study medication from subjects incorrectly randomized or contraindicated for use, however all follow-up visits and assessments must continue

Amendment 4 (20 September 2005)

- Expanded recruitment to additional countries
    - United States – approximately 8000 subjects, approximately 800 centers
    - Canada - approximately 2000 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 3000 subjects, approximately 200 centers
    - Denmark – approximately 1000 subjects, approximately 10 centers
    - Germany/Switzerland – approximately 1000 subjects, approximately 40 centers

- Netherlands – approximately 3000 subjects, approximately 30 centers
- Norway – approximately 400 subjects, approximately 60 centers
- Poland – approximately 1000 subjects, approximately 100 centers
- Russia – approximately 1000 subjects, approximately 100 centers
- United Kingdom – approximately 3000 subjects, approximately 40 centers
- South Africa – approximately 1000 subjects, approximately 50 centers

- Lowered eligible age from 55 to 50 years for men and from 65 to 60 years for women
- Added unstable angina to exclusion for prior cardiovascular event
- Added subgroup analysis for age-at-entry ≥55 (for men) or ≥65 (for women) versus younger subjects

6 Review of Efficacy

Efficacy Summary

- Treatment with rosuvastatin in subjects with no clinically evident cardiovascular disease, a LDL-C of <130 mg/dL, hsCRP ≥2 mg/L, and at least one other major ATP-III risk factor resulted in a 44% relative risk reduction and 1.2% absolute risk reduction in time to major cardiovascular events defined as the composite of cardiovascular death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina, and revascularization.
- The three pre-specified secondary outcomes (a) cardiovascular death/MI/stroke, (b) fatal or nonfatal MI, (c) fatal or non-fatal stroke which controlled for Type 1 error demonstrated a significant reduction in events in the rosuvastatin-treated group compared to the placebo-treated group.
- For the individual components of the primary efficacy composite, cardiovascular death and hospitalization for unstable angina did not reach statistical significance, although the numbers trended in favor of rosuvastatin.
- The analysis for the secondary outcome variable, total mortality did not control for Type 1 error and achieved a nominal p-value of 0.02. When subjects with a Framingham risk score >20% were excluded from the total mortality analysis, the nominal p-value was 0.05.
- There were no significant treatment differences between the treatment groups regarding noncardiovascular mortality and bone fractures.
- A small but significant increase in HDL-C and significant reductions in the other measured lipoproteins and hsCRP were observed in the rosuvastatin group compared to the placebo group.
- In an exploratory post-hoc subgroup analysis of 24% of JUPITER subjects possessing only age as a risk factor and an elevated hsCRP, unadjusted for high HDL-C, the hazard ratio was 0.91 and 95% confidence interval was 0.56, 1.46.

- In an exploratory post-hoc subgroup analysis of 8% of JUPITER subjects possessing with zero ATP-III risk factors, after adjustment for high HDL-C, the hazard ratio was 1.54 and 95% confidence interval 0.64, 3.70.

6.1 Indication

The following indication is sought by the applicant:

Prevention of cardiovascular disease in adult patients with an increased risk of cardiovascular disease based on the presence of cardiovascular disease risk markers such as an elevated hsCRP level, age, hypertension, low HDL-C, smoking or a family history of premature coronary heart disease, CRESTOR is indicated to:

- reduce the risk of total mortality
- reduce the risk of cardiovascular death
- reduce the risk of stroke
- reduce the risk of myocardial infarction
- reduce the risk of arterial revascularization
- reduce the risk of unstable angina

The indication was revised by applicant on 21 December 2009 to:

In adult patients at (b) (4) risk of cardiovascular disease based on cardiovascular disease risk markers such as age, elevated hsCRP level, hypertension, low HDL-C, smoking or a family history of premature coronary heart disease, CRESTOR is indicated to reduce the risk of total mortality and major cardiovascular events: cardiovascular death, stroke, myocardial infarction, arterial revascularization, unstable angina.

6.1.1 Methods

6.1.1.1 Adjudication procedures

Every 3 months, JUPITER subjects were asked about possible primary clinical endpoints. Supporting documentation for possible primary endpoints was compiled into event review packets by the statistical programming contractor, (b) (4) and forwarded to the Duke Clinical Research Institute (DCRI) Clinical Events Classification group.

Two physician reviewers assigned to the JUPITER project independently adjudicated each suspected endpoint using the endpoint criteria (defined in Section 6.1.1.2). If there was agreement between the two independent reviews, the adjudication was considered complete. If the reviewers did not agree, the endpoint was adjudicated by a committee of at least 3 DCRI faculty physicians.

If insufficient documentation was provided, the physician reviewer could request additional source documentation. If no further information was available, the DCRI required documentation from the applicant designee that due diligence was done in obtaining source documents. In cases where the data was insufficient to adjudicate, the event was not considered an event for the primary endpoint. Deaths listed as Insufficient Data to Adjudicate (IDA) were not included in the primary efficacy analysis.

The secondary endpoints of diabetes mellitus, deep vein thrombosis, pulmonary embolism, and bone fracture were not adjudicated.

6.1.1.2 Definition of cardiovascular endpoints

The primary JUPITER efficacy endpoint was first occurrence of a major cardiovascular event after randomization. The composite cardiovascular event was composed of cardiovascular death, nonfatal stroke, nonfatal myocardial infarction, hospitalization for unstable angina, and arterial revascularization. The following are the study definitions of the primary endpoints.

Cardiovascular causes of death

- Myocardial infarction: Fatal event fulfilling prespecified diagnostic criteria of nonfatal MI, diagnosis of MI stated in hospital discharge records, death certificate, or from autopsy evidence.
- Heart failure: Cannot be classified as due to MI and no other obvious cause
- Stroke: Fatal event fulfilling prespecified diagnostic criteria of nonfatal stroke, diagnosis of stroke stated in hospital discharge records, death certificate, or from autopsy evidence.
- Sudden death: Cannot be classified as being due to MI or stroke and the event is instantaneous or occurs within 12 hours of onset of acute chest pain, syncope, pulmonary edema, cardiogenic shock, or other cardiovascular or cerebrovascular symptoms.

Nonfatal Stroke

- Unequivocal signs of a focal or global neurologic deficit with sudden onset and of duration >24 hours. Computed tomography or magnetic resonance imaging scans or both and clinical reports will classify stroke as hemorrhagic, thromboembolic, or other.

Nonfatal Myocardial Infarction

The diagnosis of nonfatal MI was made if at least two of the following criteria were met.

- Ischemic chest pain of more than 15 minutes duration with onset during the previous 48 hours, or pulmonary edema without previously known valvular disease, or shock without suspicion of acute hypovolemia.

- A transient rise of serum CK, CK-MB, cardiac troponin, or any other clinically accepted marker of myocardial injury to values above the locally defined level for diagnosis of MI.
- Development or disappearance of localized ST elevation ≥ 1 mm, combined with the development of persistent T-wave inversion in at least two anatomically contiguous standard ECG leads or development of new left bundle branch block.

Unstable angina
Ischemic chest pain at rest or with minimal exertion, representing a change in subject's usual symptom pattern, which occurs within the preceding 48 hours, and requires hospitalization and presence of objective evidence of ischemia. Myocardial ischemia to be defined by at least one of the following criteria:

- New and/or dynamic ST depression (>0.5 mm), elevation (>1 mm) or T wave inversion (≥ 3 mm) on resting ECG.
- A definite persistent or reversible wall motion abnormality or scintigraphic perfusion defect demonstrated either spontaneously or by stress testing.
- Angiographic evidence of an epicardial coronary artery stenosis of ≥ 80% diameter reduction (or > 50% for the left main coronary artery) and/or evidence for intraluminal arterial thrombus.
- A transient elevation of serum CK, CK-MB, troponin, or any other accepted marker of myocardial ischemia to a level greater than normal but less than the locally defined decision level for the diagnosis of MI.

Arterial Revascularization
Confirmed by hospital records demonstrating either of the following:

- Coronary artery bypass graft (CABG) surgery or bypass grafting of any peripheral artery or carotid
- At least one percutaneous transluminal intervention (PTI) including either angioplasty, stent placement, or other intravascular procedure involving coronary carotid or peripheral arteries.

6.1.1.3 Definition of Secondary Endpoints (non-adjudicated)

Diabetes mellitus
The secondary endpoint definition of incident diabetes mellitus was based on physician diagnosis, new use of insulin or an oral hypoglycemic agent, evidence of a positive glucose tolerance test, or evidence of repeated fasting glucose ≥ 126 mg/dL, or random glucose >200 mg/dL with symptoms of polyuria, polydipsia, and weight loss.

Venous thrombosis or pulmonary embolism
Diagnosis confirmed based on venous ultrasonograms, angiograms, ventilation perfusion studies, computed tomography, and prescriptive evidence of new use of anticoagulation therapy.

6.1.2 Demographics and other subject characteristics

In JUPITER, overall there were no significant differences between treatment groups for demographics and baseline characteristics (Table 8). The majority of subjects enrolled were Caucasian males, approximately 38% were women, and the mean age was 66 years old.

At baseline, the majority of subjects had hypertension (57%), smokers comprised 16% of the population, almost a third (31%) of subjects met the definition for impaired fasting glucose tolerance, 12% had a family history of coronary heart disease, 76% were obese, and 41% met the criteria for metabolic syndrome.

Calculation of the Framingham risk score at baseline revealed 41% of subjects were categorized as low risk (10-year CHD risk <10%), 51% as intermediate risk (10-year CHD risk 10-20%), 9% as high risk (10-year CHD risk >20%).

Table 8: Demographic and baseline characteristics (ITT population)

	ITT population N=17802		
	Rosuvastatin 20 mg (N=8901)	**Placebo (N=8901)**	**Total (N=17802)**
Sex, n (%)			
Male	5475 (61.5)	5526 (62.1)	11001 (61.8)
Female	3426 (38.5)	3375 (37.9)	6801 (38.2)
Age (years)			
Mean	66.0 (7.64)	66.0 (7.79)	66.0 (7.71)
Median	66.0	66.0	66.0
Range	49 to 94	50 to 97	49 to 97
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 (<0.1)	0	2 (<0.1)
Age group at entry, n (%)			
Males			
<50 years	1 (<0.1)	0	1 (<0.1)
50-64 years	3044 (55.6)	3144 (56.9)	6188 (56.2)
65-74 years	1838 (33.6)	1722 (31.2)	3560 (32.4)
75+ years	592 (10.8)	660 (11.9)	1252 (11.4)
Age group at entry, n (%)			
Females			
<60 years	1 (<0.1)	1 (<0.1)	2 (<0.1)
60-74 years	2755 (80.4)	2733 (81.0)	5488 (80.7)
75-84 years	618 (18.0)	572 (16.9)	1190 (17.5)
85+ years	52 (1.5)	69 (2.0)	121 (1.8)
Body mass index, kg/m^2			
Mean (SD)	29.1 (6.69)	29.0 (5.67)	29.0 (6.20)
BMI >25 kg/m^2, n (%)	6826 (76.7)	6839 (76.8)	13665 (76.8)
Systolic BP, mmHg			
Mean (SD)	135.6 (16.75)	135.6 (16.79)	135.6 (16.77)
Median	134.0	134.0	134.0
Diastolic BP, mmHg			
Mean (SD)	80.7 (9.09)	80.7 (8.96)	80.7 (9.02)
Median	80.0	80.0	80.0
Current smoking (last month), n (%)	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)
Family history of stroke, n (%)	1792 (20.1)	1873 (21.0)	3665 (20.6)
Family history of diabetes, n (%)	2069 (23.2)	2101 (23.6)	4170 (23.4)
FSG ≥ 100 mg/dL, n (%)	2755 (31.0)	2817 (31.6)	5572 (31.3)

	ITT population N=17802		
	Rosuvastatin 20 mg (N=8901)	**Placebo (N=8901)**	**Total (N=17802)**
Metabolic syndrome[a], n (%)	3652 (41.0)	3725 (41.8)	7377 (41.4)
Framingham risk score			
Mean (SD)	11.6 (7.0)	11.6 (6.9)	11.6 (7.0)
Framingham risk category, n (%)			
Low	3615 (40.6)	3602 (40.5)	7217 (40.5)
Intermediate	4485 (50.4)	4516 (50.7)	9001 (50.6)
High	786 (8.8)	772 (8.7)	1558 (8.8)
Not calculable	15 (0.2)	11 (0.1)	26 (0.1)
eGFR, mL/min/1.73m^2			
Mean (SD)	75.4 (17.5)	75.4 (17.3)	75.4 (17.4)
Median	73.3	73.6	73.6
Range	27-206	21-181	21-206

[a] Subjects had metabolic syndrome if they had 3 or more of the following 5 factors: 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 (5.6 mmol/L)
Source: Applicant's Table 12, Pg 54, Table 13, Pg 56 JUPITER CSR

Baseline NCEP ATP-III risk factors

Table 9 lists the frequency of individual risk factors occurring in JUPITER subjects at baseline as defined by NCEP ATP-III guidelines. The next tables (Table 10 and 11) list the total number of risk factors before and after subtracting 1 risk factor for a HDL-C ≥ 60 mg/dL. Approximately 25% of all subjects had HDL-C ≥ 60 mg/dL. All subjects met the ATP-III age risk criterion, per protocol. When adjusted for high HDL-C values, approximately 60% of subjects had two or more conventional risk factors by NCEP ATP-III guidelines.

Table 9: JUPITER: Major cardiovascular NCEP-ATP III risk factors at baseline (ITT population)

Major risk factor	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)	Total N=17802 n (%)
Smoking (last month)	1400 (15.7)	1420 (16.0)	2820 (15.8)
Hypertension (BP ≥140/90 or on antihypertensives)	5079 (57.1)	5129 (57.6)	10208 (57.3)
Low HDL-C (<40 mg/dL)	1980 (22.2)	2023 (22.7)	4003 (22.5)
Family history of premature CHD	997 (11.2)	1048 (11.8)	2045 (11.5)
Age (men ≥45, women ≥55)	8901 (100.0)	8901 (100.0)	17802 (100.0)
HDL ≥ 60 mg/dL	2226 (25.0)	2241 (25.2)	4467 (25.1)
Source: Applicant's Table 11.1.1.3.1.1.1, Pg 278, CSR			

Table 10: JUPITER: Number of cardiovascular risk factors at baseline unadjusted for HDL-c ≥ 60 mg/dL (ITT population)

Total number of risk factors	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)	Overall N=17802 n (%)
1 risk factor (age only)	2199 (24.7)	2080 (23.4)	4279 (24.0)
2 risk factors	4373 (49.1)	4423 (49.7)	8796 (49.4)
3 risk factors	1931 (21.7)	2017 (22.7)	3948 (22.2)
4 risk factors	371 (4.2)	361 (4.1)	732 (4.1)
5 risk factors	27 (0.3)	20 (0.2)	47 (0.3)
Source: Applicant's Table 11.1.1.3.1.2.1, Pg 287, CSR			

Table 11: JUPITER: Number of cardiovascular risk factors at baseline adjusted for HDL-C ≥ 60 mg/dL

Total number of risk factors	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)	Overall N=17802 n (%)
0 risk factors[a]	725 (8.1)	680 (7.6)	1405 (7.9)
1 risk factor	2679 (30.1)	2640 (29.7)	5319 (29.9)
2 risk factors	3451 (38.8)	3487 (39.2)	6938 (39.0)
3 risk factors	1661 (18.7)	1730 (19.4)	3391 (19.0)
4 risk factors	358 (4.0)	344 (3.9)	702 (3.9)
5 risk factors	27 (0.3)	20 (0.2)	47 (0.3)
[a] All subjects with 0 risk factors had HDL-C ≥ 60 mg/dL Source: Applicant's Table 11.1.1.3.1.1.1, Pg 278, CSR			

Baseline lipoprotein values

There were no significant differences in baseline lipoprotein and hsCRP levels between treatment groups. Approximately 29% of JUPITER subjects had hsCRP ≤3 mg/L and the median value for all JUPITER subjects was 4.3 mg/L. As has been reported in the literature, hsCRP in women were slightly higher than in men.[24] Baseline lipoprotein and hsCRP levels are summarized by treatment group in the following table. Values are listed as means unless otherwise noted.

Table 12: JUPITER: Baseline lipoprotein and hsCRP levels (ITT population)

	Rosuvastatin 20 mg N=8901		Placebo N=8901		Overall N=17802
	N	**mg/dL (SD)**	**N**	**mg/dL (SD)**	**mg/dL (SD)**
Total cholesterol	8899	183 (24.7)	8901	183 (24.2)	183 (24.4)
Triglycerides, MEDIAN	8899	118 (73.4)	8901	118 (73.5)	118 (73.4)
HDL-C	8899	51 (15.3)	8901	51 (15.2)	51 (15.3)
LDL-C	8899	104 (18.9)	8899	105 (18.5)	104 (18.7)
Apolipoprotein A-I	8863	166 (31.0)	8857	165 (30.5)	165 (30.7)
Apolipoprotein B	8861	109 (21.7)	8856	109 (21.0)	109 (21.4)
	N	**mg/L (SD)**	**N**	**mg/L**	**mg/L**
hsCRP	8901	6.6 (8.6)	8901	6.9 (9.2)	6.8 (8.9)
hsCRP minimum		1.1		0.55	0.55
hsCRP maximum		192.0		174.5	192.0
hsCRP, MEDIAN	**N**	**mg/L**	**N**	**mg/L**	**mg/L**
Men and women	8901	4.2	8901	4.3	4.3
Men	5475	4.0	5526	4.1	4.1
Women	3426	4.6	3375	4.7	4.6
	N	**%**	**N**	**%**	**N (%)**
Baseline CRP ≤ 3 mg/L	2649	29.8	2564	28.8	5213 (29.3)
Source: Applicant's Table 17, Pg 59; Table 11.2.2.1.3.1, Pg 3014, CSR JUPITER Table 12.1.9.1.4.2, Pg 710 Appendix 12.1.9					

Baseline concomitant cardiovascular medications

Approximately a third of JUPITER subjects at baseline were taking concomitant cardiovascular medications, the majority of which targeted hypertension. Thiazide diuretics (11.9%), ACE inhibitors (11.0%), and aspirin (10.2%) were the top three concomitant medications at baseline. At baseline, a slightly higher proportion of rosuvastatin-treated subjects were on thiazides compared to placebo-treated subjects. More placebo-treated subjects at baseline were on ACE inhibitors compared to rosuvastatin-treated subjects. Concomitant aspirin medication was balanced between treatment groups at baseline.

24 Khera et al. Race and gender differences in C-reactive protein levels. JACC 2005; 46:464-69.

Table 13: Concomitant diabetic/cardiovascular medications at baseline (ITT population)

Concomitant diabetic/cardiovascular medications	Rosuva 20 mg N=8901 n(%)	Placebo N=8901 n(%)	Total N=17802 n(%)
Diabetic medications: Any	9 (0.1)	12 (0.1)	21 (0.1)
Metformin only	7 (0.1)	8 (0.1)	15 (0.1)
Sulfonylurea only	0	2 (0.0)	2 (0.0)
Metformin +sulfonylurea	1 (0.0)	0	1 (0.0)
Other antidiabetic	1 (0.0)	2 (0.0)	3 (0.0)
Cardiovascular medications: Any	3004 (33.7)	3035 (34.1)	6039 (33.9)
Antiplatelets (excluding aspirin)	4 (0.0)	6 (0.1)	10 (0.1)
Aspirin	898 (10.1)	918 (10.3)	1816 (10.2)
ACE inhibitors	955 (10.7)	998 (11.2)	1953 (11.0)
Beta-blockers	793 (8.9)	751 (8.4)	1544 (8.7)
Nitrates	30 (0.3)	30 (0.3)	60 (0.3)
Calcium channel blockers	597 (6.7)	594 (6.7)	1191 (6.7)
Thiazide diuretics	1082 (12.2)	1038 (11.7)	2120 (11.9)
Loop diuretics	263 (3.0)	279 (3.1)	542 (3.0)
Fibrates	1 (0.0)	2 (0.0)	3 (0.0)
ARBS	590 (6.6)	630 (7.1)	1220 (6.9)
Alpha blocker	319 (3.6)	343 (3.9)	662 (3.7)
Potassium sparing diuretic	202 (2.3)	201 (2.3)	403 (2.3)
Cardiac glycosides	43 (0.5)	56 (0.6)	99 (0.6)
Statin other than CRESTOR	9 (0.1)	15 (0.2)	24 (0.1)

Source: Appendix A, Table 1, Pg 11 emailed information request 17 August 2009

6.1.3 Subject Disposition

Twenty six countries participated in JUPITER. The study was originally intended to be performed solely in the United States. Due to poor recruitment, Canadian sites were added in 2003. A protocol amendment to expand recruitment to additional countries was approved in October 2004.

The table below summarizes the distribution of the 17,802 randomized subjects. The largest numbers of randomized patients are from the United States, followed by the United Kingdom, South Africa, and Canada. However, only 22.6% of the total randomized population is from the United States.

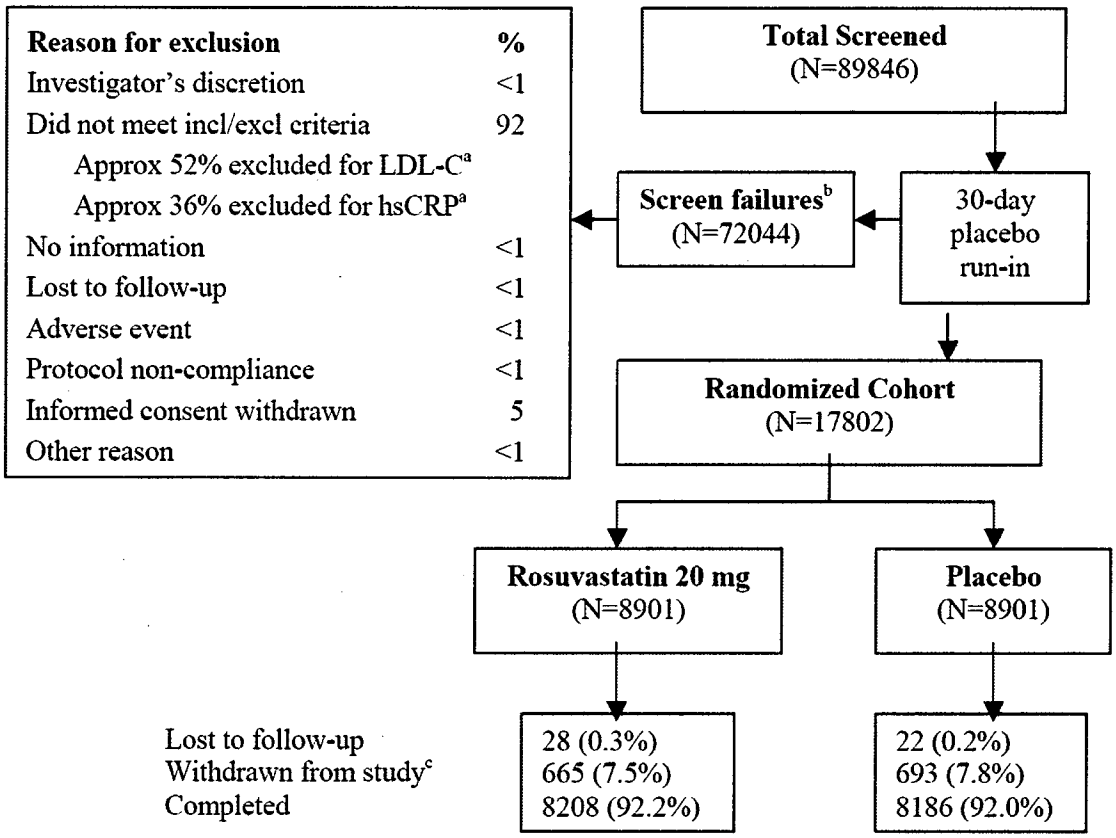
Table 14: Number of study centers and subjects randomized by country

Country	Number of Centers	Total N=17,802 n(%)
United States	628	4,021 (22.6)
United Kingdom	59	2,873 (16.1)
South Africa	44	2,497 (14.0)
Canada	131	2,020 (11.3)

Country	Number of Centers	Total N=17,802 n(%)
Netherlands	20	987 (5.5)
Poland	69	804 (4.5)
Mexico	15	741 (4.2)
Belgium	86	487 (2.7)
Colombia	24	345 (1.9)
Denmark	4	336 (1.9)
Brazil	27	327 (1.8)
Russia	41	273 (1.5)
Costa Rica	7	270 (1.5)
Argentina	28	253 (1.4)
Germany	16	222 (1.2)
Venezuela	27	209 (1.2)
Norway	46	204 (1.1)
Panama	5	202 (1.1)
Bulgaria	22	197 (1.1)
El Salvador	3	162 (0.9)
Israel	12	143 (0.8)
Estonia	10	85 (0.5)
Chile	9	83 (0.5)
Romania	10	32 (0.2)
Switzerland	1	15 (0.1)
Uruguay	4	14 (0.1)
Source: Applicant's Table 11.1.1.7.2.1 Pg 1850, Listing 12.2.1.4, Pg 5336		

Enrollment began February 2003 and the last subject was enrolled in December 2006. Of the 89,846 subjects screened, 17,802 (19.8%) subjects were randomized into the JUPITER study (Figure 4).

Figure 4: Disposition of JUPITER study subjects



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

a) 37,611 subjects excluded for LDL ≥ 130 mg/dL
25,993 subjects excluded for hsCRP < 2 mg/L
b) There were 72044 screen failure subjects; there were 5 additional subjects who were not screen failure subjects but who did not get randomized.
c) Withdrawn from study does not include those subjects lost to follow up. The number of subjects lost to follow-up is listed separately.

Source: Applicant's Figure Page 51, CSR

Overall, 7.8% of the rosuvastatin-treated group and 8% of the placebo-treated group withdrew participation from the study. There were no imbalances noted in the reasons for study withdrawal between the treatment groups.

Table 15: Number of subjects withdrawing participation from JUPITER (ITT population)

	Rosuvastatin 20 mg N=8901 n(%)	Placebo N=8901 n(%)	Total N=17802 n(%)
Number of subjects randomized	8901 (100.0)	8901 (100.0)	17802 (100.0)
Withdrew from the study	693 (7.8)	715 (8.0)	1408 (7.9)
Adverse event	46 (0.5)	33 (0.4)	79 (0.4)
Subject withdrew consent	176 (2.0)	187 (2.1)	363 (2.0)
Subject withdrew consent due to AE	54 (0.6)	66 (0.7)	120 (0.7)
Subject withdrew consent (other than for AE)	282 (3.2)	302 (3.4)	584 (3.3)
No information	13 (0.1)	11 (0.1)	24 (0.1)
Subject lost to follow-up	28 (0.3)	22 (0.2)	50 (0.3)
Protocol noncompliance	4 (0.0)	4 (0.0)	8 (0.0)
Investigator discretion	13 (0.1)	17 (0.2)	30 (0.2)
Other reason	77 (0.9)	73 (0.8)	150 (0.8)
Completed the study	8208 (92.2)	8186 (92.0)	16394 (92.1)
Source: Applicant's table 11.1.1.8.2.1.1, Pg 1857 CSR			

A higher proportion of patients in the U.S. withdrew from JUPITER, 18.5% of US subjects withdrew versus 4.8% of subjects from the rest of the world. The majority of U.S. subjects withdrew consent for a reason unspecified.

Table 16: Number of subjects withdrawing participation from JUPITER (U.S. vs. Rest of World)

	United States		Rest of World	
	Rosuvastatin 20 mg N=1990 n(%)	Placebo N=2031 n(%)	Rosuvastatin 20 mg N=6911 n(%)	Placebo N=6870 n(%)
Number of subjects randomized	1990 (100.0)	2031 (100.0)	6911 (100.0)	6870 (100.0)
Withdrew from the study	370 (18.6)	373 (18.4)	323 (4.7)	342 (5.0)
Adverse event	39 (2.0)	28 (1.4)	7 (0.1)	5 (0.1)
Subject withdrew consent	138 (6.9)	142 (7.0)	38 (0.5)	45 (0.7)
Subject withdrew consent due to AE	21 (1.1)	30 (1.5)	33 (0.5)	36 (0.5)
Subject withdrew consent (other than for AE)	112 (5.6)	116 (5.7)	170 (2.5)	186 (2.7)
No information	12 (0.6)	10 (0.5)	1 (0.0)	1 (0.0)
Subject lost to follow-up	9 (0.5)	4 (0.2)	19 (0.3)	18 (0.3)
Protocol noncompliance	3 (0.2)	3 (0.1)	1 (0.0)	1 (0.0)
Investigator discretion	12 (0.6)	10 (0.5)	1 (0.0)	0
Other reason	24 (1.2)	23 (1.1)	53 (0.8)	50 (0.7)
Completed the study	1620 (81.4)	1658 (81.6)	6588 (95.3)	6528 (95.8)

	United States		Rest of World	
	Rosuvastatin 20 mg N=1990 n(%)	Placebo N=2031 n(%)	Rosuvastatin 20 mg N=6911 n(%)	Placebo N=6870 n(%)
Source: Applicant's table 11.1.1.8.2.3, Pg 1864, CSR				

If a subject wished to withdraw from the study, investigators were to give the subject the option of discontinuing the study medication, but continuing with follow-up visits every 6 months. The following table lists the reasons for discontinuing study medication in the ITT population.

Table 17: Reason for discontinuing study medication (ITT population)

Reason	Rosuvastatin 20 mg N=8901 n(%)	Placebo N=8901 n(%)	Total N=17802 n(%)
Total	**1711 (19.2)**	**1923 (21.6)**	**3634 (20.4)**
Clinical event	72 (0.8)	153 (1.7)	225 (1.3)
Initiation of open label statin therapy	51 (0.6)	157 (1.8)	208 (1.2)
Adverse event	584 (6.6)	553 (6.2)	1137 (6.4)
Other	1002 (11.3)	1048 (11.8)	2050 (11.5)
Not specified	2 (0.0)	12 (0.1)	14 (0.1)
Applicant's Table 11.1.1.8.2.4.1, Pg 1865, CSR			

The development of certain criteria during the trial mandated study medication discontinuation, per protocol:

1. CK measures >10x ULN accompanied by unexplained muscle pain, tenderness or weakness.
2. Persistent ALT levels >3x ULN.
3. An adverse event warranting study medication discontinuation by investigator opinion.

Table 18 lists the number and frequency of subjects discontinuing study medication as a result of the three above listed criteria.

Table 18: Number and frequency of study medication discontinuations for pre-specified reasons in JUPITER protocol

Criteria for discontinuation	Rosuvastatin 20 mg N=8901 n(%)	Placebo N=8901 n(%)	Total N=17802 n(%)
CK >10x ULN	1 (0.0)	1 (0.0)	2 (0.0)
Persistent ALT >3x ULN on 2 occasions	22 (0.3)	17 (0.2)	39 (0.2)
AE that warrants study withdrawal	57 (0.7)	69 (0.8)	126 (0.8)
Applicant's Table 11.1.1.8.2.6.2, Pg 1873, CSR			

In summary, 7.8% of the rosuvastatin-treatment group and 8.0% of the placebo-treatment group withdrew from the study or were lost to follow-up. Study drug

discontinuations occurred in 19.2% of the rosuvastatin group and 21.6% of the placebo group.

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint, a composite, was time from randomization to first event of any one of the following events: cardiovascular death, nonfatal stroke, nonfatal myocardial infarction, hospitalization for unstable angina, and arterial revascularization.

When the IDMB recommended closure of the study on 29 March 2008, 328 primary endpoints had been positively adjudicated by the Clinical Endpoints Committee (CEC). When the JUPITER study closed on 20 August 2008, 66 additional primary endpoints had been positively adjudicated. Only events occurring before 31 March 2008 and adjudicated and confirmed as MCEs by the CEC were included in the primary efficacy analysis.

The primary efficacy endpoint analysis demonstrated a statistically significant difference with 1.6% of rosuvastatin subjects versus 2.8% of placebo treated subjects experiencing a MCE which translated into a 44% reduction in relative risk and a 1.2% reduction in absolute risk (Table 19).

Table 19: Summary of analysis for primary composite endpoint[a]

Number of Subjects with any Event		Event rate/1000 patient years		Hazard ratio (95% CI) p-value	Relative risk reduction	Absolute risk reduction	Number needed to treat
Rosuvastatin N=8901 n (%)	Placebo N=8901 n (%)	Rosuvastatin	Placebo	0.56 (0.46, 0.69) <0.001	44%	1.2%	83
142 (1.6)	252 (2.8)	7.6	13.6				

Taking the inverse of the absolute risk reduction gives the number needed to treat (NNT) as 83. This reviewer acknowledges that there are other statistical methods to calculate number needed to treat which include Kaplan-Meier curves which account for censoring over time and may account for the differences reported in the literature regarding JUPITER. The equation for number needed to treat of 1 over absolute risk reduction, however, is most likely what clinicians in private practice use.

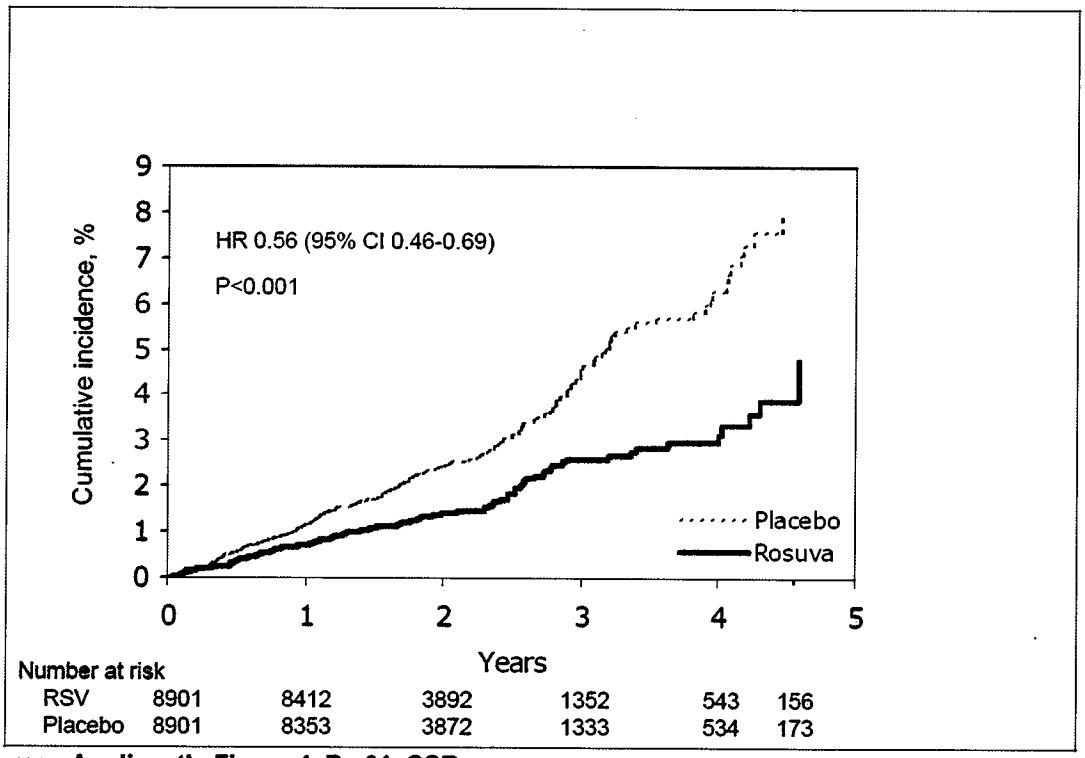
The FDA statistical reviewer performed an analysis of number needed to treat with 95% confidence intervals using Kaplan-Meier curves. Table 20 shows the number needed to treat to prevent one major cardiovascular event at the time points of 1, 2, 3, and 4 years. By Year 4 the number needed to treat was 32.

Table 20: FDA analysis of number needed to treat (NNT)

	Rosuvastatin Survival probabilities	**Placebo** Survival probabilities	**NNT (95%CI)**
Year 1	0.993	0.998	200 (128, 460)
Year 2	0.986	0.975	91 (65, 153)
Year 3	0.974	0.954	50 (33, 100)
Year 4	0.968	0.937	32 (22, 60)

Figure 5 is the Kaplan-Meier curve from which the NNT estimates were calculated and graphically presents the primary composite efficacy endpoint.

Figure 5: Kaplan Meier curve of time to primary composite endpoint



Source: Applicant's Figure 4, Pg 61, CSR

6.1.4.1 Breakdown of Events within the primary endpoint

The distribution of the first MCE that contributed to the composite primary endpoint is listed in the table below. Because this analysis was the time to first MCE, this table only shows the first MCE experienced by each subject.

Table 21: Number of events[a] by treatment group for the composite primary endpoint (ITT population)

Endpoint	Rosuvastatin 20 mg N=8901	Placebo N=8901	p-value[b]
First MCE	142	252	<0.001
Cardiovascular death	29	37	0.33
Non-fatal MI	21	61	<0.01
Non-fatal stroke	30	57	<0.01
Hospitalized unstable angina	15	27	0.069
Arterial revascularization	47	70	0.036

Source: Applicant's Table 18, Pg 62, CSR JUPITER
[a] Event occurrence counts only 1 MCE for each subject. If subject had more than 1 MCE on the same day, only 1 event is shown in above table, according to the following hierarchy: 1)unstable angina, 2) MI, 3) arterial revascularization, 4) non-fatal stroke, 5) cardiovascular death
[b]p-values except for First MCE calculated by FDA statistician, Dr. David Hoberman

The following table shows the frequency of first events for each of the components of the primary composite endpoint, and not just the events that contributed to the composite endpoint. In these analyses subjects were followed until the first occurrence of the specific event, even if the event occurred after a nonfatal event. For example, a subject experiencing a nonfatal stroke, followed by a MI would be counted twice, once for stroke and once for MI. The rosuvastatin-treated group experienced a statistically significant reduction in the frequency of nonfatal strokes, nonfatal MI, and arterial revascularization; however, a statistically significant reduction in the incidence of cardiovascular death and hospitalized unstable angina compared to the placebo group was not observed in the JUPITER trial.

Table 22: Number of first events by treatment group for each individual cardiovascular endpoint (ITT population) [a]

Endpoint	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)	HR	CI for HR	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 MI	22 (0.2)	62 (0.7)	0.35	0.22, 0.58	<0.001
Hospitalized unstable angina	16 (0.2)	27 (0.3)	0.59	0.32, 1.10	0.093
Arterial revascularization-overall	71 (0.8)	131 (1.5)	0.54	0.41, 0.72	<0.001
Coronary	50 (0.6)	101 (1.1)	0.50	0.35, 0.69	<0.001
Peripheral	17 (0.2)	28 (0.3)	0.61	0.33, 1.1.2	0.105
Carotid	6 (0.1)	4 (0.0)	1.52	0.43, 5.37	0.515

[a] Not limited to the first occurrence of a MCE. For example, a subject with a stroke, followed by an MI would be counted twice, once for stroke and once for MI. A subject with serial strokes would only be counted once.
Source: Applicant's Table 19, Pg 63, CSR

The applicant proposes the CRESTOR label state CRESTOR is indicated to: reduce the risk of cardiovascular death and reduce the risk of hospitalization for unstable angina. These individual components of the composite do not reach statistical significance. The majority of events contributing to the overall statistical significance are nonfatal.

Although the study was not powered to look at the individual components of the primary composite endpoint, an amendment to the statistical analysis plan introduced three secondary variables to support the primary endpoint. If the primary variable was statistically significant then in sequential order, at a level of 5% significance, the following variables were tested using adjudicated events.

1. Cardiovascular death, or nonfatal stroke, or nonfatal MI: Demonstrated a 48% reduction in relative risk in the rosuvastatin group compared to the placebo group.
2. Fatal or nonfatal MI: Demonstrated a 54% relative risk reduction in the rosuvastatin group compared to the placebo group.
3. Fatal or nonfatal stroke: Demonstrated a 48% relative risk reduction in the rosuvastatin group compared to the placebo group.

Table 23: Other cardiovascular efficacy endpoints (ITT population)

	Rosuva 20 mg N=8901 n(%)	**Placebo N=8901 n(%)**	**HR (95% CI)**	**p-value**
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
Source: Applicant's Table 22, Pg 67, CSR; Table 11.2.1.35.1, Pg 2929 CSR				

In the above analyses, there were nine fatal MIs in the rosuvastatin group and six fatal MIs in the placebo group which contributed to the fatal or nonfatal MI endpoint. There were three fatal strokes in the rosuvastatin group and six fatal strokes in the placebo group which contributed to the fatal or nonfatal stroke endpoint. Again, the majority of **events contributing to the mini-composite's statistical significance were nonfatal.**

6.1.4.2 Summary of primary endpoint

- Treatment with rosuvastatin in subjects with no clinically evident cardiovascular disease, a LDL-C of <130 mg/dL, hsCRP ≥2 mg/L, and at least one other major ATP-III risk factor resulted in a 44% reduction in time to major cardiovascular events defined as the composite of cardiovascular death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina, and revascularization.
- The three pre-specified secondary outcomes (a) cardiovascular death/MI/stroke, (b) non-fatal MI/MI, (c) non-fatal stroke/stroke which controlled for Type I error

demonstrated a significant reduction in events in the rosuvastatin-treated group compared to the placebo-treated group.

- Two of the individual components of the primary efficacy composite, cardiovascular death and hospitalization for unstable angina did not reach statistical significance, although the numbers trended in favor of rosuvastatin.

6.1.5 Analysis of Secondary Endpoints(s)

Prespecified secondary endpoints included time from randomization to first occurrence of:

- Death (total mortality)
- Noncardiovascular mortality
- Discontinuation of blinded study medication due to an AE
- Development of investigator-reported diabetes mellitus
- Development of venous thromboembolic events (deep vein thrombosis or pulmonary embolism)
- Bone fractures

6.1.5.1 Time to death (total mortality)

Time to death was collected from deaths that occurred during the study and through external data sources such as public death records which provided only vital status. In JUPITER, using all information available on vital status there were a total of 445 deaths, 198 in rosuvastatin-treated subjects and 247 in placebo-treated subjects. When external data sources were excluded there were a total 372 deaths, 167 in rosuvastatin and 205 in placebo treatment groups. The analysis including external data sources reached statistical significance with a nominal p-value of 0.021 and there was a trend towards significance when external vital status was omitted with a nominal p-value of 0.051. This outcome variable was not controlled for type 1 error.

Table 24: Number of events by treatment group time to death (total mortality) with and without external vital status data (ITT population)

	Number of events (% of subjects having an event)						
	Rosuvastatin 20 mg N=8901		**Placebo N=8901**				
	n	**%**	**n**	**%**	**HR**	**95% CI**	**p-value**
Death (including external vital status)	198	2.3	247	2.8	0.80	0.67, 0.97	0.021
Death (excluding external vital status)	167	1.9	205	2.3	0.82	0.67, 1.00	0.051

Source: Applicant's Table 11.2.1.18.1, Pg 2877, Table 11.2.1.19.1, Pg 2880, CSR

6.1.5.2 Time to noncardiovascular death

There was no significant treatment difference in time to noncardiovascular death between rosuvastatin and placebo-treated subjects.

Table 25: Summary and time to development of noncardiovascular death

	Number of events (% of subjects having an event)						
	Rosuvastatin 20 mg N=8901		Placebo N=8901				
	n	%	n	%	HR	95% CI	p-value
Noncardiovascular death	105	1.2	126	1.4	0.84	0.65, 1.08	0.172
Source: Applicant's Table 11.2.1.18.1, Pg 2877, Table 11.2.1.19.1, Pg 2880, CSR							

Please note that the sum of adjudicated cardiovascular deaths and deaths listed as adverse events do not equal the total mortality numbers. Total mortality numbers were retrieved from any of several case report forms: (a) Study completion/Withdrawal, (b) Vital status, (c) Adjudicated CV death, or (d) Adverse event. The applicant explained that subjects who died subsequent to study withdrawal or after being lost to follow up **could have "Death" reported on a Vital status form with no corresponding Adverse event** or Adjudicated CV death form. For withdrawals, only CV death was counted towards total mortality as the subject had withdrawn consent to use their data. In addition, there could have discrepancies between the Adverse event forms or Adjudicated CV death form and the Study completion/withdrawal form. Clinic investigators may have failed to revise their case reports to correct the inconsistency.

6.1.5.3 Time to discontinuation of blinded study medication due to adverse events

This endpoint describes subjects who discontinued taking the study drug but did not necessarily withdraw from the study. This does not include information regarding subjects who discontinued the study drug and then later withdrew participation in the study. In the time to discontinuation of study medication analysis, there were 495 (5.6%) of rosuvastatin-treated subjects and 486 (5.5%) of placebo-treated subjects who discontinued study medication early due to an adverse event.

The reasons for discontinuing study drug were similar between the two groups. There was a higher incidence of placebo-treated subjects discontinuing the study drug in order to be placed on open label statin therapy compared to rosuvastatin-treated subjects.

6.1.5.4 Time to development of (investigator-reported) diabetes mellitus

There was more investigator-reported diabetes in the rosuvastatin-treated group versus the placebo-treated group. This endpoint is discussed further in Safety section 7.3.4.9.1.

Table 26: Summary and time to development of (investigator-reported) diabetes mellitus

	Number of events (% of subjects having an event)						
	Rosuvastatin 20 mg N=8901		Placebo N=8901				
	n	%	n	%	HR	95% CI	p-value
Investigator reported diabetes	251	2.8	205	2.3	1.27	1.05, 1.53	0.015
Source: Applicant's Table 11.3.6.1.2.7 and 11.3.6.1.2.8, Pg 31998 and 31999, CSR							

6.1.5.5 Time to development of venous thromboembolic events

There was a significant treatment effect favoring rosuvastatin in the time to development of venous thromboembolic events (VTE) which was defined as either a deep vein thrombosis or pulmonary embolism. This first row of Table 27 includes only the first occurrence of a VTE for each subject. The following rows include a summary of the individual components of the VTE endpoint. As can be seen there were a larger number of deep vein thrombotic events compared to pulmonary embolic events in both groups. There was no significant treatment difference appreciated with pulmonary embolic events between the two groups, however the numbers were very small and a conclusion about a favorable effect of rosuvastatin on time to pulmonary embolism is limited.

Table 27: Summary and time to development of venous thromboembolic event[a]

	Number of events (% of subjects having an event)						
	Rosuvastatin 20 mg N=8901		Placebo N=8901				
	n	%	n	%	HR	95% CI	p-value
Venous thromboembolic events	26	0.3	46	0.5	0.57	0.35, 0.91	0.018
Deep vein thrombosis	20	0.2	37	0.4	0.54	0.31, 0.93	0.024
Pulmonary embolism	6	0.1	9	0.1	0.67	0.24, 1.87	0.437

[a] These analyses include only the first occurrence of a VTE for each subject
Source: Applicant's Table 11.2.1.23.1, 2 Pg 2893-4; Table 11.2.1.24.1, 2 Pg 2896-7; Table 11.2.1.25.1, 2 Pg 2899-900, CSR

6.1.5.6 Time to bone fractures

In JUPITER there was similar incidence of fracture in both the rosuvastatin and placebo treatment groups. The applicant performed an analysis of fractures that are typically associated with osteoporotic fractures and determined no significant treatment difference.

Table 28: JUPITER: Summary and time to development of bone fractures

	Number of events (% of subjects having an event)		
	Rosuvastatin 20 mg N=8901	Placebo N=8901	

	n	%	n	%	HR	95% CI	p-value
New bone fractures-overall	226	2.5	214	2.4	1.06	0.88, 1.28	0.548
Wrist	41	0.5	27	0.3	1.52	0.93, 2.47	0.088
Hip	21	0.2	14	0.2	1.50	0.76, 2.96	0.232
Ankle	27	0.3	23	0.3	1.18	0.67, 2.05	0.567
Vertebrae	17	0.2	17	0.2	1.01	0.57, 1.97	0.985

Source: Applicant's Table 11.2.1.26.1-2 Pg 2902-3; Table 11.2.1.27.1-2 Pg 2905-6, Table 11.2.1.28.1-2 Pg 2908-9; Table 11.2.1.29.1-2 Pg 2911-12, CSR

6.1.6 Other Endpoints

6.1.6.1 Lipoprotein and hsCRP levels

Levels of lipoproteins and hsCRP values were similar at baseline between treatment groups and are summarized at baseline, 1 year, and at the Final visit in Table 29. As expected, compared to the placebo group there was a significant increase in HDL-C and decrease in all other lipoproteins and hsCRP levels on rosuvastatin therapy after one year and at the Final visit. After 12 months of rosuvastatin, mean LDL-C was reduced by 40% in the rosuvastatin group compared to a 5% increase in the placebo group (Table 30). The median percent reduction from baseline of hsCRP in the rosuvastatin-treated subjects was 47% compared to 20% among placebo-treated subjects after one year.

Lipoprotein and hsCRP values

Table 29: Summary of lipoproteins and hsCRP values throughout study (ITT population)

	Baseline		After 12 months		At Final visit (LOCF)	
	Rosuvastati n 20 mg	Placebo	Rosuvastati n 20 mg	Placebo	Rosuvastati n 20 mg	Placebo
TC (mg/dL)						
N	8899	8901	7962	7928	8157	8151
Mean (SD)	183.23	183.39	139.15	188.85	144.02	187.18 (31.24)
Median	(24.71)	(24.16)	(33.31)	(30.02)	(35.87)	188.00
Range	186.00	185.00	133.00	188.00	137.00	69.0-530.0
	76.0-291.0	71.0-340.0	62.0-297.0	76.0-352.0	57.0-327.0	
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
Range	11.0-145.0	13.0-145.0	12.0-164.0	10.0-149.0	18.0-165.0	8.0-180.0
LDL-C (mg/dL)						
N	8899	8899	7949	7909	8154	8150
Mean (SD)	104.34	104.57	61.64 (27.57)	109.10	65.72 (30.39)	107.15 (25.99)
Median	(18.91)	(18.51)	55.00	(25.02)	57.00	108.00
Range	108.00	108.00	0.0-205.0	110.00	1.0-245.0	9.0-254.0
	12.0-148.0	6.0-170.00		6.0-254.0		
TG (mg/dL)						
N	8899	8901	7962	7928	8157	8151
Mean (SD)	137.76	137.80	114.91	138.39	115.25	134.39 (82.07)
Median	(73.42)	(73.46)	(64.90)	(75.71)	(68.80)	115.00
Range	118.00	118.0	99.00	119.00	99.00	12.0-3150.0
	19.0-499.0	24.0-496.0	18.0-1385.0	25.0-796.0)	16.0-2146.0	
Apo B-100 (mg/dL)						
N	8861	8856	7873	7858	8054	8050
Mean (SD)	108.73	108.72	70.91 (22.17)	105.41	73.32 (24.14)	102.50 (22.34)
Median	(21.71)	(21.02)	66.00	(21.80)	68.00	102.00
Range	109.00	109.00	26.0-196.0	105.00	25.0-234.0	29.0-238.0
	28.0-234.0	28.0-222.0		27.0-218.0		

	Baseline		After 12 months		At Final visit (LOCF)	
	Rosuvastati n 20 mg	Placebo	Rosuvastati n 20 mg	Placebo	Rosuvastati n 20 mg	Placebo
Apo A-1 (mg/dL)						
N	8863	8857	7887	7859	8059	8052
Mean (SD)	165.90	164.96	168.01	163.95	166.64	163.56 (33.42)
Median	(30.95)	(30.47)	(32.41)	(31.01)	(33.79)	159.00
Range	162.00	162.00	165.00	161.00	163.00	5.0-363.0
	64.0-331.0	56.0-378.0	42.0-357.0	16.0-325.0	69.0-365.0	
Apo B-100/Apo A-1 ratio						
N	8861	8856	7873	7857	8054	8050
Mean (SD)	0.68 (0.193)	0.68 (0.190)	0.44 (0.170)	0.67 (0.221)	0.46 (0.181)	0.65 (0.201)
Median	0.66	0.67	0.40	0.65	0.42	0.64
Range	0.1-1.6	0.1-2.4	0.1-1.7	0.2-10.3	0.1-1.5	0.1-4.5
hsCRP (mg/L)						
N	8901	8901	7950	7923	8613	8630
Mean (SD)	6.629 (8.59)	6.923 (9.17)	4.535 (9.86)	6.010 (10.26)	5.213 (10.72)	6.755 (12.051)
Median	4.200	4.300	2.200	3.500	2.600	3.700
Range	1.10-192.0	0.55-174.50	0.10-294.60	0.07-213.00	0.11-294.60	0.200-281.0

Source: Applicant's Table 24 Pg 74, CSR

Table 30: Summary of changes in lipoproteins and hsCRP after 1 year of study treatment and at final visit (ITT population)

	After 12 months		At final visit (LOCF)	
	Rosuvastatin 20 mg	**Placebo**	**Rosuvastatin 20 mg**	**Placebo**
TC				
N	7961	7928	8155	8151
LS Mean (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
LS Mean (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
LS Mean (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
LS Mean (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)	
Apo B-100				
N	7842	7823	8020	8012
LS Mean (SE)	-33.82 (0.205)	-2.07 (0.205)	-31.60 (0.219)	-4.73
p-value	<0.001		<0.001	
Difference (95% CI)	-31.75 (-32.32, -31.18)		-26.86 (-27.47, -26.26)	
Apo A-1				
N	7857	7825	8026	8015
LS Mean (SE)	1.95 (0.154)	-0.08 (0.155)	1.17 (0.167)	-0.34 (0.167)
p-value	<0.001		<0.001	
Difference (95% CI)	2.03 (1.60, 2.46)		1.51 (1.04, 1.97)	
Apo B-100/Apo A-1 ratio				
N	7842	7822	8020	8012
LS Mean (SE)	-33.85 (0.246)	-0.66 (0.246)	-31.08 (0.257)	-2.75 (0.257)
p-value	<0.001		<0.001	
Difference (95% CI)	-33.19 (-33.87, -32.50)		-28.33 (-29.04, -27.61)	
hsCRP				
N	7950	7923	8613	8630
LS Mean (SE)	-12.94 (2.258)	15.65 (2.262)	1.49 (2.432)	27.68 (2.430)
p-value	<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)

Source: Applicant's Table 25, Pg 75, CSR

6.1.7 Subpopulations

6.1.7.1 Prespecified subgroup analyses

In general, the treatment effect of rosuvastatin on the primary endpoint was consistent across prespecified subgroups which included age, sex, race, smoking status, BMI, baseline lipoprotein levels, HTN, and metabolic syndrome. All hazard ratios favored the rosuvastatin-treated group. The p-value for the interaction compares the hazard ratios between subgroups. There was a significant treatment interaction for the baseline hsCRP values above and below the median and 4 mg/L. However, it should be noted that the 95% confidence intervals do not extend past 1.0.

Table 31: Time to primary composite endpoint among prespecified subgroups

	Rosuvastatin		Placebo			
Subgroup	**N**	**n (rate/1000 pt years)**	**N**	**n (rate/1000 pt years**	**Hazard ratio (95% CI)**	**p-value for interaction**
AGE						
≤ 65 years at baseline	4216	42 (4.9)	4325	90 (10.3)	0.48 (0.33, 0.69)	0.338
>65 years at baseline	4685	100 (9.9)	4576	162 (16.6)	0.60 (0.47, 0.76)	
SEX						
Males	5475	103 (8.8)	5526	182 (15.5)	0.57 (0.45, 0.73)	0.817
Females	3426	39 (5.6)	3375	70 (10.4)	0.54 (0.37, 0.80)	
AGE BY SEX						
Male <65 y, Female < 75 y	5762	55 (4.7)	5837	120 (10.1)	0.46 (0.34, 0.64)	0.128
Males≥65 y, Female≥75 y	3139	87 (12.9)	3064	132 (20.1)	0.64 (0.49, 0.84)	
RACE						
Caucasian	6358	111 (7.8)	6325	202 (14.4)	0.54 (0.43, 0.69)	0.561
Non-Caucasian	2543	31 (7.0)	2576	50 (11.1)	0.63 (0.49, 0.99)	
SMOKER						
No	7496	110 (6.9)	7479	190 (12.1)	0.58 (0.46, 0.73)	0.644
Yes	1000	32 (11.7)	1420	62 (22.6)	0.51 (0.34, 0.79)	
BODY MASS INDEX						
BMI ≤ 30	5535	94 (8.2)	5547	179 (15.9)	0.519 (0.40, 0.67)	0.313
BMI >30	3339	47 (6.6)	3336	73 (10.2)	0.652 (0.45, 0.94)	
HDL-C						
HDL <40 mg/dL	1980	32 (7.6)	2023	65 (15.3)	0.50 (0.33, 0.76)	0.512
HDL ≥40 mg/dL	6919	110 (7.7)	6878	187 (13.1)	0.58 (0.46, 0.74)	
LDL-C						
≤100 mg/dL	3118	55 (8.7)	3153	86 (13.5)	0.65 (0.46, 0.91)	0.304

	Rosuvastatin		Placebo			
Subgroup	**N**	**n (rate/1000 pt years)**	**N**	**n (rate/1000 pt years**	**Hazard ratio (95% CI)**	**p-value for interaction**
>100 mg/dL	5781	87 (7.1)	5746	166 (13.7)	0.52 (0.40, 0.67)	
Above median	4571	68 (7.0)	4628	138 (14.1)	0.50 (0.37, 0.67)	0.236
Below median	4328	74 (8.3)	4271	114 (13.1)	0.64 (0.48, 0.86)	
TRIGLYCERIDES						
<200 mg/dL	7398	117 (7.6)	7384	208 (13.6)	0.56 (0.45, 0.71)	0.974
≥200 mg/dL	1501	25 (7.7)	1517	44 (13.7)	0.56 (0.34, 0.91	
HTN						
Yes	5079	89 (8.5)	5129	166 (15.8)	0.54 (0.42, 0.70)	0.559
No	3818	53 (6.6)	3768	86 (10.8)	0.61 (0.43, 0.86)	
REGION						
US	1990	58 (10.7)	2031	94 (16.9)	0.63 (0.45, 0.87)	0.395
Countries other than US	6911	84 (6.4)	6870	158 (12.2)	0.52 (0.40, 0.68)	
US or Canada	3007	81 (9.7)	3034	137 (16.3)	0.60 (0.45, 0.78)	0.536
Countries other than US/Canada	5894	61 (6.0)	5867	115 (11.4)	0.52 (0.38, 0.71)	
METABOLIC SYNDROME						
No	5218	75 (6.9)	5146	149 (14.0)	0.50 0.38, 0.66)	0.167
Yes	3652	67 (8.7)	3725	102 (13.1)	0.67 (0.49, 0.91)	
BASELINE CRP						
Above median[a]	4446	89 (9.7)	4551	128 (13.7)	0.71 (0.54, 0.92)	0.015
Below median	4454	53 (5.6)	4350	124 (13.5)	0.42 (0.30, 0.58)	
≤ 4 mg/L	4211	50 (5.6)	4113	119 (13.8)	0.41 (0.30, 0.57)	0.014
>4 mg/L	4689	92 (9.5)	4788	133 (13.5)	0.70 (0.54, 0.91)	
Baseline LDL-C and hsCRP						
Below median LDL and hsCRP	2072	24 (5.6)	1988	47 (11.3)	0.50 (0.30, 0.81)	
Above median LDL and below median hsCRP	2382	29 (5.7)	2361	77 (15.3)	0.37 (0.24, 0.57)	0.094
Above median LDL and hsCRP	2189	39 (8.5)	2267	61 (12.8)	0.66 (0.44, 0.99)	
Below median LDL and above median hsCRP	2256	50 (10.9)	2283	67 (14.7)	0.74 (0.51, 1.07)	
Baseline fasting serum glucose						
<100 mg/dL	6120	87 (6.9)	6061	167 (13.3)	0.52 (0.40, 0.67)	0.257
≥100 mg/dL	2755	55 (9.4)	2817	84 (14.2)	0.66 (0.47, 0.93)	

[a] Median baseline LDL-C was 108 mg/dL; median hsCRP was 4.25 mg/L
Applicant's Table 12.1.9.1.4.1, Pg 699, Appendix 12.1.9

6.1.7.2 Post-hoc exploratory subgroup analyses

Post-hoc subgroup analyses were done of the primary cardiovascular composite endpoint with regard to baseline hsCRP either less than or equal to 3 or greater than 3 mg/L, number of ATP-III risk factors, either less than 2 or greater than or equal to 2, and Framingham cardiovascular risk scores. In the number of risk factors subgroup, the subjects with less than 2 ATP-III risk factors, by nature of trial design have only age as their risk factor. In this subgroup with only age as a risk factor and unadjusted for high HDL-C, there was only a small relative risk reduction with a wide 95% confidence interval crossing 1.0. Approximately 25% of JUPITER subjects had less than 2 risk factors.

Table 32: Time to primary composite endpoint among post-hoc subgroups

	Rosuvastatin		Placebo			
Subgroup	N	n events (rate/1000 pt years)	N	n events (rate/1000 pt years	Hazard ratio (95% CI)	p-value for interaction
Baseline CRP						
≤3 mg/L	2649	31 (5.6)	2564	70 (13.0)	0.43 (0.28, 0.66)	0.141
>3 mg/L	6252	111 (8.5)	6337	182 (13.9)	0.62 (0.49, 0.78)	
Number of risk factors						
<2	2199	33 (7.1)	2080	35 (7.9)	0.91 (0.56, 1.46)	0.034
≥2	6702	109 (7.8)	6821	217 (15.5)	0.51 (0.40, 0.64)	
Framingham risk scores						
<10% (low risk)	3615	29 (4.0)	3602	43 (6.0)	0.67 (0.42, 1.07)	0.945
10-20% (intermediate risk)	4485	83 (8.6)	4516	171 (17.6)	0.49 0.38, 0.64)	
>20% (high risk)	786	29 (17.2)	772	38 (24.1)	0.70 (0.43, 1.14)	
SCORE risk						
<5%	4282	31 (3.5)	4218	69 (7.9)	0.44 (0.29, 0.68)	0.181
≥5%	4619	111 (11.5)	4683	183 (18.8)	0.61 (0.48, 0.78)	
Applicant's Table 12.1.9.1.4.2, Pg 710, Appendix 12.1.9						

During the EDMAC meeting regarding the JUPITER trial the applicant presented **data adjusting the number of subject's risk factors after adjusting for an HDL ≥** 60 mg/dL. After this adjustment, there were 1405 subjects (725 rosuvastatin, 680 placebo) remaining with zero ATP-III risk factors (increased age cancelled by HDL-C ≥60 mg/dL). The hazard ratio for this subgroup favored the placebo group at 1.54 with a 95% CI of 0.64, 3.70.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable

6.1.10 Additional Efficacy Issues/Analyses

The applicant performed a sensitivity analyses to assess the influence of withdrawals on the treatment effect for the primary endpoint. In each simulation, subjects who withdrew from the study were given a simulated event consistent with the observed event rate in the placebo group. Events which were beyond the efficacy data cut-off date of 30 March 2008 were censored. The generated data were incorporated into the existing data and re-analyzed. One thousand runs of the simulation were performed. The observed results support the assumption that study withdrawals did not affect the primary efficacy endpoint results (Table 33).

Table 33: Simulation of primary endpoint accounting for subject withdrawal

	Total MCE events			
	Rosuvastatin 20 mg	**Placebo**	**HR**	**p-value**
Original analysis	142	252	0.561	<0.0001
With simulated events (1000 runs)				
Mean	158	268	0.587	<0.0001
Median	158	268	0.587	<0.0001
Min	145	258	0.540	<0.0001
Max	173	284	0.648	<0.0001
SD	4	4	0.017	<0.0001
Source: Applicant's Table 11.2.1.1.5 Pg 2826, CSR				

7 Review of Safety

Safety Summary

- There were a total of 320 treatment-emergent adverse events (TEAE) leading to death in the JUPITER trial (1.6% in rosuvastatin group versus 2.0% in the placebo group).
- An imbalance was noted in the number of deaths in the Gastrointestinal SOC with 13 TEAE deaths in the rosuvastatin group compared to 1 TEAE death in the placebo group. Based on FDA review of the information supplied by the applicant, this imbalance is considered a chance finding.
- Discontinuations of study medication due to an AE were similar between treatment groups (6.6% in rosuvastatin group compared to 6.2% in placebo group. The most common reason for discontinuation of study medication in the rosuvastatin-exposed group was myalgia. Three times as many subjects

in the placebo group compared with the rosuvastatin group discontinued study treatment to initiate open-label statin treatment.

- Withdrawal from study participation in JUPITER was also similar between treatment groups. Musculoskeletal disorders were the most common reason for study withdrawal in both treatment groups.
- There was a 27% increase in investigator-reported diabetes in the rosuvastatin-treatment group compared to the placebo-treatment group.
- A post-hoc analysis of development of diabetes defined by either a HbA1c >6.5%, a fasting glucose value of ≥ 126 mg/dL, or both demonstrated a greater incidence of diabetes in the rosuvastatin-treatment group (15.3%) than in the placebo-treatment group (12.0%).
- Overall hepatic, musculoskeletal, and renal-related AEs were consistent with the known safety profile of rosuvastatin.
- A higher percentage of rosuvastatin-treated subjects experienced an ALT >3x ULN and a small percentage experienced an ALT >3x ULN on two **consecutive occasions. No Hy's law cases were observed in a rosuvastatin-**treated subject.
- Muscle-related AEs occurred at a higher incidence in the rosuvastatin treatment group compared to the placebo group. Myalgia was the most commonly reported preferred term in the rosuvastatin (8.0%) and placebo groups (7.2%). There was one case of rhabdomyolysis in JUPITER in a rosuvastatin-treated subject, a 90 year-old man with influenza and inability to arise from the floor for ~24 hours, secondary to weakness.
- CK >10x ULN occurred in two rosuvastatin-treated subjects and one placebo-treated subject.
- Hematuria and proteinuria were the most commonly occurring Renal and Urinary Disorder SOC AEs with a higher incidence in the rosuvastatin treatment group (4.4%) than in the placebo treatment group (3.7%). Acute, chronic, and unspecified renal failure occurred with similar frequency in the two treatment groups.
- Of the selected neuropsychiatric-related AEs, an imbalance in confusional state was observed, with 18 cases reported in the rosuvastatin group and four cases in the placebo group.
- The overall incidence of Neoplasm SOC treatment-emergent AEs was 6.8% in the rosuvastatin-treated group and 7.6% in the placebo-treated group. Of these AEs, only basal cell carcinoma reached a frequency of 1% of the population in the rosuvastatin group compared with 0.9% in the placebo group.
- In subjects with an on-study LDL-C less than 50 mg/dL, 2.5% (104/4154) in the rosuvastatin group and 3.9% (9/232) in the placebo group experienced a treatment-emergent serious adverse event in the Neoplasm SOC.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Table 34: Clinical trials used to evaluate safety

Study and Location	Study design Dose Duration	Patient population	Key objectives
JUPITER 1316 sites in 26 countries	Randomized, double-blind, placebo-controlled Treatment: Rosuvastatin 20 mg QD Comparator: Placebo QD 1.9 years mean duration of treatment	Men (≥50 years), Women (≥60 years) without clinically evident cardiovascular disease, LDL <130 mg/dL, hsCRP ≥2 mg/L	Effect of rosuvastatin versus placebo on: Primary: • Rate of major cardiovascular events (combined endpoint of cardiovascular death, stroke, myocardial infarction, unstable angina, or arterial revascularization) Secondary: • total mortality • noncardiovascular mortality • diabetes mellitus • venous thromboembolic events • bone fractures

Study and Location	Study design Dose Duration	Patient population	Key objectives
METEOR 61 sites in U.S. and Europe	Randomized, double-blind, placebo-controlled Treatment: Rosuvastatin 40 mg QD Comparator: Placebo QD 104 weeks	Men aged ≥ 45 and ≤ 70 and Women aged ≥ 55 and ≤ 70 with ↑ LDL-C and 10-year CHD risk < 10% by FRI. Max IMT of ≥ 1.2 mm and < 3.5 mm at baseline	Primary: • Effects of rosuvastatin 40 mg on the change in the mean maximum cIMT of the 12 vessel segments Secondary: • Effects of rosuvastatin 40 mg on the change in the mean maximum cIMT of the near and far walls of the right and left CCA, of the carotid bulb and of the ICA, and change in the mean IMT of the near and far walls of the right and left CCA. • Percent change from baseline in lipid and lipoprotein levels and CRP.
CORONA 371 sites in 21 countries	Randomized, double-blind, placebo-controlled Treatment: Rosuvastatin 10 mg QD Comparator: Placebo QD 5 years	Men and Women ≥ 60 years with symptomatic CHF	Effect of rosuvastatin versus placebo on: Primary: • Rate of combined endpoint of CV death or non-fatal MI, or non-fatal stroke Secondary: • total mortality • combined endpoint of sudden death or fatal or non-fatal MI, or PTCA, CABG, defibrillation by ICD, or resuscitation from cardiac arrest, or hospitalization for unstable angina • CV death for sudden death, fatal MI, and death from worsening heart failure • Total number of hospitalization from CV causes, unstable angina, and worsening heart failure

Study and Location	Study design Dose Duration	Patient population	Key objectives
AURORA 280 sites in 25 countries	Randomized, double-blind, placebo-controlled Treatment: Rosuvastatin 10 mg QD Comparator: Placebo QD 5.6 years	Men and women between 50 and 80 years old with end stage renal disease on hemodialysis unlikely to have kidney transplant within one year of enrollment	Effect of rosuvastatin versus placebo on: Primary: • Rate of MCE (CV death, non-fatal stroke, non-fatal MI) Secondary: • Total mortality • MCE event free survival • Time to CV death • Time to non-cardiovascular death • CHD death and non-fatal MI • Stenosis or thrombosis of vascular access • Revascularizations

7.1.2 Categorization of Adverse Events

No apparent discrepancies between the verbatim term and preferred term were discovered upon review of a random sample of 50 adverse events from the JUPITER trial.

Table 35: Categorization of adverse events (verbatim term compared to preferred term)

Patient ID	Preferred term	Verbatim term
1021-0003	Bone pain	Left hip pain (skeletal)
1002-0004	Giardiasis	Giardia
1002-0124	Erectile dysfunction	Erectile dysfunction
1006-0039	UTI	Urinary tract infection
1014-0006	Bronchitis	Bronchitis
1011-0003	Headache	Intermittent headaches
1002-0002	Intestinal perforation	Intestinal perforation
1014-0006	Staphylococcal infection	Urinary tract infection due to MRSA
1027-0002	Back pain	Lower back pain
1012-0008	Prostate cancer	Prostate cancer
1006-0003	Upper respiratory tract infection	Upper respiratory infection
1011-0015	Upper respiratory tract infection	Upper respiratory infection
1011-0001	Cellulitis	Cellulitis
1006-0075	Restless legs syndrome	Worsening of restless leg syndrome
1002-0124	Rotator cuff syndrome	Right rotator cuff tear
1031-0010	Arthritis	Worsening arthritis (L) knee
1006-0037	Colon polyp	Colon polyp
1006-0032	Constipation	Constipation
1031-0017	Onychomycosis	Toenail onychomycosis
1006-0002	Pharygnitis	Pharyngitis
1021-0003	Proteinuria	Proteinuria
1003-0003	Deep vein thrombosis	Deep vein thrombosis
1006-0039	Sinusitis	Sinusitis
1006-0005	Upper respiratory tract infection	Upper respiratory infection
1006-0102	Bronchitis	Bronchitis
1031-0010	Procedural pain	Post-operative pain left knee
1008-0005	Ear pain	Ear pain
1002-0002	Alanine aminotransferase increased	Increase SGPT (ALT) level (38 mU/mL)
1024-0003	Hematuria	Hematuria
1000-0031	Diabetes mellitus	Diabetes
1006-0060	Hypertension	Accelerated hypertension
1006-0057	Depression	Depression
1006-0039	Onychoclasis	Brittle nails
1015-0003	Abdominal pain	Abdominal pain
1011-0010	Cataract	Cataract left eye
1015-0006	Edema	Edema
1011-0011	Cystitis	Bladder infection
1000-0009	Bone pain	Leg pain (skeletal
1021-0003	Dyspepsia	Heartburn
1011-0010	Myalgia	Systemic muscle aches

Patient ID	Preferred term	Verbatim term
1000-0010	Wound	Wound in left forearm
1006-0038	Urinary tract infection	Urinary tract inf
1002-0127	Pharyngolaryngeal pain	Sore throat
1014-0006	Rash	Rash neck and back
1031-0004	Urinary tract infection	Urinary tract infection
1006-0102	Palpitations	Palpitations
1002-0006	Vomiting	Vomiting
1011-0022	Vertigo	Vertigo
1011-0001	Lumbar spinal stenosis	Spinal stenosis-lumbar
1006-0021	Malaise	Malaise
Source: ADVERSE01 Data set		

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The JUPITER trial was the major focus of the safety review. However, three long-term placebo-controlled trials, METEOR, CORONA, and AURORA were submitted prior to or during the review of this supplement. Specific safety issues discovered in the JUPITER trial, specifically deaths due to gastrointestinal disorders and incidence of diabetes-related adverse events were reviewed in these additional trials, with one pooled analysis regarding diabetes-related adverse events involving all four trials. An important caveat, CORONA and AURORA were designed to evaluate treatment benefit in subjects with congestive heart failure and end stage renal disease, respectively and therefore may represent more critically ill subjects compared to JUPITER trial subjects.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In the safety population defined as subjects receiving at least one dose of allocated study medication, the mean exposure was 1.9 years for both the rosuvastatin and placebo treatment groups.

Table 36: JUPITER drug exposure

Exposure by duration treatment (days)[a]	Rosuvastatin 20 mg N=8869	Placebo N=8864
Mean (SD)	700.5 (358.19)	689.5 (352.00)
Median	657.0	648.0
Range	0 to 1827	0 to 1967

[a]Duration of treatment calculated as number of days from the day of randomization to date of last dose on the completion/withdrawal page
Source: Applicant's Table 29, Pg 80 CSR JUPITER

Because of the recruitment pattern, mean time on-study for subjects from the US/Canada was 2.4 years, compared with 1.6 years for subjects outside the **US/Canada (see Applicant's Table 11.3.1.2.2, JUPITER CSR).**

7.2.2 Explorations for Dose Response

Only the 20 mg dose of rosuvastatin was utilized in JUPITER and therefore a dose response analysis cannot be applied to the JUPITER data.

7.2.3 Special Animal and/or In Vitro Testing

No new data was submitted with this supplement.

7.2.4 Routine Clinical Testing

The types of routine clinical testing performed in the safety evaluation of rosuvastatin were adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

No new information was submitted with this supplement.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Adverse events common to the statin drug class have been adequately evaluated by the applicant.

7.3 Major Safety Results

7.3.1 Deaths

Because mortality was an efficacy endpoint, all-cause mortality and total cardiovascular deaths are discussed in Section 6.1.4.1. Any adjudicated cardiovascular death was classified as an efficacy endpoint and not an AE if the event occurred before 31 March 2008.

Deaths during the randomized treatment phase were adjudicated by the Clinical Endpoints Committee, however if a death was not considered to be cardiovascular no organ-specific causality was adjudicated. The following table summarizes the frequency of treatment emergent AE leading to deaths during the randomized treatment phase by SOC.

Table 37: Subjects with treatment emergent AE leading to death (ITT population)

System organ class Preferred term	Rosuvastatin 20 mg N=8901 n(%)	Placebo N=8901 n(%)
Any death	**141 (1.6)**	**179 (2.0)**
Neoplasms benign, malignant and unspecified (includes cysts and polyps)	40 (0.4)	65 (0.7)
Bronchial carcinoma	3 (0.0)	0
Lung neoplasm malignant	3 (0.0)	8 (0.1)
Acute leukemia	2 (0.0)	0
Brain neoplasm	2 (0.0)	0
Gastrointestinal carcinoma	2 (0.0)	2 (0.0)
Lung cancer metastatic	2 (0.0)	2 (0.0)
Metastatic malignant melanoma	2 (0.0)	0
Metastatic neoplasm	2 (0.0)	0
Multiple myeloma	2 (0.0)	2 (0.0)
Esophageal carcinoma	2 (0.0)	1 (0.0)
Pancreatic carcinoma	2 (0.0)	2 (0.0)
Acute myeloid leukemia	1 (0.0)	0
Adenocarcinoma	1 (0.0)	0
Colon cancer	1 (0.0)	3 (0.0)
Colon cancer metastatic	1 (0.0)	3 (0.0)
Leiomyosarcoma metastatic	1 (0.0)	0
Mesothelioma	1 (0.0)	0
Myeloid leukemia	1 (0.0)	0
Neoplasm malignant	1 (0.0)	2 (0.0)
Non-Hodgkin's lymphoma	1 (0.0)	0
Non-small cell lung cancer	1 (0.0)	1 (0.0)
Esophageal adenocarcinoma	1 (0.0)	1 (0.0)
Oropharyngeal cancer stage unspecified	1 (0.0)	0
Renal cancer metastatic	1 (0.0)	0
Renal cell carcinoma	1 (0.0)	1 (0.0)
Small cell lung cancer stage unspecified	1 (0.0)	3 (0.0)
Uterine cancer	1 (0.0)	0
Astrocytoma	0	1 (0.0)
Astrocytoma malignant	0	1 (0.0)
Bile duct cancer recurrent	0	1 (0.0)
Breast cancer metastatic	0	1 (0.0)
Colon neoplasm	0	1 (0.0)
Gastric cancer	0	1 (0.0)
Gastrointestinal cancer metastatic	0	1 (0.0)
Gastro-esophageal cancer	0	1 (0.0)
Glioma	0	1 (0.0)
Hepatic cancer metastatic	0	1 (0.0)
Hepatic neoplasm malignant	0	1 (0.0)
Lung adenocarcinoma	0	1 (0.0)
Lung adenocarcinoma metastatic	0	2 (0.0)
Lung neoplasm	0	2 (0.0)
Lung squamous cell carcinoma stage unspecified	0	1 (0.0)
Metastases to liver	0	1 (0.0)
Metastatic gastric cancer	0	1 (0.0)

System organ class Preferred term	Rosuvastatin 20 mg N=8901 n(%)	Placebo N=8901 n(%)
Metastatic renal cell carcinoma	0	2 (0.0)
Metastatic squamous cell carcinoma	0	1 (0.0)
Neuroendocrine carcinoma	0	1 (0.0)
Esophageal cancer metastatic	0	2 (0.0)
Ovarian cancer	0	1 (0.0)
Pancreatic carcinoma metastatic	0	3 (0.0)
Pancreatic neoplasm	0	1 (0.0)
Pharyngeal cancer stage unspecified	0	1 (0.0)
Prostate cancer metastatic	0	1 (0.0)
Renal neoplasm	0	1 (0.0)
Sarcoma	0	1 (0.0)
Small cell lung cancer metastatic	0	1 (0.0)
Tongue neoplasm malignant stage unspecified	0	1 (0.0)
General disorders and administration site conditions	39 (0.4)	40 (0.4)
Death	36 (0.4)	37 (0.4)
Multi-organ failure	2 (0.0)	1 (0.0)
Hernia	1 (0.0)	0
General physical health deterioration	0	1 (0.0)
Sudden death	0	1 (0.0)
Infections and infestations	22 (0.2)	24 (0.3)
Pneumonia	9 (0.1)	9 (0.1)
Sepsis	4 (0.0)	2 (0.0)
Septic shock	4 (0.0)	1(0.0)
Bronchopneumonia	2 (0.0)	3(0.0)
Infected skin ulcer	1 (0.0)	0 (0.0)
Influenza	1 (0.0)	0 (0.0)
Meningococcal sepsis	1 (0.0)	0 (0.0)
Abdominal sepsis	0	1 (0.0)
Acquired immunodeficiency syndrome	0	1 (0.0)
Enterocolitis infection	0	1 (0.0)
Gastroenteritis	0	3 (0.0)
Lower respiratory tract infection	0	1 (0.0)
Pulmonary tuberculosis	0	1 (0.0)
Urosepsis	0	1 (0.0)
Respiratory, thoracic, and mediastinal disorders	14 (0.2)	20 (0.2)
Respiratory failure	5 (0.1)	4 (0.0)
Chronic obstructive pulmonary disease	3 (0.0)	3 (0.0)
Pulmonary embolism	3 (0.0)	2 (0.0)
Asthma	1 (0.0)	1 (0.0)
Dyspnea	1 (0.0)	0
Respiratory arrest	1 (0.0)	2 (0.0)
Aspiration	0	1 (0.0)
Brain hypoxia	0	1 (0.0)
Cough	0	1 (0.0)
Emphysema	0	1 (0.0)
Interstitial lung disease	0	1 (0.0)
Pneumonia aspiration	0	1 (0.0)
Pulmonary fibrosis	0	1 (0.0)

System organ class Preferred term	Rosuvastatin 20 mg N=8901 n(%)	Placebo N=8901 n(%)
Pulmonary edema	0	1 (0.0)
Gastrointestinal disorders	13 (0.1)	1 (0.0)
Gastrointestinal hemorrhage	2 (0.0)	0 (0.0)
Pancreatitis acute	2 (0.0)	0 (0.0)
Peritonitis	2 (0.0)	1 (0.0)
Abdominal pain	1 (0.0)	0 (0.0)
Duodenal ulcer	1 (0.0)	0 (0.0)
Gastroesophageal reflux disease	1 (0.0)	0 (0.0)
Inguinal hernia	1 (0.0)	0 (0.0)
Intestinal obstruction	1 (0.0)	0 (0.0)
Intra-abdominal hemorrhage	1 (0.0)	0 (0.0)
Esophageal hemorrhage	1 (0.0)	0 (0.0)
Esophageal rupture	1 (0.0)	0 (0.0)
Cardiac disorders	8 (0.1)	8 (0.1)
Cardiac failure	2 (0.0)	0 (0.0)
Myocardial infarction	2 (0.0)	5 (0.0)
Arrhythmia	1 (0.0)	1 (0.0)
Atrial fibrillation	1 (0.0)	0 (0.0)
Cardiac failure congestive	1 (0.0)	2 (0.0)
Coronary artery disease	1 (0.0)	0
Injury, poisoning, and procedural complications	3 (0.0)	8 (0.1)
Crush injury	1 (0.0)	0
Road traffic accident	1 (0.0)	2 (0.0)
Subdural hematoma	1 (0.0)	0
Cervical vertebral fracture	0	1 (0.0)
Fall	0	1 (0.0)
Head injury	0	2 (0.0)
Transfusion-related acute lung injury	0	1 (0.0)
Traumatic brain injury	0	1 (0.0)
Nervous system disorders	3 (0.0)	4 (0.0)
Cerebrovascular accident	1 (0.0)	0
Hypoglycemic coma	1 (0.0)	0
Myxedema coma	1 (0.0)	0
Amyotrophic lateral sclerosis	0	2 (0.0)
Anoxic encephalopathy	0	1 (0.0)
Senile dementia	0	1 (0.0)
Psychiatric disorders	3 (0.0)	1 (0.0)
Completed suicide	1 (0.0)	1 (0.0)
Depression	1 (0.0)	0
Mental status changes	1 (0.0)	0
Metabolism and nutrition disorders	2 (0.0)	0
Electrolyte imbalance	2 (0.0)	0
Dehydration	2 (0.0)	0
Hyperglycemia	1 (0.0)	0
Hyperkalemia	1 (0.0)	0
Hypermagnesemia	1 (0.0)	0
Hypernatremia	1 (0.0)	0
Hyperphosphatemia	1 (0.0)	0
Hypoalbuminemia	1 (0.0)	0

System organ class Preferred term	Rosuvastatin 20 mg N=8901 n(%)	Placebo N=8901 n(%)
Hypocalcemia	1 (0.0)	0
Hypokalemia	1 (0.0)	0
Metabolic acidosis	1 (0.0)	0
Vascular disorders	2 (0.0)	5 (0.1)
Arteriosclerosis	1 (0.0)	0
Circulatory collapse	1 (0.0)	1 (0.0)
Aortic stenosis	0	1 (0.0)
Deep vein thrombosis	0	1 (0.0)
Hypertension	0	1 (0.0)
Hypertensive emergency	0	1 (0.0)
Hypovolemic shock	0	1 (0.0)
Blood and Lymphatic system disorders	1 (0.0)	0
Anemia	1 (0.0)	0
Leukocytosis	1 (0.0)	0
Hepatobiliary disorders	1 (0.0)	1 (0.0)
Hepatic cirrhosis	1 (0.0)	0
Cirrhosis alcoholic	0	1 (0.0)
Renal and urinary disorders	1 (0.0)	4 (0.0)
Azotemia	1 (0.0)	0
Renal failure	1 (0.0)	1 (0.0)
Renal failure acute	1 (0.0)	2 (0.0)
Renal failure chronic	0	1 (0.0)
Source: Table 11.3.3.1.2.3, Pg 5604 CSR		

7.3.1.1 Fatal TEAEs in the cardiac and nervous system SOC

There were six rosuvastatin-treated subjects and seven placebo-treated subjects listed as fatal TEAEs in the cardiac and nervous system SOC that were not adjudicated as clinical endpoints but as AEs. The following tables (Table 38 and 39) further describe these subjects.

Table 38: Fatal treatment emergent AEs in the cardiac and nervous system SOC not adjudicated as cardiovascular death

System organ class Preferred term	Rosuva 20 mg N=8901 n(%)	Placebo N=8901 n(%)
Cardiac disorders		
Cardiac failure	2 (0.0)	0 (0.0)
Myocardial infarction	2 (0.0)	5 (0.0)
Cardiac failure congestive	1 (0.0)	2 (0.0)
Nervous system disorders		
Cerebrovascular accident	1 (0.0)	0
Source: Table 11.3.3.1.2.3, Pg 5604 CSR		

Table 39: Description of subjects with fatal TEAE listed in the cardiac or nervous system SOC that was not adjudicated as cardiovascular death

Center	Subject ID	Age	Sex	Verbatim term	Preferred term
Rosuvastatin –treatment group					
6050	0165	76	F	Cardiac failure	Cardiac failure
8523	0018	77	F	Cardiac failure	Cardiac failure
1193	0035	64	M	Congestive heart failure	Cardiac failure congestive
6017	0010	55	M	Myocardial infarction	Myocardial infarction
5011	0079	72	M	Myocardial infarction	Myocardial infarction
7653	0217	76	M	Stroke	Cerebrovascular accident
Placebo-treatment group					
7166	0237	75	M	Myocardial infarction	Myocardial infarction
5002	0611	56	M	Myocardial infarction	Myocardial infarction
2385	0057	70	F	Myocardial infarction	Myocardial infarction
1514	0006	75	M	Probable MI	Myocardial infarction
1039	0002	55	M	Myocardial infarction	Myocardial infarction
5042	0005	76	M	Exacerbation of congestive cardiac failure	Cardiac failure congestive
6042	0199	91	M	Congestive cardiac failure	Cardiac failure congestive
Source: Table 11.3.3.2.1, Pg 5622 CSR					

7.3.1.1.1 Narratives of subjects with fatal TEAE listed in cardiac or nervous system SOC that were not adjudicated as a cardiovascular death

- Narratives of rosuvastatin-treated subjects: cardiac and nervous system disorders deaths

Subject 6050-0165 - Cardiac failure: 76-year-old, Black female, non-smoker, with history of intermittent pain in her left arm since 2004, progressive loss of vision since April 2006, mild muscular wasting, bilateral cataracts, and intermittent palpitations since May 2006. Concomitant medications included Brufen for left arm pain. The subject was randomized to rosuvastatin 20 mg on 10 August 2006. On (b) (6) the patient died. According to the case report form (CRF) the cause of death was congestive cardiac failure. On Page 43.1 of the CRF the event is listed as adjudicated as a clinical event. On Page 44.1 of the CRF the box of cardiovascular/cerebrovascular death is checked. The On-Site Data Clarification Form (DCF) (Figure 6) shows a correction of these two entries due to insufficient data to adjudicate (IDA).

Figure 6: DCF for Subject 6050-0165

Protocol: 4522US/0011	Site #: 6050	Principal Investigator Name: Mahalfey
CRA Name (b) (4)		Date: 11 Aug 08

Subject #: 0165	Subject Initials (b) (6)

CRF page #	Data field to be changed	Original data field entry	Data field entry per source doc verification	Responsible delegate at site (initials)
43.1	was event adj to be a clinical event	yes	no	(b) (4)
44.1	Death	cardio/cerebro box is checked	cardio/cerebro box should not be checked	
44.1	comments	blank	1 DA	

(b) (4) 11 Aug 08 — CRA Signature, Date
Mahalfey 8/14/08 — PI or Sub-PI* Signature, Date
(b) (4) DM Signature, Date

Subject 8523-0018 – Cardiac failure: 76-year-old, Caucasian female with a history of paroxysmal tachyarrhythmia, sleep disorder, and ankle edema randomized on 4 December 2006 to rosuvastatin 20 mg and stopped taking rosuvastatin on 25 September 2007 (Day 296). During the randomized treatment phase the subject experienced the AEs of dyspnea, back pain, asthenia, and tibia fracture. After discontinuing rosuvastatin she experienced non-fatal SAEs of gastric perforation (Day 306), pulmonary embolism (Day 323), and peritonitis (Day 338). Concomitant medications included Lodoz, oxazepam, Sintrom, Lanoxin, Frusamil, Spriva, Dolol instant and Brufen. The subject experienced cardiac and renal failure on Day (b) (6) and died six days later on (b) (6). According to the e-narrative and CRF, although cardiac failure is listed as cause of death, this event was listed as a non-cardiovascular/cerebrovascular death.

Subject 1193-0035 – Cardiac congestive failure: 64-year-old, Caucasian male with bilateral knee osteoarthritis, GERD, overweight, allergic rhinitis, hiatal hernia, benign prostatic hyperplasia, hemorrhoids, fatigue, musculoskeletal back pain, hypertension, decreased testosterone level, sleep apnea, sigmoid colon diverticulosis, cervical arthritis, degenerative joint disease, neuropathy, insomnia, and cataracts was randomized to 20 mg rosuvastatin on 23 May 2005. During the randomized treatment phase of the study he experienced the secondary endpoint of diabetes (Day 324). He was discontinued from rosuvastatin treatment on Day 725 due occurrence of the primary endpoint of arterial revascularization. On Day (b) (6) the subject died of congestive heart failure within two months of experiencing the SAE of recurrent acute myeloid leukemia.

Subject 6017-0010 – Myocardial infarction: 55-year-old, African American male with hypertension randomized to rosuvastatin 20 mg on 25 January 2006. During the study, the subject experienced the AEs of headache, dysuria,

pollakiuria, and productive cough. Patient died on (b) (6) days after starting rosuvastatin. Cause of death was listed as a myocardial infarction and cardiovascular/cerebrovascular death on CRF, but was not adjudicated as a clinical event due to IDA.

Subject 5011-0079 – Myocardial infarction: 72-year-old Caucasian male with a contracture of his left hand and history of depression, randomized to rosuvastatin and died 7 days later of a myocardial infarction. Event was not adjudicated as a clinical event due to IDA-sudden cardiac death.

Subject 7653-0217 – Cerebrovascular accident: 76-year-old Black male with hypertension randomized on 17 October 2006 and died on (b) (6)) of a cerebrovascular accident. Not adjudicated as a clinical event due to "IDA-no documentation. Word of mouth CVA".

- Narratives of placebo-treated subjects: cardiac disorders death

Subject 7166-0237 – Myocardial infarction: 74-year-old Hispanic male with a history of inguinal hernia and presbyopia randomized to placebo on 21 April 2006 and stopped study drug on 9 August 2006. On Day (b) (6), the subject died of a myocardial infarction. Not adjudicated as a clinical endpoint by the CEC. Death certificate listed cause of death as MI. However was ruled IDA by CEC.

Subject 5002-0611 – Myocardial infarction: 56-year-old Caucasian male with a left shoulder pain randomized to placebo on 8 March 2006. The subject discontinued study medication on 28 June 2006 due to an adverse event of muscular thigh pain and erectile dysfunction. On Day 402, the subject was started on atorvastatin, furosemide, and lisinopril for the AEs of pulmonary edema and hypertension. On day (b) (6), the subject died of a myocardial infarction. Cause of death was not adjudicated as a cardiovascular death by the CEC.

Subject 2385-0057 – Myocardial infarction: 70-year-old Hispanic female with a history of asthma and peripheral vascular disease randomized to placebo on 5 December 2005. While on treatment she experienced the AEs of constipation, GERD, and osteoporosis. Concomitant medications included Albuterol, Singulair, Cronolyn, and Budesonide for asthma, Antivert for dizziness, Aciphex for GERD, and Evista for osteoporosis. On Day (b) (6), she died of a reported MI, which was not confirmed as a clinical event by the CEC.

Subject 1514-0006 – Myocardial infarction: 75-year-old Caucasian male with a history of COPD, HTN, peptic ulcer, macular degeneration, history of smoking, and fine expiratory wheezes was randomized to placebo on 22 December 2003 and started on 4 February 2004. On Day (b) (6) the subject died of a reported

myocardial infarction. This event was not confirmed by adjudication. Reported as IDA.

Subject 1039-0002 – Myocardial infarction: 55-year-old Caucasian male with a history of hypertension and gout randomized to placebo on 3 November 2003. On Day (b) (6) experienced unstable angina requiring hospitalization which was confirmed by adjudication. The subject discontinued study medication due this event. On day (b) (6) from randomization, the subject died of a reported myocardial infarction by the investigator. This event was not confirmed as a clinical endpoint by the CEC. On-site data clarification form states IDA. The CRF states the subject was lost to follow-up and death was noted in the obituaries.

Subject 5042-0005 – Cardiac failure congestive: 74-year-old Caucasian male with history of chronic obstructive airways disease, inguinal hernia, dyspepsia, back pain randomized to placebo on 29 March 2006. The subject discontinued study drug on Day 763. On day (b) (6), the subject died of congestive cardiac failure. Initial exacerbation of congestive heart failure occurred on Day (b) (6) requiring hospitalization. This event was not sent for adjudication as the death occurred after the March 31, 2008 cut off date.

Subject 6042-0199 – Cardiac failure congestive: 91-year-old Black male with a history of hypertension randomized on 27 July 2006 to placebo. On Day (b) (6) the subject died of congestive cardiac failure. This event was not confirmed as a cardiovascular death by the CEC due to IDA.

7.3.1.2 Fatal TEAEs in the General disorder SOC

There were 36 and 39 fatal TEAE listed as "death" in the rosuvastatin and placebo groups, respectively. These events were not classified as clinical endpoints. Using a random number table, 20% of the rosuvastatin- and placebo-treated fatal TEAE narratives listed as death were reviewed and are briefly described below.

Table 40: Description of subjects with fatal TEAE listed by preferred term as death that was not adjudicated as an efficacy endpoint

Center	Subject ID	Age	Verbatim term	Preferred term	Adjudication comments
Rosuvastatin–treatment group					
1346	0018	71	Death (unknown cause)	Death	Minimal records
2033	0003	56	Death	Death	
4112	0162	63	Death (cause unknown)	Death	
4149	0012	82	Death	Death	
5408	2073	66	Death	Death	Insufficient data

Center	Subject ID	Age	Verbatim term	Preferred term	Adjudication comments
			(unknown cause)		
6002	0020	73	Death	Death	Insufficient data
6002	0373	79	Death natural causes	Death	
6002	0467	66	Death (natural causes)	Death	Insufficient data
6004	0130	73	Death (Unknown)	Death	Insufficient data
6004	0596	82	Death (cause unknown)	Death	Limited data, but with available data, non-CV
6006	0264	60	Death due to natural causes	Death	Insufficient data
6006	0286	65	Death due to natural causes	Death	Insufficient data
6006	0418	53	Death due to natural causes	Death	
6008	0093	69	Death cause unknown	Death	Insufficient data
6017	0348	71	Death of unknown cause	Death	Insufficient data
6026	0045	68	Death-natural causes	Death	Insufficient data
6026	0077	63	Death-natural causes	Death	Insufficient data
6026	0109	76	Death-natural causes	Death	Insufficient data
6027	0036	77	Death natural causes	Death	Progressive weight loss concerning for occult malignancy
6032	0091	74	Death (natural causes)	Death	Sudden left middle cerebral artery symptoms. No records
6040	0097	63	Death (unknown cause)	Death	No comment
6040	0274	61	Death (unknown cause)	Death	Insufficient data
6042	0086	76	Death-natural causes	Death	Vomiting and diarrhea; not hospitalized
6042	0094	67	Death-natural causes	Death	Insufficient data
6042	0112	56	Death (not known)	Death	Insufficient data

Center	Subject ID	Age	Verbatim term	Preferred term	Adjudication comments
6042	0138	82	Death-natural causes	Death	Insufficient data
6042	0400	56	Death (unknown cause)	Death	Insufficient data
6042	0408	59	Death (unknown cause)	Death	Insufficient data
6042	0612	76	Death-natural causes	Death	Insufficient data
6043	0039	75	Death	Death	Unwitnessed death
6043	0208	73	Death (unknown cause)	Death	
6043	0233	60	Death (unknown cause)	Death	
6043	0457	60	Death-natural causes (unknown)	Death	
6050	0280	76	Death/Natural causes	Death	Insufficient data
8005	0006	88	Mors	Death	Insufficient data
8606	0009	56	Death cause unknown	Death	Insufficient data
Placebo-treatment group					
1000	0014	77	Death cause is undetermined	Death	
1227	0032	61	Death (unknown cause)	Death	Insufficient data
1344	0010	74	Death	Death	Found dead at home. Default to CV death per guidelines
1418	0001	67	Natural death	Death	Insufficient data. Sudden death, no autopsy; assumed CV or sudden cardiac death. No death certificate
2175	0012	82	Death-Cause unknown	Death	Insufficient data
4086	0021	57	Sudden death	Sudden death	Insufficient data
4116	0031	74	Death	Death	Found dead in bathroom. Unknown cause
5002	1488	78	Death (cause unknown) Fall (down stairs)	Death Fall	

Center	Subject ID	Age	Verbatim term	Preferred term	Adjudication comments
5439	0021	71	Unknown	Death	
5700	0001	79	Unknown death	Death	Insufficient data
6002	0114	73	Death natural causes	Death	
6002	0366	66	Death	Death	Died in sleep, so prior symptoms. Las seen was well. Site submitted a non CV death
6004	0005	75	Death (unknown)	Death	Insufficient data
6004	0282	67	Death (Unknown cause)	Death	Insufficient data
6004	0321	60	Death (Cause unknown)	Death	Basically no documentation of cause of death
6004	0338	69	Death (Unknown cause)	Death	Insufficient data
6004	0485	81	Death (cause unknown)	Death	Insufficient data. Completely unknown
6006	0258	75	Death (due to natural causes)	Death	Insufficient data
6006	0377	69	Death due to natural causes	Death	Insufficient data
6006	0392	52	Death due to unknown cause	Death	Insufficient data
6006	0675	63	Death due to natural causes	Death	Insufficient data
6008	0204	68	Death cause unknown	Death	Insufficient data
6008	0251	76	Death cause unknown	Death	Died in sleep
6013	0106	70	Death-natural causes	Death	
6013	0109	81	Death-natural causes	Death	
6017	0212	73	Death due to natural causes	Death	Insufficient data
6017	0344	74	Death due to natural causes	Death	Insufficient data
6017	0378	50	Death by natural	Death	Flu symptoms x 3d, dies en route to hospital

Center	Subject ID	Age	Verbatim term	Preferred term	Adjudication comments
			causes		
6017	0532	88	Death due to natural causes	Death	Insufficient data
6017	0762	81	Death due to natural causes	Death	Insufficient data
6026	0085	57	Death-natural causes	Death	Insufficient data
6042	0132	59	Death-cause not known	Death	Insufficient data
6042	0406	65	Death-natural causes	Death	Insufficient data
6042	0661	80	Death-natural causes	Death	Insufficient data
6043	0256	67	Death (unknown causes)	Death	No description of event
7072	0042	76	Death	Death	Insufficient data. 1 month post-hip fracture. Submitted by site as non CV
8043	0001	84	Fatal problem cause is unknown	Death	
8606	0010	73	Death cause unknown	Death	

Source: Applicant's Table 11.3.3.2.1, Pg 5622 CSR; Applicant's Listing 12.2.6.10 IR response 01 July 2009
Random number table from Wikipedia starting at Column 7, Row 1.

7.3.1.2.1 Narratives of subjects with fatal TEAE listed by preferred term of "death

- **Narratives of rosuvastatin-treated subjects: "death"**

Subject 2033-0003 – Death: 56-year-old Black male with hypertension, arthritis, obesity randomized to rosuvastatin on 27 December 2004. Death occurred on (b) (6) . **Per CRF there was "no information available other than patient died at home. Assumption is sudden cardiac death." This death was not** confirmed as a clinical endpoint due to IDA.

Subject 6004-0130 – Death: 72-year-old Black male smoker (6 cigarettes per day) with osteoarthritis randomized to rosuvastatin on 2 February 2006. The subject died on (b) (6) . The death was not confirmed as a clinical endpoint due to IDA.

Subject 6050-0280 – Death: 76-year-old Black female with bilateral pedal edema and hypertension was randomized to rosuvastatin on 18 October 2006. On Day 325 she experienced the AE of muscle weakness and on Day (b) (6) died **of reported "natural causes". No post-mortem performed. The event was not** adjudicated as a cardiovascular death.

Subject 6008-0093 – Death: 69-year-old Caucasian male smoker (2 cigarettes per day) with hypertension, insomnia, and left inguinal hernia randomized to rosuvastatin treatment on 15 May 2006 and died on Day (b) (6) He experienced a SAE of hernia requiring hospitalization which had resolved before his death and AEs of pharyngitis and dermatitis. On-site data clarification form changed the CV event to an AE with the additional comment of IDA.

Subject 6042-0086 – Death: 76-year-old Black male with peptic ulcer disease and past history of prostatitis randomized to rosuvastatin on 20 June 2006 and **died on Day** (b) (6) **Reported on CRF as "natural causes". He experienced the AE** of gastroenteritis one day before his death. The event not adjudicated as a cardiovascular/cerebrovascular death.

Subject 6002-0467 – Death: 66-year-old Black overweight male with scattered inspiratory crepitations randomized to rosuvastatin on 10 August 2006 and died **on Day** (b) (6) **of "natural causes", no postmortem performed. No other AEs prior to** death.

Subject 5408-2073 – Death: 66-year-old Caucasian female with osteoporosis and scoliosis of the thoracic spine, was randomized to rosuvastatin on 9 November 2006. The date and cause of death was unknown.

- **Narratives of placebo-treated subjects: fatal TEAE with preferred term "death"**

Subject 8606-0010 – Death: 73-year-old Caucasian female with hypertension and atrial fibrillation randomized to placebo on 14 November 2006 and died on Day (b) (6). She experienced the SAE of hyperthyroidism requiring hospitalization on Day (b) (6).

Subject 1418-0001 – Death: 67-year-old Hispanic male smoker with borderline hypertension and systolic murmur randomized to placebo on 24 November 2003. **Death occurred on Day** (b) (6) **The CRF states this was a "sudden death, no** autopsy, assumed cardiovascular or sudden car**diac death. No death certificate."** The on-site DCF determined this not to be cardiovascular death due to IDA.

Subject 6042-0661 – Death: 80-year-old Black female with hypertension was randomized to placebo on 20 November 2006. The subject died on Day (b) (6) of

reported "natural causes". No other AEs experienced prior to death. The CEC did not adjudicate this death as a cardiovascular/cerebrovascular death.

Subject 6004-0338 – Death: 69-year-old Black female with hypertension and osteoarthritis randomized to placebo on 17 May 2006 and died on Day(b) (6) of an "unknown cause". No other AEs experienced prior to death. The CEC did not adjudicate this death as a cardiovascular/cerebrovascular death due to IDA.

Subject 1227-0032 – Death: 61-year-old Caucasian male with hypertension and osteoporosis and past medical history of deep vein thrombosis randomized to placebo on 13 July 2004. Death occurred on Day(b) (6); reported as "unknown cause" on CRF. The AE of urinary tract infection was ongoing at the time of death. No post-mortem was performed. The CEC did not adjudicate event due to inadequate information.

Subject 4086-0021 – Death: 56-year-old Caucasian male with irritable bowel syndrome, aortic stenosis, hypertension, systolic ejection murmur and a history of atypical chest pain and arthritis randomized to placebo on 14 January 2004, died on Day(b) (6) Approximately 11 days prior to his death he was hospitalized for a pre-planned surgical procedure of spinal fusion, which was not listed as an AE. The CRF reports the death as "sudden death". This event was not adjudicated as a cardiovascular/cerebrovascular death due to IDA.

Subject 6017-0212 – Death: 73-year-old Black female with hypertension randomized to placebo on April 18, 2006. On Day(b) (6) she died due to "natural causes". This event was not adjudicated as a cardiovascular/cerebrovascular death due to IDA.

7.3.1.3 Fatal TEAEs in Gastrointestinal SOC

Thirteen subjects in the rosuvastatin-treated group versus one subject in the placebo-treated group had a treatment-emergent gastrointestinal disorder leading to death. Source documents were requested and reviewed regarding these gastrointestinal deaths. Upon review two deaths in the rosuvastatin-treatment group were miscoded. Subject 1280-0011 was reported as dying of gastroesophageal reflux. A subdural hematoma after a fall was the actual cause of death. Subject 5002-0367 was not confirmed dead but reported as lost to follow-up with the subject's last known location in the hospital. Of the remaining rosuvastatin-exposed group one fatality resulted from pancreatitis and peritonitis, one fatality related to peritonitis, one fatality related to pancreatitis and four fatalities resulted from gastrointestinal hemorrhage. Another two rosuvastatin-exposed subjects died of complications associated with cancer. The placebo-treated subject died of peritonitis following gastric bypass surgery. The following table and narratives further describe these fatalities.

Table 41: Description of subjects with fatal TEAEs in Gastrointestinal SOC in JUPITER

Center	Subject ID	Age	Sex	Verbatim term	Preferred term	Days on treatment	Days between AE onset and death	Country
Rosuvastatin –treatment group								
1035	0011	62	M	1. Acute pancreatitis 2. Peritonitis	1. Pancreatitis acute 2. Peritonitis	240	3	U.S.
1035	0050	83	M	Acute pancreatitis	Pancreatitis acute	405	8	U.S.
6042	0370	61	F	Acute obstruction peritonitis	Peritonitis	294	8	South America
7216	0031	57	M	Upper digestive hemorrhage	Gastrointestinal hemorrhage	127	6	Venezuela
1265	0001	67	M	Intraabdominal hemorrhage	Intraabdominal hemorrhage	1052	1	U.S.
6026	0034	69	M	Abdominal pain	Abdominal pain	595	15	South America
5002[a]	0367	71	M	Duodenal ulcer	Duodenal ulcer	816	Unknown	
7776	0042	87	M	Inguinal hernia	Inguinal hernia	72	1	Colombia
4145	0037	57	M	Sub-occlusion bowel	Intestinal obstruction	611	1	Canada
5482	0269	59	M	Esophageal bleeding	Esophageal hemorrhage	212	3	Poland
8617	0009	77	M	Gastrointestinal bleed	Gastrointestinal hemorrhage	303	1	Bulgaria
1130	0006	68	M	Ruptured esophagus	Esophageal rupture	269	1	U.S.
1280[b]	0011	70	F	GERD	Gastroesophageal reflux disease	489	Unknown	U.S.
Placebo-treatment group								
7754	0020	58	M	Peritonitis	Peritonitis	293	14	Colombia

a Miscoded, subject did not die
b Miscoded, subject died from subdural hematoma sustained after fall
Source: Applicant's Table 11.3.3.2.1 Pg 5622 JUPITER CSR

7.3.1.3.1 Narratives of subjects with fatal TEAE listed in Gastrointestinal SOC

- Narratives of rosuvastatin-treated subjects: Fatal TEAE Gastointestinal SOC

Subject 1035-0011 Acute pancreatitis, Peritonitis: A 62-year-old Caucasian male with a history of essential hypertension, peptic ulcer disease, obesity, metabolic syndrome was randomized to 20 mg rosuvastatin. During the study he recovered from the AEs of arthritis, peripheral edema, and facial palsy. On (b) (6) the subject was hospitalized for acute pancreatitis. On admission he

was hypovolemic, anuric, hypotensive, and tachycardic with elevated lipase and amylase levels. He experienced a cardiac arrest following placement of a central line catheter. Following the arrest, the subject required mechanical ventilation and experienced further medical complications of septic shock, kidney failure, metabolic acidosis, and seizure-like activity. He died on Day 242. The coroner listed the immediate cause of death as cardiorespiratory failure, along with septic shock and acute necrotic pancreatitis.

Subject 1035-0050 Acute pancreatitis: A 83-year-old Asian male with a history of chronic obstructive pulmonary disease, sinus tachycardia, and hyperthyroidism randomized to rosuvastatin. During the study he experienced the AEs of bronchitis, chronic obstructive pulmonary disease (COPD), and congestive heart failure (CHF). The CHF episode required hospitalization on Day 362 of the treatment phase. On Day 405, he experienced acute pancreatitis, acute renal failure, and metabolic derangements and died on Day 412. The immediate cause of death was listed on the death certificate as acute renal failure secondary to acute pancreatitis, coronary artery disease, and type 2 diabetes.

Subject 6042-0370 Peritonitis: A 61-year-old Black female with a history of hypertension and osteoarthritis randomized to rosuvastatin treatment. The subject was hospitalized for abdominal pain/peritonitis which started on Day 294. She died seven days later.

Subject 7216-0031 Gastrointestinal hemorrhage: A 57-year-old Hispanic male with a history of hypertension randomized to rosuvastatin therapy. On Day 126 he experienced melena, nausea, vomiting, and gastrointestinal hemorrhage. An upper esophageal endoscopy showed severe esophagitis and hiatal hernia. He withdrew consent due to this AE and died of gastrointestinal hemorrhage five days later.

Subject 1265-0001 Intra-abdominal hemorrhage: A 67-year-old Caucasian male with a history of iron-deficient anemia, alcoholism (on antabuse), hypertension, mild COPD, hypertriglyceridemia secondary to alcohol use, and smoking randomized to rosuvastatin. During the study he experienced the non-fatal SAEs of renal cell carcinoma, tachycardia, postoperative anemia, and wound dehiscence. On day 1052, two weeks post nephrectomy, he died of an intra-abdominal hemorrhage.

Subject 6026-0034 Abdominal pain: A 69-year-old Black male with a history of hypertension randomized to rosuvastatin treatment. The only AE experienced was abdominal pain which started on Day 595. He died 14 days later. Source **documents reported unconfirmed liver cancer per subject's son. Cause of death on death certificate listed as "natural causes". The applicant was unable to** obtain hospital records.

Subject 5002-0367 Duodenal ulcer: Narrative not provided. Source documents report the subject did not die.

Subject 7776-0042 Inguinal hernia: A 87-year-old Hispanic male smoker with no history of medical illness randomized to rosuvastatin therapy. He died on Day 74 from an surgical complication of perforated bowel and intra-abdominal sepsis during inguinal hernia repair.

Subject 4145-0037 Intestinal obstruction: A 57-year-old Caucasian male with a history of gastritis and COPD randomized to rosuvastatin. On Day 7 he was diagnosed with gastric cancer which was listed as recovered on Day 217. He discontinued treatment on Day 597 due to the adverse event of metastatic signet ring cell carcinoma (an adenocarcinoma which usually develops in the stomach) and died on Day 611 of an intestinal obstruction.

Subject 5482-0269 Esophageal hemorrhage: A 59-year-old Caucasian male with a history of liver cirrhosis and esophageal varices randomized to rosuvastatin treatment. He experienced the AEs of elevated ALT, AST, and bilirubin starting on Day 89 with recovery on Day 173. On Day 129, he was hospitalized for gastrointestinal hemorrhage. This event was listed as recovered by Day 135. On Day 144 he experienced peripheral edema which was treated with furosemide. On Day 212 he experienced an esophageal hemorrhage and died two days later.

Subject 8617-0009 Gastrointestinal hemorrhage: A 77-year-old Caucasian male with history of paroxysmal atrial fibrillation was randomized to rosuvastatin. On Day 227 of treatment he experienced a pathologic fracture of the L3 spinal vertebrae and was hospitalized. On Day 303 he died from a gastrointestinal hemorrhage. Study medication was stopped 66 days prior to his death following the spinal fracture

Subject 1130-0006 Esophageal rupture: A 68-year-old Caucasian male with a history of occasional acid reflux since 1997, cholecystitis on iron for anemia randomized to rosuvastatin. The only AE experienced before his death was cough on Day 52. He was found dead at home. The family reported the autopsy listed the cause of death as esophageal rupture. The family refused to release the official autopsy reports or give the exact date of death.

Subject 1280-0011 Gastroesophageal reflux: A 70-year-old Caucasian female with a history of COPD, bipolar disorder, colon polyps, and gastroesphageal reflux disease (GERD) randomized to rosuvastatin. During the treatment phase, she experienced six separate episodes of bronchitis. She discontinued study drug on Day 1278 due to personal fear of liver/muscle toxicity. At the time of her

death on Day 1577, she was suffering from GERD and depression. She was found dead at home. An autopsy ruled the cause of death as a subdural hematoma after a fall.

- Narratives of placebo-treated subjects with fatal TEAE in Gastrointestinal SOC

Subject 7754-0020 Peritonitis: A 50-year-old Hispanic male with a history of obesity, hypertension, sleep apnea, pulmonary hypertension, and bronchitis randomized to placebo. He experienced one episode of mild bronchitis on Day 168 which resolved. He underwent a gastric bypass and three days later he experienced palpitations, thoracic pain, and shortness of breath. Because of abdominal pain, a laparatomy was done which revealed perforation of the colon (Day 293). He died 13 days later.

7.3.1.4 Other rosuvastatin, placebo-controlled trials and fatal treatment-emergent adverse events in the gastrointestinal disorder SOC

Review of three other long-term rosuvastatin, placebo controlled trials, did not demonstrate a disproportionate increase in deaths due to gastrointestinal causes in rosuvastatin-exposed subjects.

In METEOR, a long-term placebo-controlled rosuvastatin trial, there were no deaths attributed to gastrointestinal disorders in either the rosuvastatin group or the placebo group.

In a second rosuvastatin, placebo-controlled trial, CORONA, five deaths and 22 deaths in the rosuvastatin and placebo treatment groups, respectively were attributed to the gastrointestinal causes. The causes listed in the rosuvastatin-treated subjects are listed below.

- Subject E0406020: 82 y M, gastritis hemorrhagic, pneumonia, not on drug
- Subject E1039011: 86y M, hematemesis, not on drug
- Subject E1047013: 90y M, hepatitis, not on drug
- Subject E1216006: 75y F, acute pancreatitis
- Subject E2035004: 76y M, gastrointestinal hemorrhage, worsening heart failure

In a third long-term placebo-controlled trial, AURORA, in subjects with end stage renal disease, there were an equal number of deaths, 29, in both the rosuvastatin and placebo groups reported as due to GI disorders (Table 42).

Table 42: Fatal treatment-emergent adverse events in the Gastrointestinal disorders SOC: AURORA trial

System organ class/Preferred term[a]	Number (%) of patients[b]	
	Placebo n= 1378	Rosuvastatin n= 1389
Gastrointestinal disorders	29 (2.1)	29 (2.1)
Gastrointestinal haemorrhage	4 (0.3)	5 (0.4)
Peritonitis	6 (0.4)	3 (0.2)
Abdominal pain	0 (0)	4 (0.3)
Ascites	1 (0.1)	0 (0)
Colitis	0 (0)	1 (0.1)
Colitis ischaemic	1 (0.1)	1 (0.1)
Colitis ulcerative	0 (0)	1 (0.1)
Diarrhoea	0 (0)	1 (0.1)
Enterocutaneous fistula	1 (0.1)	0 (0)
Gastric haemorrhage	0 (0)	1 (0.1)
Gastric ulcer	1 (0.1)	0 (0)
Gastric ulcer haemorrhage	1 (0.1)	0 (0)
Gastroduodenitis	0 (0)	1 (0.1)
Gastrointestinal ischaemia	1 (0.1)	0 (0)
Gastrointestinal perforation	1 (0.1)	0 (0)
Haematemesis	1 (0.1)	2 (0.1)
Ileus	2 (0.1)	1 (0.1)
Impaired gastric emptying	1 (0.1)	0 (0)
Intestinal infarction	1 (0.1)	2 (0.1)
Intestinal ischaemia	1 (0.1)	2 (0.1)
Intestinal obstruction	2 (0.1)	0 (0)
Intestinal perforation	1 (0.1)	0 (0)
Intra-abdominal haemorrhage	0 (0)	1 (0.1)
Mesenteric artery embolism	1 (0.1)	1 (0.1)
Mesenteric artery thrombosis	0 (0)	1 (0.1)
Oesophagitis haemorrhagic	1 (0.1)	0 (0)
Retroperitoneal haematoma	0 (0)	1 (0.1)
Upper gastrointestinal haemorrhage	1 (0.1)	0 (0)

Source: Applicant's Table 134, AURORA CSR, Pg 285-6

In summary, no pattern was discerned and overall the Division review could not confirm a relationship between rosuvastatin exposure and gastrointestinal-related causes of death

7.3.2 Nonfatal Serious Adverse Events

During the randomized treatment phase, the rosuvastatin treatment group reported 1269 (14.3%) treatment emergent non-fatal serious adverse events versus 1269 (14.3%) reported for the placebo group. Table 43 summarizes the treatment-emergent nonfatal SAEs by system organ class. Clinical events occurring between 31 March 2008 and each subject's final visit were reported as SAEs.

Table 43: JUPITER: Nonfatal treatment-emergent SAEs (ITT population)

System organ class	Rosuva 20 mg N=8901 n (%)	Placebo N=8901 n (%)
Any non-fatal SAE	**1269 (14.3)**	**1269 (14.3)**
Neoplasms benign, malignant, and unspecified (includes cysts and polyps)	258 (2.9)	261 (2.9)
Infections and infestations	200 (2.2)	220 (2.5)
Gastrointestinal disorders	184 (2.1)	171 (1.9)
Injury, poisoning, and procedural complications	161 (1.8)	142 (1.6)
Musculoskeletal and connective tissue disorders	154 (1.7)	140 (1.6)
Cardiac disorders	152 (1.7)	175 (2.0)
Respiratory, thoracic, and mediastinal disorders	101 (1.1)	108 (1.2)
Nervous system disorders	86 (1.0)	89 (1.0)
Hepatobiliary disorders	57 (0.6)	60 (0.7)
General disorders and administration site conditions	56 (0.6)	61 (0.7)
Renal and urinary disorders	56 (0.6)	75 (0.8)
Vascular disorders	44 (0.5)	69 (0.8)
Reproductive system and breast disorders	43 (0.5)	41 (0.5)
Metabolism and nutrition disorders	33 (0.4)	37 (0.4)
Blood and lymphatic system disorders	26 (0.3)	33 (0.4)
Psychiatric disorders	26 (0.3)	15 (0.2)
Eye disorders	14 (0.2)	20 (0.2)
Skin and subcutaneous tissue disorders	13 (0.1)	12 (0.1)
Endocrine disorders	12 (0.1)	7 (0.1)
Investigations	10 (0.1)	8 (0.1)
Ear and labyrinth disorders	8 (0.1)	11 (0.1)
Immune system disorders	7 (0.1)	2 (<0.1)
Congenital, familial, and genetic disorders	4 (<0.1)	3 (<0.1)
Surgical and medical procedures	3 (<0.1)	1 (<0.1)
Source: Applicant's Table 11.3.4.1.2.2, Pg 8356 CSR JUPITER		

There is a slight imbalance in the gastrointestinal disorders SOC for nonfatal SAEs (rosuvastatin 184/8901, 2.1%; placebo, 171/8901, 1.9%). When looking at the preferred terms for the GI SOC there does not appear to be a pattern of increased occurrence in a particular area of the GI system. The table below lists the nonfatal GI treatment emergent SAEs by preferred terms that occurred in the rosuvastatin group. Preferred terms that occurred in the placebo group but not in the rosuvastatin group were omitted.

Table 44: Nonfatal GI treatment emergent SAE by preferred terms occurring in rosuvastatin treatment group

System organ class	Preferred Term	Rosuvastatin 20 mg N=8901 n(%)	Placebo N=8901 n(%)
Gastrointestinal disorders		184 (2.1)	171 (1.9)
	Gastrointestinal hemorrhage	20 (0.2)	18 (0.2)
	Inguinal hernia	20 (0.2)	18 (0.2)

System organ class	Preferred Term	Rosuvastatin 20 mg N=8901 n(%)	Placebo N=8901 n(%)
	Intestinal obstruction	12 (0.1)	9 (0.1)
	Abdominal pain	8 (0.1)	7 (0.1)
	Acute pancreatitis	8 (0.1)	6 (0.1)
	Umbilical hernia	8 (0.1)	6 (0.1)
	Diverticulum	6 (0.1)	4 (<0.1)
	Diarrhea	5 (0.1)	9 (0.1)
	Hiatus hernia	5 (0.1)	2 (<0.1)
	Pancreatitis	5 (0.1)	9 (0.1)
	Small intestinal obstruction	5 (0.1)	8 (0.1)
	Abdominal hernia	4 (<0.1)	1 (<0.1)
	Abdominal pain upper	4 (<0.1)	6 (0.1)
	Colonic polyp	4 (<0.1)	4 (<0.1)
	Crohn's disease	**4 (<0.1)**	**1 (<0.1)**
	Gastritis	4 (<0.1)	4 (<0.1)
	Duodenal ulcer hemorrhage	3 (<0.1)	0
	Gastric ulcer hemorrhage	3 (<0.1)	2 (<0.1)
	Hemorrhoids	3 (<0.1)	2 (<0.1)
	Peritonitis	3 (<0.1)	3 (<0.1)
	Rectal prolapse	3 (<0.1)	0
	Colitis ischemic	2 (<0.1)	2 (<0.1)
	Colitis ulcerative	2 (<0.1)	5 (0.1)
	Diverticulum intestinal	2 (<0.1)	0
	Enterovesical fistula	2 (<0.1)	1 (<0.1)
	Erosive esophagitis	2 (<0.1)	1 (<0.1)
	Gastric ulcer	2 (<0.1)	6 (0.1)
	Gastritis erosive	2 (<0.1)	0
	Gastroesophageal reflux disease	2 (<0.1)	4 (<0.1)
	Ileus	2 (<0.1)	2 (<0.1)
	Ileus paralytic	2 (<0.1)	0
	Irritable bowel syndrome	2 (<0.1)	1 (<0.1)
	Large intestine perforation	2 (<0.1)	0
	Peptic ulcer	2 (<0.1)	2 (<0.1)
	Rectal hemorrhage	2 (<0.1)	4 (<0.1)
	Rectal polyp	2 (<0.1)	0
	Salivary gland cyst	2 (<0.1)	0
	Vomiting	2 (<0.1)	2 (<0.1)
	Abdominal distension	1 (<0.1)	0
	Abdominal strangulated hernia	1 (<0.1)	0
	Abdominal wall hematoma	1 (<0.1)	0
	Ascites	1 (<0.1)	0
	Barrett's esophagus	**1 (<0.1)**	**1 (<0.1)**
	Colonic stenosis	1 (<0.1)	1 (<0.1)
	Constipation	1 (<0.1)	1 (<0.1)
	Duodenal ulcer	1 (<0.1)	2 (<0.1)
	Duodenitis	1 (<0.1)	1 (<0.1)
	Enterocele	1 (<0.1)	0
	Food poisoning	1 (<0.1)	0

System organ class	Preferred Term	Rosuvastatin 20 mg N=8901 n(%)	Placebo N=8901 n(%)
	Gastric perforation	1 (<0.1)	0
	Gastric polyps	1 (<0.1)	0
	Gastric ulcer perforation	1 (<0.1)	0
	Gastrointestinal pain	1 (<0.1)	0
	Hematemesis	1 (<0.1)	2 (<0.1)
	Hemorrhoidal hemorrhage	1 (<0.1)	0
	Inguinal hernia, obstructive	1 (<0.1)	0
	Intra-abdominal hemorrhage	1 (<0.1)	0
	Large intestinal hemorrhage	1 (<0.1)	0
	Nausea	1 (<0.1)	2 (<0.1)
	Esophagitis	1 (<0.1)	1 (<0.1)
	Esophagitis hemorrhagic	1 (<0.1)	0
	Esophagitis ulcerative	1 (<0.1)	0
	Peptic ulcer hemorrhage	1 (<0.1)	1 (<0.1)
	Peritoneal disorder	1 (<0.1)	0
	Salivary gland calculus	1 (<0.1)	0
	Small intestinal hemorrhage	1 (<0.1)	1 (<0.1)
	Spigelian hernia	1 (<0.1)	0
	Swollen tongue	1 (<0.1)	0
	Volvulus of small bowel	1 (<0.1)	0
Source: Applicant's Table 11.3.4.1.2.2, Pg 8356, CSR JUPITER			

The imbalance noted for the psychiatric nonfatal SAEs was attributed to the preferred terms of depression and confusional state. The following table lists the preferred terms in the psychiatric disorder SOC for nonfatal SAEs.

Table 45: Nonfatal Psychiatric disorders SAEs by preferred term

System organ class	Preferred Term	Rosuvastatin 20 mg N=8901 n(%)	Placebo N=8901 n(%)
Psychiatric disorders	Any adverse event	26 (0.3)	15 (0.2)
	Depression	8 (0.1)	4 (<0.1)
	Confusional state	7 (0.1)	1 (<0.1)
	Anxiety	2 (<0.1)	2 (<0.1)
	Delirium	2 (<0.1)	1 (<0.1)
	Insomnia	2 (<0.1)	0
	Major depression	2 (<0.1)	0
	Suicidal ideation	2 (<0.1)	0
	Mental status changes	1 (<0.1)	2 (<0.1)
	Suicide attempt	1 (<0.1)	0
	Acute psychosis	0	1 (<0.1)
	Aggression	0	1 (<0.1)
	Alcohol abuse	0	1 (<0.1)
	Alcoholism	0	2 (<0.1)
	Panic attack	0	1 (<0.1)
	Psychotic disorder	0	1 (<0.1)

Source: Applicant's Table 11.3.4.1.2.2, Pg 8356, CSR JUPITER

7.3.3 Dropouts and/or Discontinuations

7.3.3.1 Study medication discontinuations due to adverse event

A distinction was made in JUPITER regarding discontinuations of study medication due to an AE versus an AE leading to study withdrawal (DAE). By completing follow-up assessments for clinical endpoints after discontinuing study medication, subjects were considered to be actively participating in JUPITER. A similar number of subjects discontinued study medication due to an AE; 584 (6.6%) in the rosuvastatin group, and 553 (6.2%) in the placebo group. There was no statistically significant difference in time to discontinuation of study medication due to an AE between the treatment groups. The reasons for discontinuing study medication are summarized in the table below. Twice as many placebo-treated subjects discontinued study medication due to a clinical event and three times as many subjects in the placebo group discontinued study treatment to initiate open-label statin treatment.

Table 46: Reasons for discontinuing study medication (ITT population)[a]

Reason	Rosuvastatin 20 mg N=8901 n(%)	Placebo N=8901 n(%)
Clinical event	72 (0.8)	153 (1.7)
Initiation of open label statin therapy	51 (0.6)	157 (1.8)
Adverse event	584 (6.6)	553 (6.2)
Other	1002 (11.3)	1048 (11.8)
Not specified	2 (0.0)	12 (0.1)

[a] Subjects may appear in more than one reason category
Source: Applicant's Table 11.1.1.8.2.4.1, Pg 1865 CSR JUPITER

The following table lists the frequency of the system organ classes listed for discontinuation of study medication. Musculoskeletal disorders (32.2% rosuvastatin versus 27.3% placebo) were the most common disorders reported for discontinuation. Within this system organ class, the most common adverse event in both groups for study medication discontinuation was myalgia (18.0% in rosuvastatin group and 13.6% in placebo group).

Table 47: Number and frequency of subjects with TEAE leading to discontinuation of study medication (ITT population)

System organ class	Rosuvastatin 20 mg N=584 n(%)	Placebo N=553 n(%)
Musculoskeletal and connective tissue disorders	188 (32.2)	151 (27.3)
Gastrointestinal disorders	97 (16.6)	84 (15.2)
Infections and infestations	60 (10.3)	51 (9.2)
Nervous system disorders	59 (10.1)	52 (9.4)

General disorders and administration site conditions	54 (9.2)	38 (6.9)
Skin and subcutaneous disorders	37 (6.3)	33 (6.0)
Investigations	25 (4.3)	25 (4.5)
Neoplasms benign, malignant and unspecified	23 (3.9)	32 (5.8)
Respiratory, thoracic and mediastinal disorders	22 (3.8)	16 (2.9)
Renal and urinary disorders	20 (3.4)	15 (2.7)
Unknown	20 (3.4)	16 (2.9)
Metabolism and nutrition disorders	15 (2.6)	12 (2.2)
Cardiac disorders	14 (2.4)	30 (5.4)
Vascular disorders	14 (2.4)	12 (2.2)
Eye disorders	13 (2.2)	5 (0.9)
Reproductive system and breast disorders	11 (1.9)	5 (0.9)
Injury, poisoning, and procedural complications	9 (1.5)	23 (4.2)
Hepatobiliary disorders	8 (1.4)	12 (2.2)
Psychiatric disorders	8 (1.4)	17 (3.1)
Ear and labyrinth disorders	6 (1.0)	6 (1.1)
Immune system disorders	3 (0.5)	3 (0.5)
Blood and lymphatic system	2 (0.3)	2 (0.3)
Source: Response to FDA IR: Table 6.1 20 January 2010		

7.3.3.2 Withdrawal of study participation due to adverse event

Overall, 7.8% of the rosuvastatin-treated group and 8% of the placebo-treated group withdrew from the study. Approximately, 1.6% (143/8901) of rosuvastatin-treated subjects versus 1.8% (158/8901) of placebo-treated subjects experienced an AE that led to study withdrawal or DAE. The DAEs that lead to study withdrawal are summarized in the following table.

Table 48: Number and frequency of subjects with TEAE leading to study withdrawal (ITT population)

System organ class	Rosuvastatin 20 mg N=8901 n(%)	Placebo N=8901 n(%)
Any DAE	**143 (1.6)**	**158 (1.8)**
Musculoskeletal disorders	37 (0.4)	31 (0.3)
Gastrointestinal disorders	22 (0.2)	11 (0.1)
Neoplasms benign, malignant, and unspecified (includes cysts and polyps)	22 (0.2)	24 (0.3)
General disorders and administration site conditions	14 (0.2)	21 (0.2)
Nervous system disorders	8 (0.1)	18 (0.2)
Infections and infestations	7 (0.1)	3 (0.0)
Injury, poisoning, and procedural complications	6 (0.1)	1 (0.0)
Cardiac disorders	5 (0.1)	10 (0.1)
Skin and subcutaneous tissue disorders	5 (0.1)	5 (0.1)
Investigations	4 (0.0)	5 (0.1)
Vascular disorders	4 (0.0)	5 (0.1)
Hepatobiliary disorders	3 (0.0)	4 (0.0)
Psychiatric disorders	3 (0.0)	2 (0.0)
Reproductive system and breast disorders	3 (0.0)	0

Respiratory, thoracic, and mediastinal disorders	3 (0.0)	9 (0.1)
Metabolism and nutrition disorders	2 (0.0)	9 (0.1)
Renal and urinary disorders	1 (0.0)	3 (0.0)
Blood and lymphatic system disorders	0	1 (0.0)
Source: Applicant's Table 36, Pg 89 CSR JUPITER		

Musculoskeletal disorders were the most common reason for study withdrawal in both treatment groups. Myalgia was the preferred term listed most frequently in the rosuvastatin treatment group (25/8901, 0.3%) and placebo treatment group **(15/8901, 0.2%) as reason for withdrawal (Applicant's Table 11.3.5.1.2.2, Pg** 26172 CSR JUPITER). There was a slightly higher number of DAEs due to gastrointestinal disorders in the rosuvastatin group. Of these the most common treatment emergent AE was abdominal pain (three rosuvastatin subjects, two placebo subjects) in both groups.

7.3.4 Significant Adverse Events

7.3.4.1 Hepatic adverse events

In JUPITER a total of 216 (2.4%) rosuvastatin-treated subjects and 186 (2.1%) placebo-treated subjects experienced a hepatic-related adverse event. The most common AE was related to abnormal laboratory levels and occurred with higher frequency in the rosuvastatin-treatment group. The following table lists any hepatic-related AE that occurred in the randomized treatment phase (not just treatment emergent AEs). There were two cases of chronic hepatic failure in rosuvastatin-treated subjects and two cases of hepatic failure in placebo-treated subjects.

Table 49: JUPITER: Number and percentage of subjects with hepatic-related adverse events reported ant any time during the randomized treatment phase, by SOC and preferred term (ITT population)[a]

System Organ Class Preferred Term	**Rosuvastatin** **N=8901** **n (%)**	**Placebo** **N=8901** **n (%)**
Any hepatic adverse event	**216 (2.4)**	**186 (2.1)**
Investigations	**165 (1.9)**	**134 (1.5)**
ALT increased	127 (1.4)	93 (1.0)
Hepatic enzyme increased	30 (0.3)	31 (0.3)
AST increased	7 (0.1)	6 (0.1)
GGT increased	7 (0.1)	5 (0.1)
Alkaline phosphatase increased	4 (<0.1)	3 (<0.1)
Liver function test abnormal	2 (<0.1)	2 (<0.1)
Blood bilirubin increased	1 (<0.1)	4 (<0.1)
Blood LDH increased	1 (<0.1)	0
Hepatobiliary disorders	**48 (0.5)**	**53 (0.6)**

System Organ Class Preferred Term	**Rosuvastatin** **N=8901** **n (%)**	**Placebo** **N=8901** **n (%)**
Hepatic steatosis	17 (0.2)	22 (0.2)
Hepatic function abnormal	13 (0.1)	6 (0.1)
Hepatomegaly	6 (0.1)	6 (0.1)
Hepatic cirrhosis	3 (<0.1)	4 (<0.1)
Hepatitis	3 (<0.1)	2 (<0.1)
Chronic hepatic failure	2 (<0.1)	0
Jaundice cholestatic	2 (<0.1)	2 (<0.1)
Autoimmune hepatitis	1 (<0.1)	0
Hepatosplenomegaly	1 (<0.1)	0
Jaundice	1 (<0.1)	6 (0.1)
Liver disorder	1 (<0.1)	2 (<0.1)
Alcoholic liver disease	0	1 (<0.1)
Hepatic failure	0	2 (<0.1)
Hepatitis alcoholic	0	2 (<0.1)
Hepatitis cholestatic	0	1 (<0.1)
Hepatitis toxic	0	1 (<0.1)
Infections and infestations	**4 (<0.1)**	**3 (<0.1)**
Hepatitis C	2 (<0.1)	1 (<0.1)
Hepatitis A	1 (<0.1)	1 (<0.1)
Hepatitis B	1 (<0.1)	1 (<0.1)
Gastrointestinal disorders	**3 (<0.1)**	**7 (0.1)**
Ascites	3 (<0.1)	7 (0.1)
Skin and subcutaneous tissue disorders	**1 (<0.1)**	**0**
Yellow skin	1 (<0.1)	0

[a] AE number in this table are all AEs occurring during the randomized treatment period and not just treatment-emergent AEs
Source: Table 11.3.6.1.1.4, Page 31981, CSR

The two chronic hepatic failure AEs in the rosuvastatin treatment group are discussed below:

- Subject 7162-0136: An 82-year-old Hispanic man with a history of chronic obstructive pulmonary disease on theophylline and salbutamol was randomized to rosuvastatin 20 mg on 14 March 2006. He reported chronic liver failure on Day 226 and withdrew from the study due to this event. Approximately two years later, the subject was still alive and had not experienced any of the primary efficacy endpoints. The labs available do not show an elevation in ALT; on Week -4 the ALT was 11 U/L and on Week 26 (Day 185) the ALT was 16 U/L.

- Subject 1270-0015, a 71-year-old Caucasian man, was randomized to rosuvastatin 20 mg on 20 May 2004. His past medical history was significant for prostate cancer (1997) and skin cancer (1996). During the study he

experienced the adverse events of proteinuria (Day -30), urinary casts (Day 91), and hematuria (Day 182). Concomitant medications at baseline included hydroxyzine for insomnia, and diphenhydramine hydrochloride (Benadryl) for seasonal allergies. He was treated for five days with levaquin for a kidney infection on Days 218-223. Available labs showed a normal ALT of 8 U/L at baseline that peaked to 45 U/L on Day 91 and remained elevated. On Day 592 hepatic cirrhosis and chronic hepatic failure was noted. The subject died on Day (b) (6) of pneumonia and septic shock secondary to end-stage liver disease and cirrhosis.

7.3.4.2 Hepatic biochemistry

Clinically significant laboratory findings related to the hepatic system were defined as an ALT elevation >3x ULN on 2 occasions. Serum AST, bilirubin, and alkaline phosphatase were not routinely monitored in JUPITER; however, at the discretion of the site investigator a bilirubin level could be measured. Evidence **for severe hepatotoxicity may be signaled by a set of findings called Hy's Law.** These findings consist of an increased rate of transaminase elevations, no significant evidence of obstruction, and a rise in bilirubin to 2x ULN in the **absence of concurrent hepatic infection or injury. No Hy's law cases were** identified in rosuvastatin-treated subjects. Two subjects were identified with bilirubin >2x ULN, AST >3x ULN, and alkaline phosphatase <2x ULN. One was a placebo-treated subject and the other was a rosuvastatin-treated subject with a concurrent AE of hepatitis C.

- Subject 6018-0025: A 64-year-old Caucasian male with a history of benign prostatic hypertrophy randomized to placebo and experienced significant elevations in ALT 1338 U/L, AST 606 (ULN 22 mU/mL), bilirubin 2.75 (ULN 1.10 mg/dL), alkaline phosphatase of 95 (ULN 70 mU/mL), and CK 154 U/L approximately 3 months after randomization. The subject discontinued study medication, but continued participation in follow-up visits. At his final visit, almost 2 years after starting the JUPITER trial, his ALT was slightly elevated at 45 U/L, CK was 112 U/L. He was on no concomitant medications.

- Subject 8488-0022: A 62-year-old Caucasian male with a history of osteopenia, supraventricular tachycardia, and obstructive pulmonary disease randomized to 20 mg rosuvastatin on 28 March 2006. He was diagnosed on Day 367 with an elevated ALT (530 U/L), elevated AST (672 U/L), elevated bilirubin 7.86, alkaline phosphatase of 95, and Hepatitis C. He discontinued study medication on 5 May 2006 due to this SAE; however, he did not withdraw his participation in the JUPITER trial. Repeat ALT 6 months later demonstrated a reduction to 71 U/L with normal values of ALT one year after diagnosis.

An ALT >3x ULN on 2 consecutive occasions was defined as "clinically important" and subjects were asked to discontinue the study medication, but were followed for the study duration. It was left to the clinical investigator's discretion regarding further work-up of the abnormal laboratory values.

The following table lists the number and frequency of subjects with significantly elevated ALT and/or AST values.

Table 50: JUPITER: Number (%) of subjects with elevations of ALT in the randomized treatment phase (ITT population)

ALT (U/L)	**Rosuvastatin 20 mg N=8624 n (%)**	**Placebo N=8364 n (%)**
AST >3x ULN and/or ALT >3x ULN	124 (1.4)	88 (1.0)
ALT >3x ULN on 2 consecutive occasions	23 (0.3)	17 (0.2)
AST >5x ULN and/or ALT >5x ULN	53 (0.6)	25 (0.3)
AST >10x ULN and/or ALT >10x ULN	12 (0.1)	6 (0.1)
Source: Applicant's Table 43, Pg 101 CSR JUPITER, IR response to 13 October 2009		

The percentage of subjects in the JUPITER trial with an ALT >3x ULN and/or an AST >3x ULN was similar to the percentage observed in a pooled analysis of placebo-controlled trials which demonstrated 1.1% of subjects taking rosuvastatin versus 0.5% of subjects treated with placebo had an elevated ALT according to the current CRESTOR label. In a 2007 analysis funded by the applicant, safety data from 16,876 patients receiving rosuvastatin 5 to 40 mg observed ≤0.2% occurrence of ALT >3x ULN on 2 consecutive occasions.[25] These numbers are similar to what was observed in the JUPITER trial.

7.3.4.3 Skeletal muscle adverse events

Muscle-related AEs occurred at a higher incidence in the rosuvastatin-treatment group compared to the placebo-treatment group (Table 51). Myalgia was the most commonly reported preferred term in the rosuvastatin (8.0%) and placebo groups (7.2%). There was one case of rhabdomyolysis in JUPITER in a rosuvastatin-treated subject.

- Subject 1778-001: A 90-year-old man on rosuvastatin pending his final visit 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, CK was 13,000 and creatinine was 1.5 mg/dL (baseline creatinine 4 years prior was 1.3 mg/dL). Following hydration, he recovered fully; creatinine at final visit was 1.1 mg/dL.

25 Shepherd et al. Safety of rosuvastatin: update on 16,876 rosuvastatin-treated patients in a multinational clinical trial program. Cardiology 2007;107:433-443.

There was twice the number of rosuvastatin-treated subjects with investigator reported elevated CK compared to placebo-treated subjects. The applicant **claims these events may or may not have met the applicant's criterion for a "clinically important" CK elevation defined as a CK >10x ULN. If the laboratory** value was reported by the investigator as abnormal it was considered an AE of interest; however, it may not have met the predefined definition of a clinically important CK elevation.

Table 51: JUPITER: Number and percentage of subjects with muscle-related adverse events reported during the randomized treatment phase, by SOC and preferred term (ITT population)[a]

System Organ Class Preferred Term	Rosuvastatin N=8901 n(%)	Placebo N=8901 n(%)
Any muscle-related AE	**1421 (16.0)**	**1375 (15.4)**
Investigations	**63 (0.7)**	**38 (0.4)**
Blood creatine phosphokinase increased	61 (0.7)	34 (0.4)
Blood creatine increased	2 (<0.1)	4 (<0.1)
Myoglobin blood increased	1 (<0.1)	0
Musculoskeletal and connective tissue disorders	**1297 (14.6)**	**1225 (13.8)**
Myalgia	714 (8.0)	639 (7.2)
Muscle spasm	333 (3.7)	314 (3.5)
Musculoskeletal pain	295 (3.3)	319 (3.6)
Muscular weakness	84 (0.9)	72 (0.8)
Musculoskeletal discomfort	16 (0.2)	12 (0.1)
Myositis	9 (0.1)	8 (0.1)
Muscle disorder	8 (0.1)	4 (<0.1)
Muscle tightness	8 (0.1)	1 (<0.1)
Muscle fatigue	4 (<0.1)	5 (0.1)
Muscle twitching	3 (<0.1)	1 (<0.1)
Musculoskeletal disorder	3 (<0.1)	4 (<0.1)
Muscle hemorrhage	1 (<0.1)	0
Myosclerosis	1 (<0.1)	1 (<0.1)
Rhabdomyolysis	1 (<0.1)	0
Myopathy	0	1 (<0.1)
Injury, poisoning, and procedural complications	**112 (1.3)**	**154 (1.7)**
Muscle strain	99 (1.1)	133 (1.5)
Muscle injury	14 (0.2)	20 (0.2)
Muscle rupture	2 (<0.1)	2 (<0.1)

[a] AE numbers in this table are all AEs occurring during the randomized treatment period and not just treatment-emergent AEs
Source: Applicant's Table 38, Pg 93, CSR JUPITER

7.3.4.4 Skeletal muscle biochemistry

Myopathy was defined as muscle aches or weakness with an increase in CK >10x ULN and was recorded as an adverse event. If markedly elevated CK levels (>10x ULN) were accompanied by unexplained muscle pain, tenderness, or weakness, study medication was discontinued.

During the randomized treatment phase of JUPITER, there were two rosuvastatin-treated subjects and one placebo-treated subject with CK elevations >10x ULN which was predefined as a clinically significant laboratory event (Table 52). Of the subjects with a CK >10x ULN, there were no concomitant increase in creatinine levels to suggest kidney injury.

Table 52: JUPITER: Subjects with CK >10xULN (1200 U/L) in randomized treatment phase (ITT population)

Subject	Treatment	Age/ Race/Sex	Visit	Days from randomization	CK (U/L)	Creatinine (mg/dL)	Comments
1241-0002	Rosuva 20 mg	60 W/M	Week-4	-28	63	1.0	1 month before CK levels drawn, had muscle spasm (back) AE for 4 days
			Final visit	1638	2874	0.9	
7651-0133	Rosuva 20 mg	M	Week-4	-25	46	unknown	Two hours a day of vigorous exercise previous 3 weeks. No symptoms
			Final visit	597	11404	1.0	
6042-0013	Placebo	63 B/M	Week-4	-27	152	1.1	AE of paresthesia started Day 71 and was ongoing throughout study
			Final visit	687	1588	1.3	

Source: Applicant's Table 11.3.7.2.21, Pg 77939, Table 11.3.6.3 Pg 34941, CSR JUPITER

At the final visit, the CK values for the rosuvastatin-treated group had increased by a mean of 11.1 U/L and in the placebo-treated group by a mean of 2.3 U/L. The difference in mean CK values between the two groups at the final visit was approximately 8.0 U/L.

7.3.4.5 Renal adverse events

In JUPITER there were a greater number of renal-related AEs in the rosuvastatin group (535/8901, 6.0%) as compared to the placebo group (480/8901, 5.4%). Of

the renal AEs, hematuria and proteinuria were the most common, occurring with a higher incidence in the rosuvastatin treatment group. Acute, chronic, and unspecified renal failure occurred with similar frequency in the two treatment groups.

Table 53: JUPITER: Number and percentage of subjects with renal-related adverse events reported during the randomized treatment phase, by SOC and preferred term (ITT population)

System Organ Class Preferred Term	Rosuvastatin N=8901 n (%)	Placebo N=8901 n (%)
Any renal-related AE[a]	**535 (6.0)**	**480 (5.4)**
Investigations	**110 (1.2)**	**93 (1.0)**
Urine analysis abnormal	40 (0.4)	43 (0.5)
Blood creatinine increased	39 (0.4)	30 (0.3)
Red blood cells urine	18 (0.2)	12 (0.1)
Blood urea increased	5 (0.1)	1 (<0.1)
Protein urine present	5 (0.1)	8 (0.1)
Glomerular filtration rate decreased	3 (<0.1)	1 (<0.1)
Urine output decreased	3 (<0.1)	0
Blood urine present	2 (<0.1)	1 (<0.1)
Protein urine	2 (<0.1)	0
Red blood cells urine positive	2 (<0.1)	0
Urine color abnormal	1 (<0.1)	0
Renal and urinary disorders	**452 (5.1)**	**406 (4.6)**
Hematuria	241 (2.7)	203 (2.3)
Proteinuria	149 (1.7)	127 (1.4)
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)
Urine flow decreased	8 (0.1)	15 (0.2)
Renal disorder	5 (0.1)	4 (<0.1)
Microalbuminuria	4 (<0.1)	3 (<0.1)
Azotemia	3 (<0.1)	2 (<0.1)
Anuria	2 (<0.1)	1 (<0.1)
Oliguria	2 (<0.1)	1 (<0.1)
Urine odor abnormal	2 (<0.1)	1 (<0.1)
Glomerulonephritis	1 (<0.1)	1 (<0.1)
Nephritis	1 (<0.1)	0
Nephrotic syndrome	1 (<0.1)	0
Hemoglobinuria	0	1 (<0.1)
Kidney fibrosis	0	1 (<0.1)
Renal atrophy	0	1 (<0.1)
Metabolism and nutrition disorders	**3 (<0.1)**	**2 (<0.1)**
Metabolic acidosis	2 (<0.1)	2 (<0.1)
Acidosis	1 (<0.1)	0

System Organ Class Preferred Term	Rosuvastatin N=8901 n (%)	Placebo N=8901 n (%)
[a] AE numbers in this table are all AEs occurring during the randomized treatment period and not just treatment-emergent AEs Source: Applicant's Table 39, Pg 95 CSR JUPITER		

7.3.4.6 Renal biochemistry

The number and percent of subjects with serum creatinine elevations increased >100% above baseline in the randomized treatment phase are listed in the following table.

Table 54: Serum creatinine elevations increased >100%

Serum creatinine (µmol/L)	Rosuvastatin 20 mg (N=7450) n (%)	Placebo (N=7410) n (%)
Creatinine >100% above baseline	10 (0.1)	6 (0.1)
Source: Applicant's Table 45, Pg 102 CSR JUPITER		

Urinalysis was performed at baseline and every 6 months during follow-up. The following table lists the urine dipstick protein and blood values at baseline and at the final visit in both treatment groups. Shifts in the amount of blood and protein in subject's urine were similar between the treatment groups.

Table 55: JUPITER: Urine dipstick protein and blood at Baseline and Final visit

	Rosuvastatin 20 mg (N=8901)		Placebo (N=8901)	
	Baseline n (%)	Final n (%)	Baseline n (%)	Final n (%)
Urine protein				
0	7223 (81.1)	5526 (62.1)	7256 (81.5)	5585 (62.7)
Trace	1063 (11.9)	970 (10.9)	1052 (11.8)	941 (10.6)
+	432 (4.9)	507 (5.7)	447 (5.0)	420 (4.7)
++	123 (1.4)	135 (1.5)	99 (1.1)	105 (1.2)
+++	16 (0.2)	22 (0.2)	11 (0.1)	20 (0.2)
++++	1 (<0.1)	2 (<0.1)	3 (<0.1)	2 (<0.1)
NR	40 (0.4)	8 (0.1)	30 (0.3)	3 (<0.1)
Urine blood				
0	7924 (89.0)	6244 (70.1)	7909 (88.9)	6280 (70.6)
Trace	487 (5.5)	465 (5.2)	489 (5.5)	406 (4.6)
+	268 (3.0)	244 (2.7)	273 (3.1)	223 (2.5)
++	118 (1.3)	145 (1.6)	137 (1.5)	111 (1.2)
+++	62 (0.7)	65 (0.7)	60 (0.7)	55 (0.6)
NR	39 (0.4)	7 (0.1)	30 (0.3)	1 (<0.1)
a +30; ++ 100; +++300; ++++ ≥2000 mg/dL; NR Not recorded b + small; ++ moderate; +++large; NR Not recorded Source: Applicant's Table 46, Pg 103 CSR JUPITER				

The following table shows the incidence of an increase in protein or blood by urine dipstick in the two treatment groups and persistence of the finding. While there was a higher incidence in the rosuvastatin group there was a similar percentage of persistence of the findings between the two groups

Table 56: Incidence and persistence of proteinuria and hematuria by urine dipstick

	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.

7.3.4.7 Renal function

7.3.4.7.1 Estimated GFR

The mean estimated GFR (eGFR) was similar in the treatment groups at baseline. Both groups experienced a decrease in eGFR during follow-up. Mean eGFR fell less in the rosuvastatin group. The eGFR fell from baseline -7.23 ml/min/1.73 m^2 in the rosuvastatin group versus -7.72 ml/min/1.73 m^2 in the placebo group.

In both groups the majority of subjects (64.3% rosuvastatin, 63.7% placebo) at baseline had an eGFR that fell within the definition of mild impairment (60 to <90 ml/min/1.73 m^2). An estimated GFR was considered normal at ≥ 90 ml/min/1.73 m^2. Both treatment groups experienced a similar frequency of shifts in eGFR. No subject treated with rosuvastatin with a normal eGFR at baseline had a clinically significant reduction in eGFR (<30 ml/min/1.73 m^2).

7.3.4.7.2 Creatinine clearance

The majority of subjects in both treatment groups had a creatinine clearance in the normal (>80 ml/min) to mildly impaired range (50 to ≤ 80 ml/min). There were no significant differences between treatment groups at baseline or final visit. Shifts in mean creatinine clearance were similar among the rosuvastatin and placebo treatment groups.

7.3.4.8 Neuropsychiatric adverse events

Due to the concern over statin use and neurocognitive and psychiatric adverse effects, including memory impairment, memory loss, confusion, depression, and anxiety, selected nervous system and psychiatric disorder adverse events were reviewed. Please note Table 57 does not include all nervous system and psychiatric disorder AEs experienced in the JUPITER trial.

Table 57: JUPITER: Number and percentage of subjects with selected nervous system and psychiatric disorders adverse events reported during the randomized treatment phase, by SOC and preferred term (ITT population)

SOC Preferred Term	**Rosuvastatin 20 mg** **N=8901** **n (%)**	**Placebo** **N=8901** **n (%)**
Any adverse event	**568 (6.4)**	**586 (6.6)**
Nervous system disorders	**69 (0.8)**	**76 (0.9)**
Amnesia	30 (0.3)	33 (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 (<0.1)	1 (<0.1)
Amnestic disorder	2 (<0.1)	1 (<0.1)
Global amnesia	2 (<0.1)	1 (<0.1)
Senile dementia	1 (<0.1)	2 (<0.1)
Cognitive disorder	0	6 (0.1)
Vascular dementia	0	1 (<0.1)
Psychiatric disorders	**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 (<0.1)
Depressed mood	12 (0.1)	12 (0.1)
Nervousness	8 (0.1)	7 (0.1)
Generalized anxiety disorder	2 (<0.1)	1 (<0.1)
Major depression	2 (<0.1)	0
Suicidal ideation	2 (<0.1)	0
Completed suicide	1 (<0.1)	1 (<0.1)
Suicide attempt	1 (<0.1)	0
Depression suicidal	0	1 (<0.1)
Depressive symptom	0	1 (<0.1)
Initial insomnia	0	1 (<0.1)
Personality change	0	1 (<0.1)
Source: IR response Applicant Table 11.3.6.1.1.7B		

The applicant reported that 18 rosuvastatin-treated subjects versus 4 placebo-treated subjects experienced the AE of "confusional state". Seven of the 18 confusional states in rosuvastatin-treated subjects were considered serious adverse events. Four subjects were not on study medication at the time and

others had concurrent medical conditions and/or medications ongoing at the time of the event. The following table provides further details of the rosuvastatin-treated subjects experiencing the confusional adverse events.

Table 58: JUPITER: Description of rosuvastatin-treated subjects experiencing AE of confusional state

Center	Subject ID	Age	Sex	Verbatim term as reported	Day of study event occurred	Overall duration of treatment with study medication (days)	Medications listed at time of event	Comments	Rechallenge	Additional neuropsychiatric AE after "confusional state"
1031	0031	76	F	Confusion	670	1247	Prevacid, Donnatal, Morphine, Zofran, Maalox, Tylenol, Dilaudid	Concurrent with AE of confusional state had abdominal pain, N/V, fever diagnosed with infective cholecystitis requiring hospitalization and surgery	No rechallenge did not stop medication	None
1244	0018	55	M	Intermittent confusion	Not on rosuva at time of event	722	Digoxin, amiodarone, ASA	Current medical history of atrial fibrillation and PMH of depression. Discontinued study medication on Day 722 due to elevated CK and myalgia. One year later experienced concurrent with intermittent confusion, intermittent chest spasms, headache, dyspnea, constipation, and depression	No rechallenge	Depression (not on treatment)
1282	0013	74	M	Confusion	1190	1269	ASA, Penicillin, Coumadin, Lanoxin, Warfarin, Lisinopril, Accupril, Zyrtec, Diovan	Prior AEs experienced within 6 months of event: Day 1069: Fall with scalp laceration, Day 1101 Anxiety, Day 1136 UTI with kidney stone	No rechallenge did not stop during AE. Stopped medication 6 weeks after confusional state due to "investigator discretion"	None
1668	0124	82	F	Confusion	250	607	Aleve, HCTZ, KCL	Day 196 AE of frontal meningioma. Eight days prior to event experienced the AE of Fall and Left shoulder strain with nerve impingement.	No rechallenge did not stop medication	Dementia
1802	0113	87	M	Confusion (SAE)	79	373	PPI, Atenolol/HCTZ, Ramipril, Lorazepam, benadryl, ibuprofen, clopidogrel sulfate, KCL	Hx of BPH, GI bleed, peptic ulcer, renal insufficiency, rhinitis. Admitted to hospital after daughter found at home disoriented and confused. On admission, neuro exam was benign, and he was alert and oriented. Head CT neg, EKG sinus rhythm, multiple premature atrial complexes, left anterior fascicular block, probable old anteroseptal infarct, CXR lungs clear. Discharged two days later to subacute rehab facility	No rechallenge did not stop medication	Insomnia
2067	0021	84	F	Confusion	Not on rosuvastatin at time of event	186	ASA, Calcium	Experienced concurrent AE of depression. Later started on Remeron for depression and Geodon	No rechallenge not on medication at time of event	Depression

Center	Subject ID	Age	Sex	Verbatim term as reported	Day of study event occurred	Overall duration of treatment with study medication (days)	Medications listed at time of event	Comments	Rechallenge	Additional neuropsychiatric AE after "confusional state"
2249	0001	69	F	Confusion	12	1167	Glucosamine, Actonel	Had AE of light-headedness and muscular weakness prior to randomization. Experienced concurrent AEs of urinary hesitation, bronchitis, and blurred vision (levaquin)	No rechallenge, did not stop medication during AE	None
2324	0019			Confusion (SAE)	327	327	Levothyroid, Prozac, HCTZ, Losartan, Oxybutynin	Hospitalized due to joint pain exacerbation and confusion, and leukocytosis for 5 days. The subject showed signs of confusion when trying to explain to hospital staff about her study therapy. Study therapy was discontinued and the subject was started on lovastatin. Events noted in discharge summary included acute renal failure, bilateral Babinski signs, and possible small right posterior communicating aneurysm	No rechallenge, stopped medication during AE, no restart	
4010	0060	72	M	Confusion	250	246	Flovent, Ventolin, Metoprolol, Gravol (for N/V)	Brought to ER with back pain, tachycardia, and hypotension. Diagnosed with contained abdominal aneurysm rupture. Repair on Day 247, Concurrent AE of pneumonia on Day 250		
4048	0074	77	M	Confusion	377	725	Rivasa, Viagra, Prevacid, Prinivil, Efudex, Warfarin, Lanoxin, Diltiazem, Tapazole,	Hospitalized for the concurrent AE of pericarditis and pericardial effusion. Morphine listed as concurrent medication on same day as confusional state. Experienced a second AE of confusional state on Day 387 with concurrent AE of pericardial effusion which required hospitalization	No rechallenge, did not stop medication during AE	Additional episode of confusional state on treatment assocated with hospitalization
4099	0006	70	M	Confusion	454	1616	Dyazide, Ativan, Clonazepam	Concurrent AEs of depression, insomnia, anxiety, Parkinson's disease	No rechallenge did not stop medication	Anxiety/insomnia, depression
4141	0044	74	M	Confusion	Not on rosuva at time of event	302	Indocid, Norvasc, Meloxicam, Percocet, Tylenol #3	Off rosuvastatin at time of event. Experienced concurrent AE of muscle weakness, Percocet and Tylenol #3 for bilateral hip pain listed as concurrent medication on day of confusional state. AE reported 15 days later of diffuse large B-cell lymphoma	No rechallenge not on treatment at time of event	

Center	Subject ID	Age	Sex	Verbatim term as reported	Day of study event occurred	Overall duration of treatment with study medication (days)	Medications listed at time of event	Comments	Rechallenge	Additional neuropsychiatric AE after "confusional state"
5001	1388	62	M	Confusion is due to opioid use (SAE)	591	819	Morphine	Admitted to hospital due to pain at sternotomy wound and confusion secondary to increase opioid use. Condition improved after morphine stopped.	No rechallenge, did not stop medication during AE	
5007	0782	74	F	Confusion (SAE)	655	726	Nifedipine, ASA, Indapamide, erythromycin, amoxicillin	Patient admitted to hospital with mild confusion. Diagnosed with hyponatremia, hypokalemia secondary to thiazide diuretic and mild normocytic anemia, Investigations showed signs of UTI and weight loss	No rechallenge did not stop medication during AE , stopped medication 9 weeks after event	
5037	0069	76	M	Intermittent confusion	Not on treatment at time of event	79	Diclofenac, tramadol, paracetamol	Off treatment at time of event. Experienced TIA within 2 months of event	No rechallenge did not stop medication during AE	
6410	0023	81	M	Acute confusional state (SAE)	461	952	ASA	Hospitalized for acute confusional state, recovered. No neurological deficit or lab findings. Head CT normal. Study drug was continued. No concurrent AEs noted. Current illness of BPH, varicose veins, past med hx of osteoarthritis	No rechallenge did not stop medication during AE	
7154	0002	77	M	Acute syndrome confusional (SAE)	170	176	Amantadine, enalapril, ASA, Cardura, levothyroxine, ASA	Recently diagnosed with Parkinson's disease and had started amantadine. Hospitalized for acute confusional syndrome, presenting with visual hallucinations. Consulting neurologist felt the events were related to an increased dose of amantadine, while hospitalized diagnosed with nosocomial pneumonia and infective endocarditis prolonging hospitalization. Subject withdrew from study due to these events	No rechallenge, stopped medication during AE, no restart	
8487	0008	82	F	Confused (SAE)	396	396	Sertraline, paracetamol, thiamine, omeprazole, brotizolam	Hospitalized with fever, confusional state, died of multi-organ failure/septic shock	No restart/subject died	

Source: Applicant's Table 1 IR response 09 November 2009, Applicant's Table 4.1 IR response 5 January 2010

Overall the narratives for these cases are uninformative with respect to assessing drug causality. None of the cases had an appropriate dechallenge/rechallenge test as all subjects either continued the study medication during the adverse event or stopped the study medication permanently. The applicant's assessment of this imbalance and their review of the case narratives raised the possibility that confounding factors contributed to the "confusional state". However, randomized, placebo-controlled studies should eliminate or at least reduce the possibility of confounding factors preferentially affecting one treatment group over the other. It is quite possible and even expected that an equal number of subjects in the rosuvastatin and placebo groups had medical histories in which factors other than study drug treatment could be linked with "confusional state".

This gets to the issue of JUPITER not being designed to systematically examine neurocognitive function. The clinical significance of the imbalance is unclear, but given prior statin data, may represent a signal worthy of more rigorous evaluation and would apply to the statin drug class. This issue is currently under review by the Office of Surveillance and Epidemiology.

7.3.4.9 Metabolic adverse events

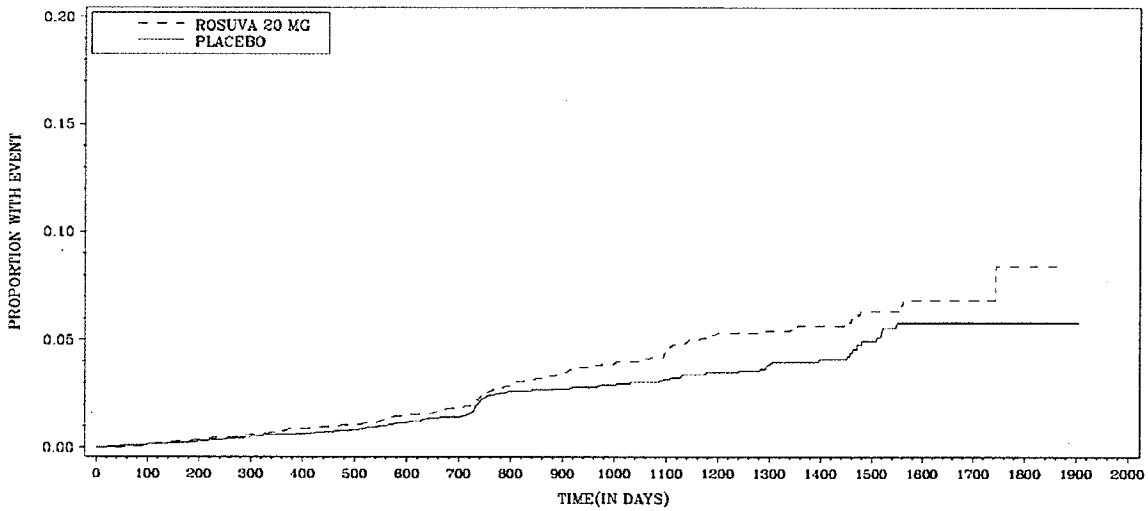
7.3.4.9.1 Investigator-reported diabetes mellitus

A prespecified, unadjudicated secondary endpoint was time to investigator-reported diabetes which was assessed every 3 months. In JUPITER there was a higher frequency of rosuvastatin-treated subjects (251/8901, 2.8%) reported with diabetes as compared to the placebo-treated subjects (205/8901, 2.3%) (Table 59, Figure 7).

Table 59: JUPITER: Summary and time to development of (investigator-reported) diabetes mellitus (without 30 March 2008 cutoff)

	Number of events (% of subjects having an event)						
	Rosuvastatin 20 mg N=8901		Placebo N=8901				
	n	%	n	%	HR	95% CI	p-value
Investigator reported diabetes	251	2.8	205	2.3	1.27	1.05, 1.53	0.015
Source: Applicant's Table 11.3.6.1.2.7 and 11.3.6.1.2.8, Pg 31998 and 31999, CSR							

Figure 7: JUPITER: Kaplan-Meier curve of time to investigator-reported diabetes (without 30 March 2008 cutoff) (ITT population)



Criteria used to qualify as new-onset diabetes was new use of insulin or an oral hypoglycemic agent, a positive glucose tolerance test, a random glucose level over 200 mg/dL with symptoms of diabetes, or repeated fasting glucose levels ≥126 mg/dL. The following table summarizes the criteria met for diabetes.

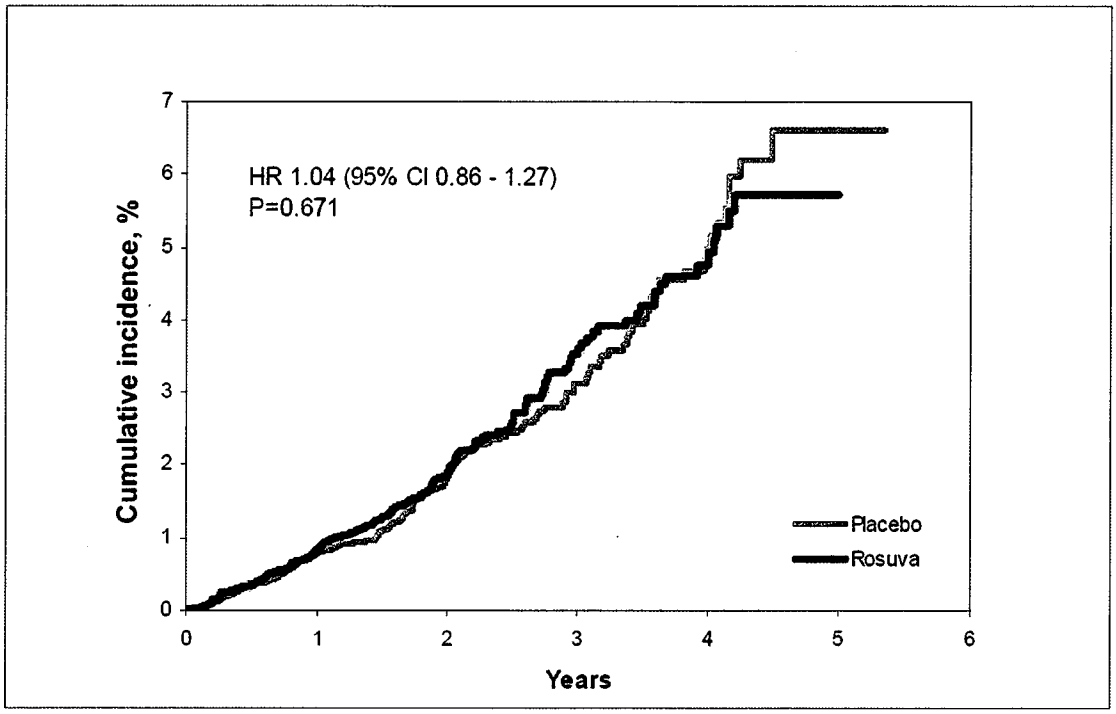
Table 60: JUPITER: Summary of criteria for investigator-reported diabetes (without 30 March 2008 cutoff) (ITT population)

Reason given for diabetes reported[a]	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)	Total N=17802 n (%)
Total incident cases of diabetes	251 (2.8)	205 (2.3)	456 (2.6)
New use of insulin	8 (3.2)	5 (2.4)	13 (2.9)
New use of oral hypoglycemic agent	122 (48.6)	106 (51.7)	228 (50.0)
Positive glucose tolerance test (>200 mg/dL)	55 (21.9)	38 (18.5)	93 (20.4)
Repeated fasting glucose ≥126 mg/dL	151 (60.2)	130 (63.4)	281 (61.6)
Random blood sugar ≥ 200 mg/dL	28 (11.2)	19 (9.3)	47 (10.3)
Other[b]	13 (5.2)	8 (3.9)	21 (4.6)

[a] More than one reason per person included in table
[b] Diagnosis made with criteria that was unspecified or different from listed reasons
Source: Table 11.3.6.1.2.12, Pg 32003, CSR

An analysis of time-to-first use of diabetic medication was performed including subjects with or without investigator-reported diabetes. There was no statistically significant difference between rosuvastatin and placebo treatment groups (Figure 8). It should be noted that use of antidiabetic medication was only one criteria for reporting diabetes.

Figure 8: Kaplan-Meier plot of time to use of diabetic medication



Source: Applicant's Figure 1, IR email 01 September 2009, Pg 6

The applicant defined diabetes-free survival as subjects who died from any cause or were reported with diabetes. The diabetes-free survival analysis was not statistically different between treatment groups (Table 61).

Table 61: Summary and time to diabetes or death (any cause) ITT population

	Number of events (% of subjects having an event)						
	Rosuvastatin 20 mg N=8901		Placebo N=8901				
	n	%	n	%	HR	95% CI	p-value
Diabetes or death due to any cause (without 30 March 2008 cutoff)	423	4.8	419	4.7	1.02	0.89, 1.17	0.742

Source: Applicant's Table 11.2.1.36.1-2, Pg 2932-3, CSR

It is the opinion of this reviewer that this analysis suggests a survivor-bias, meaning, the rosuvastatin-treated subjects experienced more diabetes because they lived longer than their placebo-treated counterparts. However, a rough calculation by the FDA statistical reviewer took the average of the diabetes incidence and applied the resulting overall incidence of 2.5% to the number of deaths in the rosuvastatin and placebo groups. This yielded an additional 6.2 cases in the placebo arm, and similarly 5 cases in the

rosuvastatin arm. Based on this calculation, the difference in survival between the two groups did not contribute to the imbalance in investigator-reported diabetes.
In a post hoc analysis, the applicant evaluated the baseline characteristics of the JUPITER cohort who developed investigator-reported diabetes versus those who did not. As expected subjects who developed investigator-reported diabetes were more likely to have a diagnosis of impaired fasting glucose, metabolic syndrome, and be overweight at baseline. However, overall, the JUPITER treatment groups were balanced at baseline with regard to metabolic syndrome, fasting glucose, and body mass index (BMI).

Table 62: Baseline characteristics of subjects with and without investigator-reported diabetes

	Diabetes		No diabetes	
	Rosuva 20 mg	**Placebo**	**Rosuva 20 mg**	**Placebo**
N	251	205	8650	8696
FSG ≥100 mg/dL, %	76.5	76.1	29.6	30.6
FSG (mean), mg/dL	107.3	108.8	94.3	94.6
BMI ≥25 kg/m^2, %	92.4	91.7	76.3	76.6
BMI (mean), kg/m^2	32.66	32.41	28.96	29.92
Weight (kg)	93.49	92.94	81.72	81.74
TG ≥150 mg/dL, %	57.0	51.7	31.9	32.5
Metabolic syndrome, %	77.7	79.0	40.0	41.0
Source: Applicant's Table 40, Pg 97, Table 11.3.8.1.13-14, Pg 79456-7, CSR				

The applicant reported that in the group with impaired fasting glucose (≥100 mg/dL) there was significant 34% reduction in time to first MCE (Table 63).

Table 63: JUPITER: Prespecified subgroup analysis of number of MCE in subjects with impaired fasting glucose at baseline (ITT population)

	Number of events				
	Rosuva 20 mg N=8901	**Placebo N=8901**			
	n	**n**	**HR**	**95% CI**	**p-value**
< 100 mg/dL	87	167	0.52	0.40, 0.67	0.257
≥ 100 mg/dL	55	84	0.66	0.47, 0.93	
Source: Applicant's Table 12.1.9.1.4.1, Pg 699, CSR					

Subjects in the rosuvastatin treatment group had slightly greater weight gain during the period of follow-up when compared to subjects in the placebo group (mean change 0.44 kg rosuvastatin vs 0.15 kg placebo) however, when separated by who developed diabetes and who did not this trend was not observed. Both the rosuvastatin and placebo treated subjects who developed diabetes had less weight gain compared to baseline than subjects who did not develop diabetes.

Table 64: JUPITER: Change in weight from baseline in those with and without development of diabetes

	Diabetes		No diabetes	
	Rosuvastatin 20 mg	Placebo	Rosuvastatin 20 mg	Placebo
Change in weight from baseline (kg)	0.10	-0.96	0.45	0.18
Source: Applicant's Table 40, Pg 97, Table 11.3.8.1.13-14, Pg 79456-7, CSR				

Fasting blood glucose and HbA1c was assessed at baseline, Year 2, annually, and at the final visit. There were no differences in fasting glucose levels between the two treatment groups. Overall there was a trend of increasing fasting glucose levels (increase of 3% mean change from baseline) in both groups. HbA1c levels rose in both groups, with a significantly different change from baseline of 0.08% percentage points between the two treatment groups.

Table 65: JUPITER: Fasting glucose and HBA1c 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	95 (11.5)	8878	95 (11.8)	0.134
Year 2	3520	100 (17.9)	3502	100 (18.0)	0.344
Year 3	1198	100 (19.3)	1140	99 (15.9)	0.137
Year 4	440	99 (15.3)	414	98 (15.5)	0.147
Final	7124	98 (19.7)	7002	98 (18.9)	0.442
Change in fasting glucose, mg/dL					
Baseline to Year 2	3515	5 (16.0)	3499	4 (16.2)	0.057
Baseline to Year 3	1197	4 (17.0)	1140	3 (14.2)	0.097
Baseline to Year 4	440	2 (13.1)	414	2 (14.1)	0.423
Baseline to Final	7104	3 (18.3)	6985	3 (17.6)	0.078
HbA1c, %					
Baseline	8856	5.7 (0.42)	8853	5.7 (0.45)	0.0014
Year 2	3514	5.9 (0.48)	3497	5.8 (0.47)	<0.0001
Year 3	1195	5.9 (0.46)	1134	5.8 (0.42)	<0.0001
Year 4	439	5.9 (0.49)	409	5.9 (0.43)	0.038
Final	7136	6.0 (0.50)	7054	6.0 (0.49)	<0.0001
Change in HbA1c, %					
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
Source: Applicant's Table 41-42, Pg 98-99, CSR					

As noted above, HbA1c was not considered criteria in investigator-reported diabetes nor a one-time occurrence of a fasting glucose ≥126 mg/dL. The applicant submitted tables summarizing subjects developing diabetes by treatment and visit using the criteria of HbA1c of >6.5%, the occurrence of fasting glucose ≥126 mg/dL at any time in the study, and either HbA1c >6.5% or fasting glucose ≥126 mg/dL. As shown below there was an imbalance showing a higher incidence in the rosuvastatin-treated group of developing

diabetes using HbA1c, fasting glucose levels, or either value. These numbers are also higher than the 251 and 205 cases of investigator-reported diabetes.

Table 66: Subjects developing diabetes using HbA1c >6.5% (ITT population)

	Rosuvastatin 20 mg N=8901		Placebo N=8901		p-value[a]
	N		N	n(%)	
Month 24	3474	326 (9.4)	3454	227 (6.6)	<0.001
Month 36	1184	113 (9.5)	1122	57 (5.1)	<0.001
Month 48	431	45 (10.4)	401	24 (6.0)	0.020
Final	7132	900 (12.6)	7054	653 (9.3)	<0.001

[a] Chi-square test comparing the distribution between treatments
Source: Table 11.3.6.1.2.4, Pg 31995 CSR

Table 67: Subjects developing diabetes using FSG ≥ 126 mg/dL at least once (ITT population)

	Rosuvastatin 20 mg N=8901		Placebo N=8901		p-value[a]
	N		N	n(%)	
Month 24	3486	180 (5.2)	3461	178 (5.1)	0.969
Month 36	1188	82 (6.9)	1129	58 (5.1)	0.075
Month 48	432	25 (5.8)	407	21 (5.2)	0.690
Final	7120	422 (5.9)	7000	374 (5.3)	0.151

[a] Chi-square test comparing the distribution between treatments
Source: Table 11.3.6.1.2.5, Pg 31996 CSR

Table 68: Subjects developing diabetes using HbA1c >6.5% or FSG ≥ 126 mg/dL at least once (ITT population)

	Rosuvastatin 20 mg N=8901		Placebo N=8901		p-value[a]
	N		N	n(%)	
Month 24	3500	405 (11.6)	3481	331 (9.5)	<0.001
Month 36	1192	152 (12.8)	1132	93 (8.2)	<0.001
Month 48	433	54 (12.5)	407	32 (7.9)	<0.001
Final	7196	1100 (15.3)	7102	855 (12.0)	<0.001

[a] Chi-square test comparing the distribution between treatments
Source: Table 11.3.6.1.2.6, Pg 31997 CSR

- Other data sources regarding diabetes and CRESTOR

The applicant reported that there was no statistically significant difference in diabetes reported as an AE in METEOR and CORONA, two long-term, placebo-controlled studies of rosuvastatin. The agency asked for the analysis to support the above statement. The results of this analysis included information from an additional long-term **placebo-controlled trial, AURORA. The three trials' databases were searched for** diabetes-related adverse events. Of note, CORONA and AURORA did not exclude subjects based on the presence of impaired fasting glucose or diabetes mellitus and fasting plasma glucose or HbA1c levels were not obtained during these studies.

The search of the databases for diabetes-related adverse events used all of the SMQ terms in the narrow list of hyperglycemia/new onset diabetes mellitus preferred terms and selected preferred terms from the broad list of Version 11.1. See Appendix 9A and 9B for the complete list.

The following table lists the mean fasting glucose levels at baseline and at final visit in the METEOR and JUPITER trials. There are no large differences between the treatment and placebo groups in either trial.

Table 69: Fasting glucose levels at baseline and final visit, METEOR and JUPITER trials (Safety and ITT population, respectively)

	METEOR		JUPITER	
Fasting glucose, mg/dL	**Rosuvastatin 40 mg N=700**	**Placebo N=281**	**Rosuvastatin 20 mg N=8901**	**Placebo N=8901**
Baseline (Week 0)	**N=640**	**N=254**	**N=8875**	**N=8878**
Mean	95	97	95	95
Standard deviation	12.2	14.4	11.5	11.8
Min	61	67	40	39
Max	211	236	175	223
Final	**N=520**	**N=207**	**N=7124**	**N=7002**
Mean	99	99	98	98
Standard deviation	14.9	14.9	19.7	18.9
Min	67	74	14	12
Max	220	202	552	401
Applicant's Table 11.3.7.1.3.1, Pg 71656, JUPITER CSR, Table 1, Pg 5 IR request email 21 August 2009				

The following table lists the number, frequency, and statistical significance of treatment-emergent diabetes-related adverse events in METEOR, CORONA, AURORA, and JUPITER. Only JUPITER had a significant difference against rosuvastatin in frequency of diabetes-related events. However, when the data listed in Table 70 regarding diabetic-related AE was combined from the 3 trials and JUPITER to estimate relative risk and the 95% confidence interval by the Mantel-Haenszel approach, the relative risk is 1.18 (95% CI 1.04, 1.34) suggesting there is an 18% risk of developing a diabetes-related AEs in rosuvastatin-exposed subjects versus unexposed subjects (Table 71, Figure 9).

Table 70: Number and frequencies of treatment-emergent diabetes-related adverse events during the treatment phase in METEOR, CORONA, AURORA, and JUPITER trials

	METEOR p-value[a] = 0.0431		**CORONA (randomized pop) p-value = 0.6437**		**AURORA (randomized pop) p-value = 0.9006**		**JUPITER (randomized pop) p-value = 0.002**	
MedDRA preferred term	**Rosuva 40 mg N=701 n (%)**	**Placebo N=282 n (%)**	**Rosuva 10 mg N=2416 n (%)**	**Placebo N=2405 n (%)**	**Rosuva 10 mg N=1003 n (%)**	**Placebo N=1042 n (%)**	**Rosuva 20 mg N=8901 n (%)**	**Placebo N=8901 n (%)**
Any diabetic AE	**8 (1.1)**	**8 (2.8)**	**139 (5.8)**	**131 (5.4)**	**21 (2.1)**	**21 (2.0)**	**448 (5.0)**	**361 (4.1)**

	METEOR p-value[a] = 0.0431		CORONA (randomized pop) p-value = 0.6437		AURORA (randomized pop) p-value = 0.9006		JUPITER (randomized pop) p-value = 0.002	
MedDRA preferred term	**Rosuva 40 mg N=701 n (%)**	**Placebo N=282 n (%)**	**Rosuva 10 mg N=2416 n (%)**	**Placebo N=2405 n (%)**	**Rosuva 10 mg N=1003 n (%)**	**Placebo N=1042 n (%)**	**Rosuva 20 mg N=8901 n (%)**	**Placebo N=8901 n (%)**
Diabetes mellitus	1 (0.1)	4 (1.4)	84 (3.5)	82 (3.4)	6 (0.6)	11 (1.1)	237 (2.7)	186 (2.1)
Blood glucose increased	5 (0.7)	1 (0.4)	12 (0.5)	14 (0.6)	0	2 (0.2)	82 (0.9)	50 (0.6)
Glucose tolerance impaired	0	0	5 (0.2)	2 (0.1)	2 (0.2)	1 (0.1)	41 (0.5)	42 (0.5)
Glycosylated hemoglobin increased	0	0	0	2 (0.1)	0	0	41 (0.5)	21 (0.2)
Hyperglycemia	1 (0.1)	0	21 (0.9)	19 (0.8)	8 (0.8)	2 (0.2)	28 (0.3)	28 (0.3)
Glycosuria	0	0	0	0	0	0	27 (0.3)	32 (0.4)
Impaired fasting glucose	0	0	0	0	0	0	13 (0.1)	21 (0.2)
Blood glucose abnormal	0	0	1 (<0.1)	1 (<0.1)	0	0	4 (<0.1)	4 (<0.1)
Polyuria	0	1 (0.4)	2 (0.1)	0	0	0	4 (<0.1)	3 (<0.1)
Ketonuria	0	1 (0.4)	0	0	0	0	3 (<0.1)	5 (0.1)
Metabolic syndrome	0	0	1 (<0.1)	0	0	0	3 (<0.1)	4 (<0.1)
Thirst	1 (0.1)	0	1 (<0.1)	1 (<0.1)	2 (0.2)	1 (0.1)	3 (<0.1)	2 (<0.1)
Glucose tolerance test abnormal	0	0	0	0	0	0	1 (<0.1)	0
Insulin resistance	0	0	0	0	0	0	1 (<0.1)	1 (<0.1)
Polydipsia	0	1 (0.4)	1 (<0.1)	0	0	0	0	2 (<0.1)
Diabetes mellitus inadequate control	0	0	19 (0.8)	18 (0.7)	0	1 (0.1)	0	0
Diabetic ketoacidosis	0	0	1 (<0.1)	0	0	1 (0.1)	0	0
Hyperglycemic hyperosmolar nonketotic	0	0	1 (<0.1)	0	0	0	0	0
Glucose urine present	0	0	0	1 (<0.1)	0	0	0	0
Type 2 diabetes mellitus	0	0	0	0	4 (0.4)	4 (0.4)	0	0

[a] p-value calculated by chi-square test
Source: Applicant's Tables 2, 3, 4 Pg 5-7 IR response 21 August 2009 and 10 September 2009

Figure 9: Forest plot of METEOR, CORONA, AURORA, and JUPITER diabetes-related AE data*

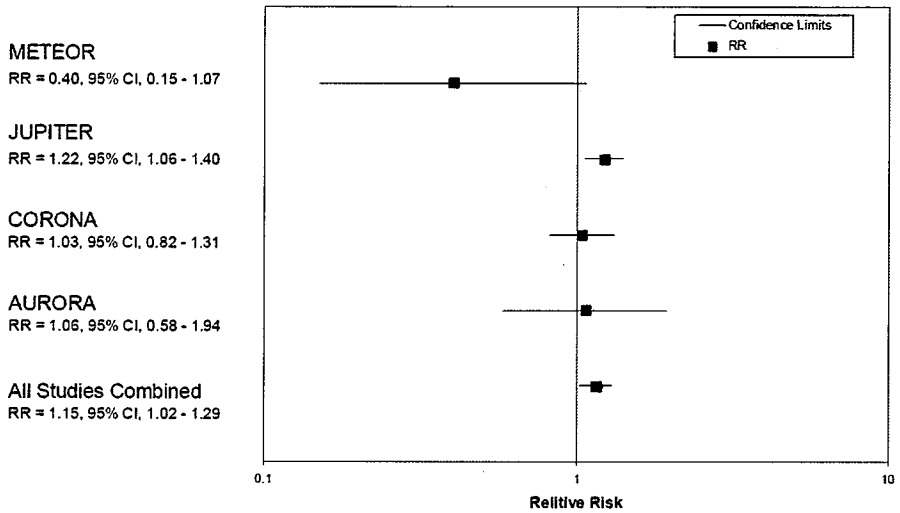


***Figure not corrected for Errata in CORONA analysis see Table 71 for corrected CORONA and all studies combined numbers**

Table 71: Corrected results of Mantel Haenszel analysis of diabetes-related adverse events for rosuvastatin placebo-controlled trials

Trial	Hazard ratio (95% CI)
JUPITER	1.22 (1.06, 1.40)
METEOR	0.40 (0.15, 1.07)
CORONA	1.14 (0.82, 1.58)
AURORA	1.06 (0.58, 1.94)
All trials combined	**1.18 (1.04, 1.34)**
Source: Applicant briefing book Errata list, Pg 4 (reference to Page 75)	

Additional analysis done by the applicant included evaluating the FDA Adverse Event Reporting System (AERS) database for potential signals related to diabetes and statin use.

Using the Empirica Signal 7.0 data mining tool reports through 2Q2008 were analyzed in all marketed statins (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, simvastatin, and rosuvastin).

The following table lists the results of two data mining runs. The first reported when a statin was considered a suspect medication and another reports when the statin was

considered either a suspect or concomitant medication. The applicant used the EB05 score of ≥ 1.8 as the threshold for a potential safety signal. Only preferred terms for which there was at least one drug-event combination with an EB05 ≥ 1.8 are shown.

While the applicant points out that there are no preferred terms related to diabetes with an EB05 ≥ 1.8 for rosuvastatin, this does not necessarily exclude this statin from the possibility of altered glucose metabolism. These results are crude counts and the denominators are unknown. Data mining serves a purpose for generating hypotheses but is extremely limited in excluding safety concerns.

Table 72: Applicant data-mining of AERS database for diabetes-related terms

	Suspect		Suspect of concomitant	
MedDRA PT **Statins**	**n**	**EB05**	**n**	**EB05**
Diabetes mellitus				
Lovastatin	76	2.260	128	1.510
Atorvastatin	377	1.686	829	1.400
Pravastatin	50	0.877	174	1.046
Simvastatin	76	0.610	409	1.009
Fluvastatin	12	0.526	60	1.218
Rosuvastatin	24	0.235	59	0.454
Pitavastatin	0	NA	1	0.273
Diabetes mellitus inadequate control				
Atorvastatin	70	0.913	341	1.871
Simvastatin	32	0.688	197	1.516
Pitavastatin	1	0.307	4	1.264
Pravastatin	14	0.583	71	1.192
Rosuvastatin	17	0.686	33	1.126
Lovastatin	0	NA	22	1.063
Fluvastatin	1	0.063	15	0.742
Glucose tolerance impaired				
Atorvastatin	26	2.525	59	2.179
Simvastatin	5	0.555	20	0.927
Fluvastatin	1	0.225	1	0.291
Rosuvastatin	2	0.175	2	0.222
Pravastatin	1	0.139	7	0.679
Lovastatin	0	NA	2	0.418
Overweight				
Atorvastatin	11	2.125	19	1.572
Simvastatin	3	0.610	8	0.855
Rosuvastatin	2	0.315	4	0.700
Pravastatin	1	0.221	3	0.582
Fluvastatin	0	NA	2	0.631
Type 2 diabetes mellitus				
Atorvastatin	55	1.441	211	1.935

	Suspect		Suspect of concomitant	
MedDRA PT Statins	**n**	**EB05**	**n**	**EB05**
Simvastatin	21	0.870	112	1.455
Lovastatin	1	0.152	17	1.295
Pravastatin	5	0.358	40	1.288
Fluvastatin	2	0.257	7	0.600
Rosuvastatin	3	0.072	18	0.486
Source: Applicant's Table 3, Pg 8, IR email 01 September 2009				

- Conclusions regarding diabetes events:

Based on the available clinical evidence it appears that as a drug class statins increase the incidence of diabetes mellitus. However, there are no prospective clinical trials with an adjudicated predefined endpoint of diabetes incidence examining the relationship between statin use and diabetes incidence and resulting complications of hyperglycemia induced microvascular disease. It is well established that people with diabetes are at high risk for major cardiovascular events and are more likely to die due to a cardiovascular event. Large clinical trials have demonstrated that with and without clinically evident cardiovascular disease statins provide a significant treatment benefit in people with diabetes.[26,27] In JUPITER, 31% of study subjects were diagnosed with impaired fasting glucose at baseline and within this subgroup a treatment benefit was observed [HR 0.66 (95% CI 0.47, 0.93)]. However, the JUPITER trial was relatively short in its treatment duration (median 1.9 years) and therefore the long-term **complications are unknown. At this time, it is this clinical reviewer's opinion that the** treatment benefit observed in the JUPITER trial outweighs the risk, but further clinical trials are needed to further define this benefit/risk ratio.

7.3.5 Submission Specific Primary Safety Concerns

None

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The following table provides an overview of the frequency of different categories of treatment-emergent adverse events in JUPITER. The proportion of subjects who had

26 Collins et al. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomized placebo-controlled trial. Lancet 2003;361:2005-16.
27 Calhoun et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicenter randomized placebo-controlled trial. Lancet 2004; 364:685-96.

any adverse event, any event leading to death, or withdrawal, or any serious adverse event was similar between the treatment groups.

Table 73: JUPITER: Overview of frequency of treatment-emergent adverse event categories (ITT population)

Event category	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)
Any adverse event	6968 (78.3)	6907 (77.6)
AE leading to death	141 (1.6)	179 (2.0)
Withdrawals due to AE (DAE)	143 (1.6)	158 (1.8)
Serious AE (SAE)	1341 (15.1)	1372 (15.4)
Source: Applicant's Table 11.3.2.1.2.2, Pg 4587 CSR JUPITER		

The most common treatment-emergent adverse events by preferred term occurring with a frequency of ≥2% in the rosuvastatin treatment group are listed below.

Table 74: JUPITER: The most common treatment-emergent adverse events occurring with a frequency of ≥ 2%

Preferred term	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)
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)
Diarrhea	417 (4.7)	406 (4.6)
Influenza	357 (4.0)	324 (3.6)
Sinusitis	356 (4.0)	332 (3.7)
Arthralgia	341 (3.8)	287 (3.2)
Headache	338 (3.8)	356 (4.0)
Edema peripheral	329 (3.7)	263 (3.0)
Fatigue	325 (3.7)	311 (3.5)
Muscle spasms	318 (3.6)	282 (3.2)
Dizziness	308 (3.5)	352 (4.0)
Constipation	294 (3.3)	263 (3.0)
Musculoskeletal pain	281 (3.2)	297 (3.3)
Diabetes mellitus	267 (3.0)	222 (2.5)
Lower respiratory tract infection	254 (2.9)	244 (2.7)
Insomnia	226 (2.5)	208 (2.3)
Abdominal pain	224 (2.5)	227 (2.6)
Rash	219 (2.5)	222 (2.5)
Nausea	218 (2.4)	202 (2.3)

Preferred term	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)
Hematuria	216 (2.4)	181 (2.0)
Dyspepsia	212 (2.4)	226 (2.5)
Pneumonia	199 (2.2)	242 (2.7)
Non-cardiac chest pain	196 (2.2)	209 (2.3)
Pharyngitis	195 (2.2)	198 (2.2)
Anemia	192 (2.2)	183 (2.1)
Pain in extremity	191 (2.1)	183 (2.1)
Gastroesophageal reflux disease	190 (2.1)	226 (2.5)
Depression	184 (2.1)	214 (2.4)
Cataract	180 (2.0)	196 (2.2)
Source: Applicant's Table 11.3.2.1.3.1, Pg 4650 CSR JUPITER		

7.4.2 Laboratory Findings

7.4.2.1 Overview of laboratory testing in the development program

In JUPITER, ALT and a urinalysis was performed at the screening visit, safety visit (3-months post randomization), and every 6 months after randomization until the final visit. Creatinine kinase was checked at the screening visit and at the final visit. Serum creatinine was checked at the screening visit, 12 month visit, and final visit. Fasting serum glucose and HbA1c was checked at the screening visit, Year 2, then annually, and at final visit. A complete blood count was performed at the screening visit and final visit. Laboratory values corresponding to hepatic, skeletal, renal, and metabolic adverse events of interest are included in the previous Sections 7.3.4.2, 7.3.4.4, 7.3.4.6, and 7.3.4.9, respectively.

7.4.2.2 Hematology

Both groups experienced a decrease in platelet counts from baseline, however rosuvastatin-treated subjects saw a larger drop consistent with similar changes seen in previous clinical trials.

Table 75: Mean decrease in platelet count in JUPITER and recent clinical trials from baseline

	Rosuvastatin treated					Placebo treated	
	JUPITER 20 mg ($x10^9$/L)	METEOR 40 mg ($x10^9$/L)	ASTEROID 40 mg ($x10^9$/L)	ORION 5 mg ($x10^9$/L)	ORION 40/80 mg ($x10^9$/L)	JUPITER ($x10^9$/L)	METEOR ($x10^9$/L)
Mean change in platelet count from baseline	-20.1	-27	-7	-9	-34	-7	-4
Source: Applicant's Table 11.3.7.1.1.5, Pg 71465 CSR JUPITER Supplement 010, Section 7.7.3.1.4, Pg 49, FDA clinical review							

Further analysis of the drop in platelet count characterized the number of subjects with platelet counts <$50x10^9$/L and <$100x10^9$/L. There were 17 subjects with platelet counts

<100x10^9/L in the rosuvastatin group compared with 13 in the placebo group. Of these, two of the rosuvastatin-treated subjects reported bleeding AEs; one with a final platelet count of 92x10^9/L had a hematoma, and another rosuvastatin-treated subject with a final platelet count of 91x10^9/L had a hemorrhoidal hemorrhage. These adverse events were not considered serious.

Three rosuvastatin-treated subjects versus one placebo-treated subject had a platelet count <50x10^9/L at the final visit. It should be noted that the placebo-treated subject had a low platelet count only at the screening visit whereas the rosuvastatin-treated subjects had normal platelet levels at screening and significantly abnormal ones at the final visit. Of these three subjects, subject 7026-0008 experienced the SAE of worsening of bone marrow dysplasia which was treated with folic acid. The other two subjects did not report any AEs associated with thrombocytopenia. According to the applicant no follow-up information is available.

Table 76: Listing of JUPITER subjects with platelet count <50x10^9/L

Subject ID	Treatment	Sex	Visit week	Days from randomization	Platelet (10^9/L)	Adverse events
5587-0007	Rosuva	F	Week -4	-31	191	Hypertension
			Final visit	665	5	Dry cough
5587-0045	Rosuva	F	Week-4	-28	161	None reported
			Final visit	577	10	
7026-008	Rosuva	M	Week-4	-28	316	Worsening bone marrow dysplasia (Day 447)
			Final visit	708	32	

Source: Applicant's Table 11.3.7.2.23.1, Pg 77945 CSR JUPITER

There was an equal frequency of blood and lymphatic system disorders AEs in the two treatment groups (3.3% rosuvastatin and placebo). The preferred term of thrombocytopenia occurred in a slightly higher number of rosuvastatin subjects 14 (0.2%) or 82/100,000 person-years versus placebo subjects 10 (0.1%) 60/100,000 person-years (Table 11.3.2.1.3.3). There were no incidences of thrombocytopenic purpura in the rosuvastatin group and one in the placebo group.

Thrombocytopenia is listed in the current CRESTOR label as a rare event (<1%) as part **of a "hypersensitivity reaction"; it is kept under review by the applicant and is reported in** the periodic safety report. In the PSUR covering the time period 07 November 2007 to 06 November 2008 a review of all global patient safety AE reports of **"thrombocytopenia/platelet count decreased" was performed. During this period, there** were 19 medically confirmed spontaneous reports (7 serious, 12 non-serious) and seven nonmedically confirmed spontaneous reports (1 serious, 6 non-serious) of **"thrombocytopenia/platelet count decreased".**

Of the 19 medically confirmed reports, none had a positive rechallenge, however no details of whether rosuvastatin was reinstated were given. Nine individuals had a positive dechallenge, three had a negative dechallenge, and seven lacked sufficient information to assess rechallenge/dechallenge testing. Only one of the reports was

from the United States. The majority of the reports occurred at the 2.5 mg does 8/19 (42%). The challenge of post-marketing reports is the lack of sufficient information and confounding factors, such as concomitant therapies which make a conclusion about the relationship between rosuvastatin and thrombocytopenia difficult.

7.4.3 Vital Signs

Vital signs data, including systolic blood pressure, diastolic blood pressure, and pulse rate were recorded at baseline and at the final visit.

There were no clinically relevant changes in vital signs over time in JUPITER.

7.4.4 Electrocardiograms (ECGs)

Not applicable

7.4.5 Special Safety Studies/Clinical Trials

Not applicable

7.4.6 Immunogenicity

Not applicable

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Uniform dosing of 20 mg rosuvastatin was administered to all JUPITER subjects and therefore dose dependency for adverse events cannot be assessed.

7.5.2 Time Dependency for Adverse Events

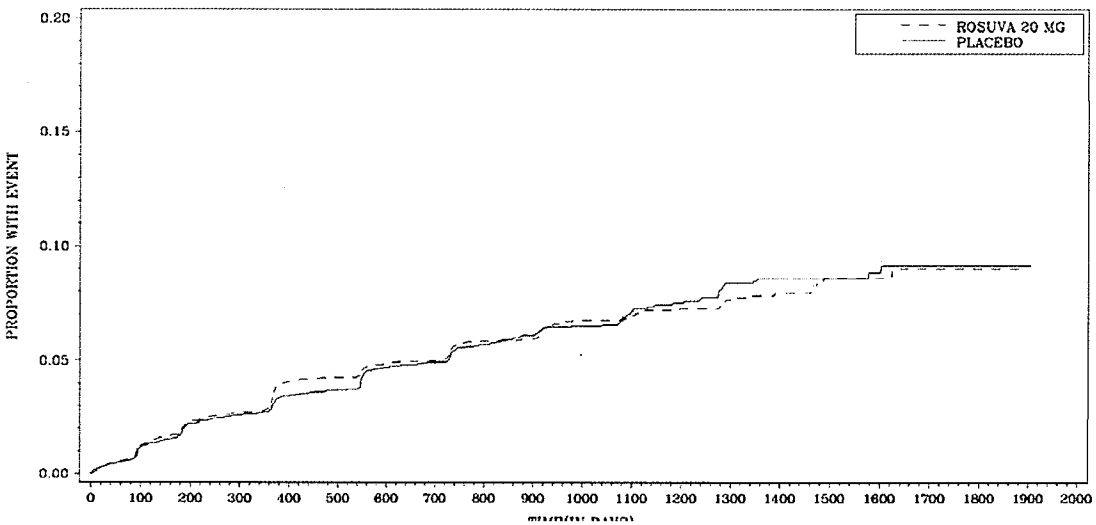
A secondary outcome endpoint was time to discontinuation of study medication due to an adverse event. The time to discontinuation of study medication was similar between both groups (p=0.758).

Table 77: JUPITER: Time to discontinuation of study medication due to an adverse event (ITT population)

Time to first event (days)	**Rosuvastatin 20 mg N=8901**	**Placebo N=8901**
Mean	1537.6	1517.6
Min	1	1
Max	1879	1904

Source: Applicant's Table 11.3.5.1.3.1, Pg 26229, JUPITER CSR

Figure 10: Kaplan-Meier curve for discontinuations of study medication due to adverse events



7.5.3 Drug-Demographic Interactions

7.5.3.1 Effect of gender

The overall frequency of AEs was similar for both men and women in the rosuvastatin (78.9% and 77.3%, respectively) and placebo groups (78.8% and 75.6%, respectively). The most common AEs for men receiving rosuvastatin were back pain (7.7%), nasopharyngitis (7.7%), and myalgia (7.5%). The most common AEs for women receiving rosuvastatin were urinary tract infection (15.1%), bronchitis (8.1%), and myalgia (7.8%).

7.5.3.2 Effect of age

There was similar frequency of AEs between the rosuvastatin and placebo groups in subjects ≤65 years and >65 years. In subjects who were ≥70 years old (32%), there was a similar frequency of overall AEs between the groups (81.1% versus 80.1%, respectively).

7.5.3.3 Effect of ethnicity

Approximately 1.6% of the overall JUPITER study population reported Asian ethnicity. The overall frequency of AEs was similar for Asian subjects in the rosuvastatin and placebo groups (64.6% versus 64.0%, respectively). There was a slightly higher proportion of AEs leading to death and serious AEs in rosuvastatin-treated Asian

subjects compared to placebo-treated Asian subjects. There were seven (4.8%) AEs leading to death versus two (1.5%) in the rosuvastatin and placebo groups, respectively. There were 21 (14.3%) SAEs versus eight (5.9%) in the rosuvastatin and placebo groups, respectively. It is currently recommended in the CRESTOR label that Asian subjects start at a daily CRESTOR dose of 5 mg, based on pharmacokinetic studies which have demonstrated an approximate 2-fold increase in median exposure to rosuvastatin in Asian subjects when compared with Caucasian controls.

7.5.3.4 Effect of LDL <50 mg/dL

The safety profile was similar in subjects who had an LDL-C <50 mg/dL at any point during JUPITER. Of subjects with a LDL-C <50 mg/dL, rosuvastatin-treated subjects had 630/4154 (15.2%) treatment emergent SAE versus 51/232 (22%) in placebo-treated subjects (Applicant Table 11.3.4.1.2.7, Pg 8679, JUPITER CSR).

7.5.4 Drug-Disease Interactions

7.5.4.1 Effect of hypertension at baseline

The frequency of AEs was similar for hypertensive subjects in the rosuvastatin and placebo groups (78.0% and 77.1%, respectively).

7.5.4.2 Effect of renal impairment (<60 ml/min/1.73 m^2)

Approximately 18% of JUPITER subjects had a eGFR of <60 ml/min/1.73 m^2 qualifying as renally impaired. Overall frequency of AEs were similar between the two groups (82.7% and 83.6%, rosuvastatin and placebo, respectively).

7.5.5 Drug-Drug Interactions

7.5.5.1 Vitamin K antagonist anticoagulants

Previous clinical pharmacology studies have shown that rosuvastatin therapy potentiates warfarin therapy. It is currently recommended that INR be monitored both at initiation or cessation of therapy with rosuvastatin or after a dose adjustment in order to detect changes in INR values. JUPITER did not routinely monitor INR nor prothrombin time values.

The frequency of "Any AE" were similar for subjects receiving a vitamin K antagonist anticoagulant in the rosuvastatin and placebo groups (93.8% and 93.1%, respectively).

7.5.5.2 Gemfibrozil

Gemfibrozil was a disallowed medication due to its known treatment interaction of significantly increasing rosuvastatin concentrations. In JUPITER, 50 subjects (20 rosuvastatin and 30 placebo) received gemfibrozil during the study. Among these **subjects the frequencies of "any AE" were similar (100.0% and 96.7%, rosuvastatin and** placebo, respectively). Myalgia was the most common musculoskeletal AE, occurring in six subjects in each group.

7.5.5.3 Cyclosporine

Cyclosporine was a disallowed medication due to its known treatment interaction of significantly increasing rosuvastatin concentrations. Four subjects (two rosuvastatin and two placebo) received cyclosporine. All experienced an adverse event. The numbers are too small to draw any conclusions regarding cyclosporine use and adverse events in the JUPITER trial.

7.5.5.4 Lopinavir/Ritonavir

Protease inhibitors are not recommended for use concomitantly with rosuvastatin due the increase in plasma concentrations of rosuvastatin with coadministration. No subjects in JUPITER received lopinavir/ritonavir.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

A meta-analysis published in 2007 described an inverse relationship between low LDL-C achieved with statin treatment and the risk of newly diagnosed cancer.[28] A higher incidence of cancer and cancer death was observed in subjects taking the combination of ezetimibe/simvastatin in the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial.[29] In JUPITER, only one rosuvastatin-treated subject had ezetimibe as a concomitant medication. Recently a large-scale record-linkage study did not find an association between statin use and the incidence of cancer.[30]

7.6.1.1 Fatal events due to cancer

In JUPITER, there were a smaller number of Neoplasm treatment-emergent adverse events leading to death in the rosuvastatin group (40/8901, 0.4%) versus the placebo group (65/8901, 0.7%). Overall, however, neoplastic adverse events were the leading

28 Alsheikh-Ali et al. Effect of the magnitude of lipid lowering on risk of elevated liver enzymes, rhabdomyolysis, and cancer. JACC 2007; 50:409-18
29 Rossebo et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. NEJM 2008;359:1343-56
30 Haukka et al. Incidence of cancer and statin usage-record linkage study. Int J Cancer 2009

cause of death in both treatment groups. A similar pattern was also seen with Neoplasm SAEs. The following two tables list the number and frequency of treatment-emergent adverse events leading to death and serious adverse events in the Neoplasm SOC.

Table 78: Number and percentage of subjects with TEAE leading to death in the Neoplasm SOC (ITT population)

System organ class Preferred Term	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)
Neoplasms benign, malignant, and unspecified (includes cysts and polyps)	**40 (0.4)**	**65 (0.7)**
Respiratory		
Bronchial carcinoma	3 (<0.1)	0
Lung neoplasm malignant	3 (<0.1)	8 (0.1)
Lung cancer metastatic	2 (<0.1)	2 (<0.1)
Non-small cell lung cancer	1 (<0.1)	1 (<0.1)
Small cell lung cancer stage unspecified	1 (<0.1)	3 (<0.1)
Mesothelioma	1 (<0.1)	0
Lung adenocarcinoma	0	1 (<0.1)
Lung adenocarcinoma metastatic	0	2 (<0.1)
Lung neoplasm	0	2 (<0.1)
Lung squamous cell carcinoma stage unspecified	0	1 (<0.1)
Small cell lung cancer metastatic	0	1 (<0.1)
Gastrointestinal/Hepatic		
Gastrointestinal carcinoma	2 (<0.1)	2 (<0.1)
Esophageal carcinoma	2 (<0.1)	1 (<0.1)
Pancreatic carcinoma	2 (<0.1)	2 (<0.1)
Colon cancer	1 (<0.1)	3 (<0.1)
Colon cancer metastatic	1 (<0.1)	3 (<0.1)
Esophageal adenocarcinoma	1 (<0.1)	1 (<0.1)
Oropharyngeal cancer stage unspecified	1 (<0.1)	0
Bile duct cancer recurrent	0	1 (<0.1)
Colon neoplasm	0	1 (<0.1)
Gastric cancer	0	1 (<0.1)
Gastrointestinal cancer metastatic	0	1 (<0.1)
Gastro-esophageal cancer	0	1 (<0.1)
Hepatic cancer metastatic	0	1 (<0.1)
Hepatic neoplasm malignant	0	1 (<0.1)
Metastases to liver	0	1 (<0.1)
Metastatic gastric cancer	0	1 (<0.1)
Esophageal cancer metastatic	0	2 (<0.1)
Pancreatic carcinoma metastatic	0	3 (<0.1)
Pancreatic neoplasm	0	1 (<0.1)
Pharyngeal cancer stage unspecified	0	1 (<0.1
Tongue neoplasm malignant stage unspecified	0	1 (<0.1)
Brain		
Brain neoplasm	2 (<0.1)	0
Astrocytoma	0	1 (<0.1)

System organ class Preferred Term	Rosuvastatin 20 mg N=8901 n (%)	Placebo N=8901 n (%)
Astrocytoma malignant	0	1 (<0.1)
Glioma	0	1 (<0.1)
Hematologic		
Acute leukemia	2 (<0.1)	0
Multiple myeloma	2 (<0.1)	2 (<0.1)
Acute myeloid leukemia	1(<0.1)	0
Myeloid leukemia	1 (<0.1)	0
Non-Hodgkin's lymphoma	1 (<0.1)	0
Skin		
Metastatic malignant melanoma	2 (<0.1)	0
Metastatic squamous cell carcinoma	0	1 (<0.1)
Renal		
Renal cancer metastatic	1 (<0.1)	0
Renal cell carcinoma	1 (<0.1)	1 (<0.1)
Metastatic renal cell carcinoma	0	2 (<0.1)
Renal neoplasm	0	1 (<0.1)
Reproductive/GU/Breast		
Uterine cancer	1 (<0.1)	0
Breast cancer metastatic	0	1 (<0.1)
Ovarian cancer	0	1 (<0.1)
Prostate cancer metastatic	0	1 (<0.1)
Endocrine		
Adenocarcinoma	1 (<0.1)	0
Neuroendocrine carcinoma	0	1 (<0.1)
Soft tissue/smooth muscle		
Leiomyosarcoma metastatic	1 (<0.1)	0
Sarcoma	0	1 (<0.1)
General		
Metastatic neoplasm	2 (<0.1)	0
Neoplasm malignant	1 (<0.1)	2 (<0.1)
Source: Applicant's Table 11.3.3.1.2.3, Pg 5604, CSR JUPITER		

Table 79: Number and percentage of subjects with treatment-emergent SAE in the Neoplasm SOC (ITT population)

System organ class	Event	Rosuva 20 mg N=8901 n(%)	Placebo N=8901 n(%)
Neoplasms benign, malignant, and unspecified (includes cysts and polyps)		286 (3.2)	306 (3.4)
	Prostate cancer	37 (0.4)	41 (0.5)
	Breast cancer	21 (0.2)	24 (0.3)
	Colon cancer	21 (0.2)	25 (0.3)
	Basal cell carcinoma	12 (0.1)	6 (0.1)
	Lung neoplasm malignant	12 (0.1)	6 (0.1)
	Non-Hodgkin's lymphoma	**9 (0.1)**	**3 (0.0)**
	Bladder cancer	6 (0.1)	9 (0.1)

System organ class	Event	Rosuva 20 mg N=8901 n(%)	Placebo N=8901 n(%)
	Endometrial cancer	6 (0.1)	1 (0.0)
	Non-small cell lung cancer	6 (0.1)	2 (0.0)
	Bronchial carcinoma	5 (0.1)	0
	Gastrointestinal carcinoma	5 (0.1)	5 (0.1)
	Lung adenocarcinoma	5 (0.1)	3 (0.0)
	Pancreatic carcinoma	5 (0.1)	6 (0.1)
	Renal cell carcinoma	5 (0.1)	6 (0.1)
	Squamous cell carcinoma of skin	5 (0.1)	0
	Gastric cancer	4 (0.0)	4 (0.0)
	Lung cancer metastatic	4 (0.0)	3 (0.0)
	Lymphoma	4 (0.0)	3 (0.0)
	Malignant melanoma	4 (0.0)	4 (0.0)
	Transitional cell carcinoma	4 (0.0)	1 (0.0)
	Uterine cancer	4 (0.0)	0
	Breast cancer in situ	3 (0.0)	1 (0.0)
	Colon neoplasm	3 (0.0)	1 (0.0)
	Lung squamous cell carcinoma stage unspecified	3 (0.0)	2 (0.0)
	Metastatic malignant melanoma	3 (0.0)	0
	Metastatic neoplasm	3 (0.0)	0
	Multiple myeloma	3 (0.0)	3 (0.0)
	Acute leukemia	2 (0.0)	0
	Bladder neoplasm	2 (0.0)	7 (0.1)
	Brain neoplasm	2 (0.0)	0
	Chronic lymphocytic leukemia	2 (0.0)	2 (0.0)
	Colon adenoma	2 (0.0)	2 (0.0)
	Hepatic cancer metastatic	2 (0.0)	1 (0.0)
	Hepatic neoplasm malignant	2 (0.0)	2 (0.0)
	Lung neoplasm	2 (0.0)	7 (0.1)
	Meningioma	2 (0.0)	1 (0.0)
	Metastases to bone	2 (0.0)	2 (0.0)
	Metastases to liver	2 (0.0)	1 (0.0)
	Myelodysplastic syndrome	2 (0.0)	0
	Myeloid leukemia	2 (0.0)	0
	Esophageal adenocarcinoma	2 (0.0)	1 (0.0)
	Ovarian cancer	2 (0.0)	5 (0.1)
	Pituitary tumor benign	2 (0.0)	0
	Renal cancer	2 (0.0)	1 (0.0)
	Renal cancer metastatic	2 (0.0)	0
	Squamous cell carcinoma	2 (0.0)	1 (0.0)
	Thyroid neoplasm	2 (0.0)	1 (0.0)
	Ureteric cancer	2 (0.0)	1 (0.0)
	Acute myeloid leukemia	1 (0.0)	0
	Acute myeloid leukemia recurrent	1 (0.0)	0
	Acute myelomonocytic leukemia	1 (0.0)	0
	Adenocarcinoma	1 (0.0)	1 (0.0)
	Adrenal neoplasm	1 (0.0)	0
	B-cell small lymphocytic lymphoma	1 (0.0)	0

System organ class	Event	Rosuva 20 mg N=8901 n(%)	Placebo N=8901 n(%)
	Benign breast neoplasm	1 (0.0)	0
	Benign colonic neoplasm	1 (0.0)	0
	Benign salivary gland neoplasm	1 (0.0)	0
	Bladder cancer recurrent	1 (0.0)	0
	Bladder papilloma	1 (0.0)	1 (0.0)
	Bowen's disease	**1 (0.0)**	**1 (0.0)**
	Breast cancer metastatic	1 (0.0)	1 (0.0)
	Carcinoid tumor of the small bowel	1 (0.0)	0
	Cardiac myxoma	1 (0.0)	0
	Cervix carcinoma stage III	1 (0.0)	0
	Cholesteatoma	1 (0.0)	0
	Colon cancer metastatic	1 (0.0)	3 (0.0)
	Colon cancer stage I	1 (0.0)	0
	Diffuse large B-cell lymphoma	1 (0.0)	0
	Ganglioneuroma	1 (0.0)	0
	Gastrointestinal cancer metastatic	1 (0.0)	1 (0.0)
	Gastrointestinal stromal tumor	1 (0.0)	0
	Gastroesophageal cancer	1 (0.0)	1 (0.0)
	Head and neck cancer	1 (0.0)	0
	Hodgkin's disease	**1 (0.0)**	**1 (0.0)**
	Large cell carcinoma of the respiratory tract stage unspecified	1 (0.0)	0
	Laryngeal cancer	1 (0.0)	1 (0.0)
	Leiomyosarcoma metastatic	1 (0.0)	0
	Leukemia	1 (0.0)	2 (0.0)
	Lip and/or oral cavity cancer	1 (0.0)	0
	Lipoma	1 (0.0)	2 (0.0)
	Lung carcinoma cell type unspecified stage III	1 (0.0)	0
	Mesothelioma	1 (0.0)	0
	Metastatic renal cell carcinoma	1 (0.0)	3 (0.0)
	Nasopharyngeal cancer	1 (0.0)	0
	Neoplasm malignant	1 (0.0)	2 (0.0)
	Neurilemmoma	1 (0.0)	0
	Neuroendocrine carcinoma of the skin	1 (0.0)	0
	Neurofibroma	1 (0.0)	0
	Non-Hodgkin's lymphoma recurrent	**1 (0.0)**	**0**
	Ocular neoplasm	1 (0.0)	0
	Esophageal squamous cell carcinoma	1 (0.0)	0
	Oropharyngeal cancer stage unspecified	1 (0.0)	0
	Ovarian adenoma	1 (0.0)	0
	Ovarian neoplasm	1 (0.0)	2 (0.0)
	Pelvic neoplasm	1 (0.0)	0
	Penis carcinoma	1 (0.0)	0
	Polycythemia vera	1 (0.0)	0

System organ class	Event	Rosuva 20 mg N=8901 n(%)	Placebo N=8901 n(%)
	Prostate cancer recurrent	1 (0.0)	1 (0.0)
	Prostatic adenoma	1 (0.0)	0
	Pseudomyxoma peritonei	1 (0.0)	0
	Rectal cancer	1 (0.0)	8 (0.1)
	Rectosigmoid cancer	1 (0.0)	0
	Renal neoplasm	1 (0.0)	1 (0.0)
	Rhabdomyosarcoma	1 (0.0)	0
	Signet-ring cell carcinoma	1 (0.0)	0
	Skin cancer	1	0
	Small cell lung cancer stage unspecified	1 (0.0)	3 (0.0)
	T-cell lymphoma	1 (0.0)	0
	Testis cancer	1 (0.0)	0
	Throat cancer	1 (0.0)	0
	Thyroid cancer	1 (0.0)	2 (0.0)
	Tongue neoplasm malignant stage unspecified	1 (0.0)	1 (0.0)
	Ureteric cancer metastatic	1 (0.0)	0
	Waldenstrom's macroglobulinemia	**1 (0.0)**	**3 (0.0)**
Source: Applicant's Table 11.3.4.1.2.3, Pg 8456 CSR JUPITER			

In JUPITER, the overall incidence of Neoplasm SOC treatment-emergent adverse events was 6.8% in the rosuvastatin-treated group and 7.6% in the placebo-treated group. Of these AEs, only basal cell carcinoma reached a frequency of 1% in the rosuvastatin group compared with 0.9% in the placebo group. There was a similar **frequency in Neoplasm treatment-emergent AE in both treatment groups (Applicant's** Table 11.3.2.1.3.1, Pg 216 4865, CSR).

To address the concern regarding low LDL-C levels and cancer, of subjects with a LDL-C less than 50 mg/dL 2.5% (104/4154) in the rosuvastatin group and 3.9% (9/232) in the placebo group experienced a treatment-emergent SAE in the Neoplasm SOC group.

In the periodic safety update report covering the period of 07 November 2007 to 06 November 2008, there were 33 initial reports of cancer involving 35 cancer events. Two were serious study reports, 10 medically confirmed spontaneous reports (9 serious, 1 non-serious); and 21 serious nonmedically confirmed spontaneous reports. Of the 12 medically confirmed reports (2 serious study reports and 10 spontaneous reports) a causal link between CRESTOR and the cancer events was not reasonably identified due to the following factors: four (33%) had ≤ 6 months of CRESTOR exposure before diagnosis; two (17%) reports had confounding factors, and one (8%) report had a possible or likely alternative cause; five (42%) reports had insufficient information to draw a conclusion.

7.6.2 Human Reproduction and Pregnancy Data

No subject reported pregnancy during the JUPITER trial.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable

7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

The latest periodic safety update report (PSUR) covering November 2008 to November 2009 will be summarized, focusing on hepatic, musculoskeletal, and renal cumulative spontaneous reporting adverse event rates. During this PSUR period, 2410 case reports met the criteria for inclusion and were associated with 4501 adverse events. Interpreting spontaneous reporting of adverse events must be done with caution. In regards to the hepatic, musculoskeletal, and renal safety profile of rosuvastatin, it is the opinion of this clinical reviewer that no new safety issues have been identified.

8.1 Update of regulatory actions taken for safety reasons

The agency requested hepatic failure be added to the CRESTOR ADVERSE REACTIONS, Post-marketing section as class labeling based on a review of post-marketing reports of liver failure associated with the use of statins. Additional Information was updated on the pharmacokinetic drug interactions with protease inhibitors.

8.2 Patient exposure

The estimated clinical study patient exposure to rosuvastatin was 3845 rosuvastatin-treated patients during this PSUR period and 60,000 patients cumulatively through 31 October 2009.

The estimated post-marketing exposure was (b) (4) prescriptions during this PSUR period and (b) (4) prescriptions, (b) (4) patients, and (b) (4) patient-years cumulatively through 31 October 2009.

8.3 Hepatic events

As shown in Table 80, a cumulative review through 06 November 2009 identified 258 spontaneous reports of hepatitis, 102 spontaneous reports of jaundice, and 2282 spontaneous reports of abnormal liver function. With a total patient exposure of approximately (b) (4) patients, the cumulative reporting rates per million patients for **hepatitis** (b) (4) **) and jaundice (**(b) (4)**) remain 'very rare' and, for abnormal liver function, remains 'rare' (** (b) (4) **per million patients). The majority of these reports were 'abnormal liver function', which comprised 85% of the total number of cumulative** reported hepatic AEs.

The reporting rate per million patients was highest for CRESTOR 2.5 mg. Of the 384 reports associated with CRESTOR 2.5 mg, the majority (376/384, 97.9%) were from Japan and were non-serious abnormal liver function events. No new safety issue was identified. Increased hepatic transaminases are listed events in the CRESTOR label.

Table 80: Cumulative spontaneous reporting rates of hepatic events group by preferred term and dose

Daily dose (mg)	Fatal reports with any hepatic event[a]	Hepatic failure[b,c]	Hepatitis[d]	Jaundice[e]	Abnormal liver function[f]	# of patients	Total # of reports	# of reports (excluding abnormal liver function)	RR per million patients (all reports)	RR per million patients (excluding abnormal liver function)
2.5	2	3	7	6	368	(b) (4)	384	16	(b) (4)	
5	0	1	28	6	216		251	35		
10	15	15	135	60	997		1207	210		
20	3	8	22	10	178		218	40		
40	1	1	6	1	62		70	8		
Other[g]	0	0	0	0	14		14	0		
Unk	5	12	60	19	447		538	91		
Total	26	40	258	102	2282		2682	400		

Note: Serious and non-serious, medically confirmed and non-medically confirmed reports with any hepatic event are presented in only 1 category according to the following hierarchy: hepatic failure, hepatitis, jaundice, and abnormal liver function.

a Fatal reports are not included in the total report counts, as they are already counted under the specific hepatic terms.

b Includes reports with the following PTs: Acute hepatic failure, Hepatic failure, Hepatic necrosis, Hepatorenal failure, Hepatitis fulminant.

c Excludes 6 medically confirmed reports (2004UW06341, 2005GB02339, 2005UW08809, 2006SE05896, 2007AP03942, 2007UW07920) and 5 non-medically confirmed reports (2006UW09364, 2007UW27166, 2008UW01085, 2009SE20268, 2009UW18126) with PTs of Ascites, Hepatic cirrhosis, and Hepatorenal syndrome. These reports have been reviewed and determined not to represent hepatic failure.

d Includes reports with the following PTs: Autoimmune hepatitis, Chronic hepatitis, Cytolytic hepatitis, Hepatitis, Hepatitis acute, Hepatitis cholestatic, Hepatitis chronic active, Hepatitis toxic, Hepatocellular injury.

e Includes reports with the following PTs: Jaundice, Jaundice cholestatic, Jaundice neonatal, Ocular icterus, Yellow skin.

f Includes reports with the following PTs: Alanine aminotransferase increased, Aspartate aminotransferase increased, Bilirubin conjugated increased, Bilirubin urine, Blood alkaline phosphatase increased, Blood bilirubin increased, Blood bilirubin unconjugated increased, Gamma-glutamyltransferase increased, Hepatic enzyme abnormal, Hepatic enzyme increased, Hepatic function abnormal, Hyperbilirubinaemia, Hypertransaminasaemia, International normalised ratio increased, Liver disorder, Liver function test abnormal, Prothrombin level decreased, Prothrombin time prolonged, Total bile acids increased, Transaminases abnormal, Transaminases increased.

g Doses other than 5, 10, 20, or 40 mg.

MedDRA: Medical Dictionary for Regulatory Activities; NA: Not available (no estimated exposure); PT: Preferred Term; RR: reporting rate; Unk: unknown.

Source: PSUR#12, Table 39, Pg 146

8.4 Musculoskeletal events

8.4.1 Rhabdomyolysis

A comparison of the overall and dose-specific reporting rates of rhabdomyolysis by ACC/AHA/NHLBI criteria demonstrates similar spontaneous reporting rates in the latest PSUR (#12) compared to the previous annual PSUR period (PSUR #11) (Table 81).

Table 81: Rhabdomyolysis: periodic spontaneous reporting rates for reports meeting ACC/AHA/NHLBI criteria in PSUR #12 versus PSUR #11

	Annual PSUR #11		Annual PSUR #12	
Dose (mg)	**# of reports[a]**	**RR per million Rx**	**# of reports[a]**	**RR per million Rx**
2.5	4	(b) (4)	5	(b) (4)
5	5		0	
10	7		8	
20	5		3	
40	5		1	
Other[b]	1		0	
Unknown	3		2	
Total[c]	30		19	

PSUR #11: 07 November 2007 through 06 November 2008; PSUR #12: 07 November 2008 through 06 November 2009.
a Includes all serious and non-serious medically confirmed and non-medically confirmed spontaneous reports with PT Rhabdomyolysis.
b Doses other than 2.5, 5, 10, 20, or 40 mg.
c Total includes all spontaneous reports with PT Rhabdomyolysis, but estimated exposure does not include exposure for 'other' and 'unknown' doses.
ACC/AHA/NHLBI: American College of Cardiology/American Heart Association/National Heart, Lung and Blood Institute; NA: not applicable (no estimated exposure); PT: Preferred Term; RR: reporting rate; Rx: prescriptions.

Source: PSUR #12, Table 9, Pg 52

Global reporting rates meeting ACC/AHA/NHLBI criteria by dose for spontaneous reports of rhabdomyolysis are presented in Table 82.

Table 82: Cumulative global reporting rates by dose for spontaneous reports of rhabdomyolysis meeting ACC/AHA/NHLBI criteria

Dose (mg)	Total number of reports that meet ACC/AHA/NHLBI criteria[a]	RR per million patients[b]	RR per million Rx[b]	RR per million patients-years[b]
2.5	13		(b) (4)	
5	11			
10	87			
20	28			
40	51			
Other[c]	3			
Unknown	10			
Total[d]	203			

a ACC/AHA/NHLBI definition of rhabdomyolysis: muscle symptoms (eg, muscle aches, muscle soreness, and muscle weakness); marked CK elevation (10 x ULN); and creatinine elevation usually with brown urine and urinary myoglobin.
b For denominators, see Section 5.2.
c Doses other than 2.5, 5, 10, 20, or 40 mg.
d Total includes all events, but estimated exposure does not include exposure for 'other' and 'unknown' doses.
ACC/AHA/NHLBI: American College of Cardiology /American Heart Association/National Heart, Lung and Blood Institute; CK: creatine kinase; NA: not applicable (no estimate of exposure); RR reporting rate; Rx: prescriptions; ULN: upper limit of normal.

Source: PSUR #12, Table 51, pg 169.

8.4.2 Myopathy, myositis, and CK increase

Table 83 presents the cumulative global reporting rates for myopathy, myositis, and CK increase for CRESTOR by dose through 6 November 2009.

Table 83: Cumulative global reporting rates for myopathy, myositis, and CK increase by dose

	Myopathy				Myositis				CK increase			
Daily dose (mg)	# of reports[a]	RR/ mil patients	RR/mil Rx	RR/ mil p-y	# of reports[a]	RR/ mil patients	RR/ mil Rx	RR/mil p-y	# of reports[a]	RR/ mil patients	RR/mil Rx	RR/mil p-y
2.5	34	(b) (4)	(b) (4)	(b) (4)	4		(b) (4)		296		(b) (4)	
5	25		(b) (4)		11				173			
10	99				81				873			
20	23				19				143			
40	4				10				59			
Other[b]	0				1				10			
Unk	47				31				327			
Total	232				157				1881			

a Includes all spontaneous reports (serious and non-serious, medically confirmed and non-medically confirmed).
b Doses other than 2.5, 5, 10, 20, or 40 mg.
CK: creatine kinase; mil: million; NA: not applicable; PSUR: Periodic Safety Update Report; p-y: patient-years; RR: reporting rate; Rx: prescriptions; Unk: unknown.

Source: PSUR#12, Table 54, Pg 174

8.5 Renal events

Periodic and cumulative spontaneous reporting rates by dose for renal failure are presented in Table 84.

Table 84: Periodic and cumulative spontaneous reporting rates by dose for renal failure

	07 November 2008 to 06 November 2009		Cumulative through 06 November 2009			
Dose (mg)	# of reports[a]	RR per mil Rx	# of reports[a]	RR per mil patients	RR per mil Rx	RR per mil p-y
2.5	2	(b) (4)	8	(b) (4)		
5	2		17			
10	11		111			
20	7		33			
40	4		25			
Other[b]	0		1			
Unk	19		69			
Total[c]	45		264			

a Includes all serious and non-serious, medically confirmed and non-medically confirmed spontaneous reports.
b Doses other than 2.5, 5, 10, 20, or 40 mg.
c Total includes all events, but estimated exposure does not include exposure for other and unknown doses.
Mil: million; NA: not applicable (no estimated exposure); p-y: patient-years; RR: reporting rate; Rx: prescription; Unk: unknown.

Source: PSUR#12, Table 64, Pg 202

Periodic and cumulative spontaneous reporting rates by dose for renal impairment are presented in Table 85.

Table 85: Periodic and cumulative spontaneous reporting rates by dose for renal impairment

	07 November 2008 to 06 November 2009		Cumulative through 06 November 2009			
Dose (mg)	# of reports[a]	RR per mil Rx	# of reports[a]	RR per mil patients	RR per mil Rx	RR per mil p-y
2.5	8	(b) (4)	37	(b) (4)		
5	4		20			
10	12		133			
20	5		44			
40	3		29			
Other[b]	1		3			
Unk	26		68			
Total[c]	59		334			

a Includes all serious and non-serious, medically confirmed and non-medically confirmed spontaneous reports.
b Doses other than 2.5, 5, 10, 20, or 40 mg.
c Total includes all events, but estimated exposure does not include exposure for other and unknown doses.
Mil: million; NA: not applicable (no estimated exposure); p-y: patient-years; RR: reporting rate; Rx: prescription; Unk: unknown.

Source: PSUR#12, Table 65, Pg 203

9 Appendices

Appendix A: MedDRA SMQ Version 11.1 "narrow" hyperglycemia/new onset diabetes mellitus preferred terms used in analysis of METEOR, CORONA, and AURORA trials of diabetes-related AEs.

SMQ Name	Preferred Term	System Organ Class	High Level Group Term	High Level Term	PT Code
Hyperglycaemia/new onset diabetes mellitus (SMQ)	[redacted]	Investigations	Metabolic, nutritional and blood gas investigations	Carbohydrate tolerance analyses (incl diabetes)	10005557
Hyperglycaemia/new onset diabetes mellitus (SMQ)	[redacted]	Pregnancy, puerperium and perinatal conditions	Maternal complications of pregnancy	Pregnancy complicated by maternal disorders	10012596
Hyperglycaemia/new onset diabetes mellitus (SMQ)	[redacted]	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Diabetes mellitus (incl subtypes)	10012601
Hyperglycaemia/new onset diabetes mellitus (SMQ)	[redacted]	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Diabetes mellitus (incl subtypes)	10012607
Hyperglycaemia/new onset diabetes mellitus (SMQ)	[redacted]	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Diabetes mellitus (incl subtypes)	10012631
Hyperglycaemia/new onset diabetes mellitus (SMQ)	[redacted]	Nervous system disorders	Neurological disorders NEC	Coma states	10012650
Hyperglycaemia/new onset diabetes mellitus (SMQ)	[redacted]	Nervous system disorders	Neurological disorders NEC	Coma states	10012668
Hyperglycaemia/new onset diabetes mellitus (SMQ)	[redacted]	Nervous system disorders	Neurological disorders NEC	Coma states	10012669
Hyperglycaemia/new onset diabetes mellitus (SMQ)	[redacted]	Metabolism and nutrition disorders	Diabetic complications	Diabetic complications NEC	10012671
Hyperglycaemia/new onset diabetes mellitus (SMQ)	[redacted]	Nervous system disorders	Neurological disorders NEC	Coma states	10012672
Hyperglycaemia/new onset diabetes mellitus (SMQ)	[redacted]	Investigations	Metabolic, nutritional and blood gas investigations	Carbohydrate tolerance analyses (incl diabetes)	10017395
Hyperglycaemia/new onset diabetes mellitus (SMQ)	[redacted]	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Diabetes mellitus (incl subtypes)	10018209
Hyperglycaemia/new onset diabetes mellitus (SMQ)	[redacted]	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Hyperglycaemic conditions NEC	10018429
Hyperglycaemia/new onset diabetes mellitus (SMQ)	[redacted]	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Hyperglycaemic conditions NEC	10018430
Hyperglycaemia/new onset diabetes mellitus (SMQ)	[redacted]	Renal and urinary disorders	Urinary tract signs and symptoms	Urinary abnormalities	10018473
Hyperglycaemia/new onset diabetes mellitus (SMQ)	[redacted]	Renal and urinary disorders	Urinary tract signs and symptoms	Urinary abnormalities	10018475
Hyperglycaemia/new onset diabetes mellitus (SMQ)	[redacted]	Investigations	Renal and urinary tract investigations and urinalyses	Urinalysis NEC	10018478
Hyperglycaemia/new onset diabetes mellitus (SMQ)	[redacted]	Investigations	Metabolic, nutritional and blood gas investigations	Carbohydrate tolerance analyses (incl diabetes)	10018484
Hyperglycaemia/new onset diabetes mellitus (SMQ)	[redacted]	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Hyperglycaemic conditions NEC	10020635
Hyperglycaemia/new onset diabetes mellitus (SMQ)	[redacted]	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Hyperglycaemic conditions NEC	10022489
Hyperglycaemia/new onset diabetes mellitus (SMQ)	[redacted]	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Hyperglycaemic conditions NEC	10022490
Hyperglycaemia/new onset diabetes mellitus (SMQ)	[redacted]	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Diabetes mellitus (incl subtypes)	10022491
Hyperglycaemia/new onset diabetes mellitus (SMQ)	[redacted]	Metabolism and nutrition disorders	Acid-base disorders	Metabolic acidoses (excl diabetic acidoses)	10023379
Hyperglycaemia/new onset diabetes mellitus (SMQ)	[redacted]	Renal and urinary disorders	Urinary tract signs and symptoms	Urinary abnormalities	10023388
Hyperglycaemia/new onset diabetes mellitus (SMQ)	[redacted]	Metabolism and nutrition disorders	Acid-base disorders	Metabolic acidoses (excl diabetic acidoses)	10023391

Hyperglycaemia/new onset diabetes mellitus (SMQ)	Neonatal diabetes mellitus syndrome	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Diabetes mellitus (incl subtypes)	10028933
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Pancreatogenic 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-independent 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)	Ketone ketoacid body present	Investigations	Metabolic, nutritional and blood gas investigations	Metabolism tests NEC	10057597
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Hyperglycaemic hyperosmolar non-ketotic syndrome	Metabolism and nutrition disorders	Diabetic complications	Diabetic complications neurological	10063554
Hyperglycaemia/new onset diabetes mellitus (SMQ)	Blood c-peptide 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 B: MedDRA SMQ Version 11.1 "broad" hyperglycemia/new onset diabetes mellitus preferred terms (highlighted) used in analysis of METEOR, CORONA, and AURORA trials of diabetes-related AEs.

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)	[redacted]	Investigations	Metabolic, nutritional and blood gas investigations	Carbohydrate tolerance analyses (incl diabetes)	10018428
Hyperglycaemia/new onset diabetes mellitus (SMQ)	[redacted]	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)	[redacted]	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)	[redacted]	Metabolism and nutrition disorders	Glucose metabolism disorders (incl diabetes mellitus)	Diabetes mellitus (incl subtypes)	10021664
Hyperglycaemia/new onset diabetes mellitus (SMQ)	[redacted]	Immune system disorders	Autoimmune disorders	Endocrine autoimmune disorders	10022472
Hyperglycaemia/new onset diabetes mellitus (SMQ)	[redacted]	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)	[redacted]	Metabolism and nutrition disorders	Electrolyte and fluid balance conditions	Fluid intake increased	10036067
Hyperglycaemia/new onset diabetes mellitus (SMQ)	[redacted]	Renal and urinary disorders	Urinary tract signs and symptoms	Urinary tract signs and symptoms NEC	10036142
Hyperglycaemia/new onset diabetes mellitus (SMQ)	[redacted]	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

9.1 Literature Review/References

The literature was reviewed regarding hsCRP, global risk assessments for cardiovascular disease risk, and the association between statin use and diabetes. References appear as footnotes throughout this review.

9.2 Labeling Recommendations

This section describes this clinical reviewer's major recommendations and rationale for changes to the CRESTOR label after review of the JUPITER data. Proposed changes by the reviewer are in italics and final label wording is bolded.

The applicant provided a revised indication and usage statement on 21 December 2009 listed below:

Section 1 INDICATIONS AND USAGE

1.6 Prevention of Cardiovascular Disease

- Adult patients at (b) (4) risk of cardiovascular disease based on cardiovascular disease risk markers such as age, elevated hsCRP level, hypertension, low HDL-C, smoking or a family history of premature coronary heart disease, CRESTOR is indicated to reduce the risk of total mortality and major cardiovascular events: cardiovascular death, stroke, myocardial infarction, arterial revascularization, unstable angina.

This clinical reviewer recommends the following changes to **Section 1.6** of the CRESTOR label.

1.6 Primary Prevention of Cardiovascular Disease

In individuals without clinically evident coronary heart disease but with an increased risk of cardiovascular disease based on age ≥50 years in men and ≥60 years in women, an elevated hsCRP ≥ 2 mg/L and the presence of one additional cardiovascular disease risk marker such as hypertension, low HDL-C, smoking, or a family history of premature coronary heart disease, CRESTOR is indicated to:

- *Reduce the risk of nonfatal stroke*
- *Reduce the risk of nonfatal myocardial infarction*
- *Reduce the risk of arterial revascularization procedures*

The heading of Section 1.6 is changed to reflect that JUPITER was a primary prevention trial conducted in adults without clinical evident cardiovascular disease.

The definition of (b) (4) **risk seen in the applicant's proposal is too vague and** lends itself to wide interpretation by health care practitioners.

Because a subgroup analysis in 25% of JUPITER subjects with only age as a risk factor before adjustment for high HDL-C, suggested no treatment benefit with rosuvastatin, it **is the clinical reviewer's opinion that subjects must have age, hsCRP** ≥ 2 mg/L and at least one traditional risk factor to identify the appropriate treatment population with rosuvastatin for primary prevention of cardiovascular disease.

It is a concern of this clinical reviewer that granting an indication based on the primary composite endpoint may give health care practitioners the impression that rosuvastatin demonstrated a statistically significant decrease in cardiovascular death and hospitalization for unstable angina when it did not. Analysis of the individual components of the primary endpoint (not prespecified in the protocol) revealed statistical significance for three of six components: nonfatal stroke, nonfatal MI, and arterial revascularization procedures.

Review of other statin labels with indications for primary prevention of cardiovascular risk based on composite endpoint trials provides precedent for granting only the statistically significant components of a composite endpoint, even when the overall composite endpoint has achieved statistical significance.

<u>Lovastatin</u>
In the AFCAPS trial, the primary composite endpoint defined as "acute major coronary event" included fatal and nonfatal myocardial infarction, unstable angina, and sudden cardiac death. Although lovastatin achieved a statistically significant treatment difference for the primary composite endpoint (p<0.0001), the granted indication (b) (4) Two of the individual components, myocardial infarction (p=0.002) and unstable angina (p=0.002), were independently statistically significant and were granted indications in the lovastatin label. The secondary endpoint of reduction in risk of undergoing coronary revascularization

procedures was statistically significant (p=0.001) and was included in lovastatin's indication.

Atorvastatin

In the ASCOT trial, the composite primary endpoint [nonfatal MI (symptomatic and silent) + coronary heart disease death] reached statistical significance, p=0.0005. Examination of the individual components revealed only nonfatal symptomatic myocardial infarction was significantly reduced in the atorvastatin group compared to placebo. The applicant sought an indication for (b) (4)

The applicant also sought indications for reduction of risk of stroke (b) (4) , the only individual component (other than nonfatal symptomatic MI) that achieved predefined statistical significance favoring atorvastatin was reduction in number of revascularization procedures (p=0.00016), although the reduction in risk of chronic stable angina came very close to significance (p=0.01354). The LIPITOR label after the initial ASCOT review was granted the indications for reduction in risk for myocardial infarction, revascularization procedures and angina. **The indications for** (b) (4) **stroke, or** (b) (4) **were not granted.**

The decision to later grant the indication for risk reduction of stroke was based on additional evidence from the CARDS trial which used atorvastatin in patients with type 2 diabetes and achieved a statistical significance for reduction in stroke (p=0.016) when independently analyzed.

The indications granted from the CARDS trial included only the statistically significant individual components of the primary composite endpoint which were myocardial infarction (p=0.004) and stroke (p=0.016). The primary composite endpoint studied in the CARDS trial included MI, acute CHD death, unstable angina, coronary revascularization, or stroke. There were no significant differences between the treatment groups for angina (p=0.599), revascularization procedures (p=0.158), and acute CHD death (p=0.22).

Pravastatin

In WOSCOPS the primary composite endpoint was CHD death and nonfatal MI. Non-fatal MI was independently statistically significant (p=0.006) and was granted an indication. (b) (4) was omitted from the indication for pravastatin. The tertiary endpoint of myocardial revascularization procedures was statistically significant (p=0.009). Death due to all cardiovascular causes was an all-inclusive endpoint defined

near the end of the WOSCOPS trial composed of definite and suspect CHD deaths, **other cardiac deaths, and other vascular deaths. FDA's analysis of this tertiary endpoint** yielded a p-value of 0.042. Reduction in risk of cardiovascular mortality (p=0.042) with no increase in death from non-CV causes (p=0.6) was granted an indication in the ZOCOR label.

Simvastatin

The Heart Protection Study (HPS) included high risk subjects for major cardiovascular events. For example, subjects with established cardiovascular disease and subjects with non-coronary conditions such as non-coronary occlusive disease, diabetes mellitus, and treated hypertension. Therefore HPS was considered a primary and secondary cardiovascular disease prevention trial. HPS attained statistical significance on all primary, secondary, and tertiary endpoints included in the label. Total mortality was a primary endpoint and achieved a p-value of 0.0003 with 1328 events in the simvastatin group compared to 1507 events in the placebo group. CHD mortality was a primary endpoint and achieved a p-value of 0.0005 with 587 events in the simvastatin group compared to 707 events in the placebo group. The applicant requested with the submission the indication for total mortality by reducing CHD deaths, not total mortality by itself.

It is this clinical reviewer's recommendation that total mortality not be included as an indication in the CRESTOR label. There are two statin labels (pravastatin and simvastatin) with indications that refer to mortality but do not lend precedent for granting a total mortality indication for JUPITER.

The PRAVACHOL (pravastatin) label has the indication for reduction in risk of cardiovascular mortality with no increase in death from noncardiovascular causes. The original application requested an indication for (b) (4) The (b) (4) was not granted. In addition, the statistically significant impact of pravastatin treatment was a (b) (4)

Cardiovascular mortality was a composite endpoint defined late in the trial as definite and suspect CHD deaths, other cardiac deaths, and other vascular deaths and did achieve (b) (4). JUPITER did not demonstrate a treatment benefit with rosuvastatin in reduction of cardiovascular death (p=0.315) **although the numbers trended in rosuvastatin's favor. Retrospectively, the** cardiovascular mortality endpoint in the WOSCOPS trial was flawed in its definition and **interpretation of its statistical significance in this clinical reviewer's opinion.**

The ZOCOR (simvastatin) label has the indication for reduction in risk of total mortality by reducing CHD deaths based on data from HPS. Total mortality and CHD mortality

were primary endpoints in HPS and achieved robust statistical significance (total mortality, p=0.0003 and CHD mortality, p=0.0005) with simvastatin treatment. These results were most likely driven by the enriched population of subjects with established CHD. When looking at subgroup analyses of subjects with no diabetes and without CHD the benefits were small and did not achieve statistical significance for total mortality (p=0.53) or CHD mortality (p=0.27).

With the addition of statins to the dyslipidemic treatment regimen, members of the medical community and public were concerned that statins might increase noncardiovascular mortality. The agency sought to address this safety not efficacy concern by including indications regarding cardiovascular and noncardiovascular mortality in earlier statin labels.

Moreover, a total mortality indication is (b) (4) (b) (4)

Final agreed upon wording between Division and Applicant

1.6 Primary Prevention of Cardiovascular Disease

In individuals without clinically evident coronary heart disease but with an increased risk of cardiovascular disease based on age ≥ 50 years old in men and ≥ 60 years old in women, hsCRP ≥ 2 mg/L, and the presence of at least one additional cardiovascular disease risk factor such as hypertension, low HDL-C, smoking, or a family history of premature coronary heart disease, CRESTOR is indicated to:

- **reduce the risk of stroke**
- **reduce the risk of myocardial infarction**
- **reduce the risk of arterial revascularization procedures**

Section 5 WARNINGS AND PRECAUTIONS

This clinical reviewer proposes in **Section 5.5 Endocrine Effects** the following statements to address the increase in HbA1c and fasting serum glucose observed in the JUPITER trial.

Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including CRESTOR.

In JUPITER, there was a significantly higher frequency of diabetes mellitus reported in patients taking rosuvastatin (2.8%) versus patients taking placebo (2.3%). Mean HbA1c was significantly increased by 0.1% in rosuvastatin-treated patients compared to placebo-treated patients. The number of patients with a HbA1c > 6.5% at the end of the trial was significantly higher in rosuvastatin-treated versus placebo-treated patients

Final agreed upon wording between Division and Applicant

Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including CRESTOR.

Second paragraph moved to Section 6 Adverse Reactions

Section 6 ADVERSE REACTIONS

Because a JUPITER subject could discontinue study medication due to an adverse event but still participate in the trial, this clinical reviewer proposes the following changes in **Section 6.1 Clinical studies** to give more useful information regarding the adverse events associated with study medication discontinuation.

Applicant's proposed wording

(b) (4)

Clinical reviewer's proposed wording

A higher percentage of rosuvastatin-treated patients versus placebo-treated patients, 6.6% and 6.2%, respectively discontinued study medication due to an adverse event, irrespective of treatment causality. The most common adverse reactions that led to study medication discontinuation was: myalgia.

Final agreed upon wording between Division and Applicant

In the JUPITER study, 17,802 participants were treated with rosuvastatin 20 mg (n=8901) or placebo (n=8901) for a mean duration of 2 years. A higher percentage of rosuvastatin-treated patients versus placebo-treated patients, 6.6% and 6.2%, respectively, discontinued study medication due to an adverse event, irrespective of treatment causality. Myalgia was the most common adverse reaction that led to treatment discontinuation.

Section 14 CLINICAL STUDIES

This clinical reviewer proposes four major changes to the applicant's proposed Section 14.8 language:

- Exclusion of the secondary mini-composites of (a) cardiovascular death or fatal or non-fatal stroke or fatal or non-fatal MI, (b) fatal or non-fatal stroke, and (c) fatal or non-fatal myocardial infarction.
- Omission of the secondary outcome of total mortality.
- Addition of the number of events and p-values for the individual components of the primary composite endpoint.
- Addition of one post-hoc subgroup analysis that had no significant treatment benefit.

Although the mini-composites attained statistical significance, it is misleading to include them in the clinical studies section as this may imply to health care practitioners that treatment with rosuvastatin significantly decreased fatalities related to coronary heart disease compared to placebo. The difference between the rosuvastatin and placebo groups may be largely attributable to the nonfatal events as the numbers of fatal events were small. Negotiations with the applicant resulted in separating the absolute number of events for each of the mini-composites within the clinical studies label.

<u>Applicant's proposed wording for Section 14.8</u>

Section 14.8 Prevention of Cardiovascular Disease

(b) (4)

(b) (4)

Reviewer's recommendations for Section 14.8:

14.8 Primary Prevention of Cardiovascular Disease
*In the **J**ustification for the **U**se of Statins in **P**rimary Prevention: An **I**ntervention **T**rial **E**valuating **R**osuvastatin (JUPITER) study, the effect of CRESTOR (rosuvastatin calcium) on the occurrence of major cardiovascular (CV) disease events was assessed in 17802 men (≥50 years) and women (≥60 years) who had no clinically evident cardiovascular disease, LDL-C levels <130 mg/dL (3.3 mmol/l) and hs-CRP levels ≥2 mg/L. The study population had an estimated baseline coronary heart disease risk of 11.3% over 10 years based on the Framingham risk criteria and included a high percentage of patients with additional risk factors such as hypertension (58%), low HDL-C levels (23%), cigarette smoking (16%) or a family history of premature CHD (12%). Study participants had a median baseline LDL-C of 108 mg/dL and hsCRP of 4.3 mg/L. Study participants were randomly assigned to placebo (n=8901) or rosuvastatin 20 mg once daily (n=8901) and were followed for a mean duration of 2 years. The JUPITER*

study was stopped early by the Data Safety Monitoring Board due to meeting pre-defined stopping rules for efficacy in rosuvastatin-treated subjects.

The primary endpoint was a composite consisting of the time-to-first occurrence of any of the following major CV events: CV death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for unstable angina or an arterial revascularization procedure.

Rosuvastatin significantly reduced the risk of major CV events (252 events in the placebo group vs. 142 events in the rosuvastatin group) with a statistically significant (p<0.001) relative risk reduction of 44% and absolute risk reduction of 1.2% (see Figure 2). The risk reduction for the primary endpoint was consistent across the following predefined subgroups: age, sex, race, smoking status, family history of premature CHD, body mass index, LDL-C, HDL-C and hsCRP levels.

Of the individual components of the primary endpoint, rosuvastatin significantly reduced the risk of non-fatal myocardial infarction (62 events in the placebo group versus 22 events in the rosuvastatin group, p<0.001), non-fatal stroke (58 events in the placebo group versus 30 events in the rosuvastatin group, p=0.003), and arterial revascularization procedures (131 events in the placebo group versus 71 events in the rosuvastatin group, p<0.001). There were no significant differences between the treatment groups for death due to cardiovascular causes (p=0.315) or hospitalizations for unstable angina (p=0.093).

In a post-hoc subgroup analysis in 25% of JUPITER subjects with a hsCRP ≥ 2 mg/L and no other traditional risk factors (smoking, BP ≥140/90 or taking antihypertensives, low HDL-C), there was no significant treatment benefit with rosuvastatin treatment.

At one year, rosuvastatin increased HDL-C and reduced LDL-C, hsCRP, total cholesterol and serum triglyceride levels (p<0.001 for all versus placebo).

Final agreed upon wording between Division and Applicant

14.8 Primary Prevention of Cardiovascular Disease

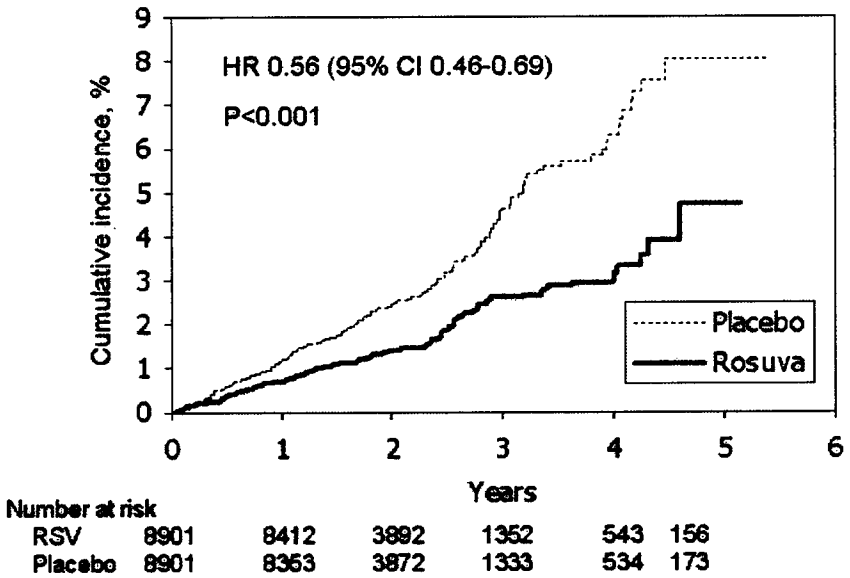
In the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study, the effect of CRESTOR (rosuvastatin calcium) on the occurrence of major cardiovascular (CV) disease events was assessed in 17,802 men (≥50 years) and women (≥60 years) who had no clinically evident cardiovascular disease, LDL-C levels <130 mg/dL (3.3 mmol/l) and hs-CRP levels ≥2 mg/L. The study population had an estimated baseline coronary heart disease risk of 11.6% over 10 years based on the Framingham risk criteria and included a high percentage of patients with additional risk factors such as hypertension (58%), low HDL-C levels (23%),

cigarette smoking (16%), or a family history of premature CHD (12%). Study participants had a median baseline LDL-C of 108 mg/dL and hsCRP of 4.3 mg/L. Study participants were randomly assigned to placebo (n=8901) or rosuvastatin 20 mg once daily (n=8901) and were followed for a mean duration of 2 years. The JUPITER study was stopped early by the Data Safety Monitoring Board due to meeting predefined stopping rules for efficacy in rosuvastatin-treated subjects.

The primary end point was a composite end point consisting of the time-to-first occurrence of any of the following major CV events: CV death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina or an arterial revascularization procedure.

Rosuvastatin significantly reduced the risk of major CV events (252 events in the placebo group vs. 142 events in the rosuvastatin group) with a statistically significant (p<0.001) relative risk reduction of 44% and absolute risk reduction of 1.2% (see Figure 2). The risk reduction for the primary end point was consistent across the following predefined subgroups: age, sex, race, smoking status, family history of premature CHD, body mass index, LDL-C, HDL-C, and hsCRP levels.

Figure 2. Time to first occurrence of major cardiovascular events in JUPITER



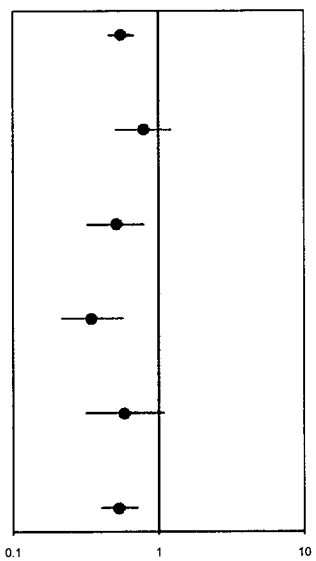
The individual components of the primary end point are presented in Figure 3. Rosuvastatin significantly reduced the risk of nonfatal myocardial infarction, nonfatal stroke, and arterial revascularization procedures. There were no significant treatment differences between the rosuvastatin and placebo groups for death due to cardiovascular causes or hospitalizations for unstable angina.

Rosuvastatin significantly reduced the risk of myocardial infarction (6 fatal events and 62 nonfatal events in placebo-treated subjects vs. 9 fatal events and 22 nonfatal events in rosuvastatin-treated subjects) and the risk of stroke (6 fatal events and 58 nonfatal events in placebo-treated subjects vs. 3 fatal events and 30 nonfatal events in rosuvastatin-treated subjects).

In a post-hoc subgroup analysis of JUPITER subjects (n=1405; rosuvastatin=725, placebo=680) with a hsCRP ≥2 mg/L and no other traditional risk factors (smoking, BP ≥140/90 or taking antihypertensives, low HDL-C) other than age, after adjustment for high HDL-C, there was no significant treatment benefit with rosuvastatin treatment.

Figure 3. Major CV events by treatment group in JUPITER

End point	Number of events Rosuva 20 mg (n=8901) n (rate*)	Placebo 20 mg (n=8901) n (rate)	HR (95% CI)	P value
Primary end point (MCE)	142 (7.6)	252 (13.6)	0.56 (0.46, 0.69)	<0.001
Cardiovascular death**	35 (1.9)	44 (2.4)	0.80 (0.51, 1.24)	0.315
Nonfatal Stroke	30 (1.6)	58 (3.1)	0.52 (0.33, 0.80)	0.003
Nonfatal MI	22 (1.2)	62 (3.3)	0.35 (0.22, 0.58)	<0.001
Hospitalized unstable Angina	16 (0.9)	27 (1.5)	0.59 (0.32, 1.10)	0.093
Arterial revascularization	71 (3.8)	131 (7.1)	0.54 (0.41, 0.72)	<0.001



*event rate/1000-patient years
**Cardiovascular death included fatal MI, fatal stroke, sudden death, and other adjudicated causes of CV death

At one year, rosuvastatin increased HDL-C and reduced LDL-C, hsCRP, total cholesterol and serum triglyceride levels (p<0.001 for all versus placebo).

Section 17 PATIENT COUNSELING INFORMATION

Because the JUPITER trial demonstrated a significant increase in investigator-reported diabetes mellitus in rosuvastatin-treated subjects, this reviewer recommends the addition of **Section 17.5 Glucose metabolism.**

17.5 Glucose metabolism
It is recommended that HbA1c and fasting glucose levels be checked before and 12 weeks after initiation of therapy, after dose elevations, and periodically (e.g., semiannually) thereafter.

Patients must be advised to report promptly unexplained symptoms of diabetes mellitus, such as increased thirst, urination or blurred vision.

Final label: Section 17.5 was not added to final label

9.3 Advisory Committee Meeting

On 15 December 2009, five questions, bolded below, regarding the JUPITER trial were posed to the Endocrinologic and Metabolism Division Advisory Committee (EDMAC). A summary of the discussion generated and vote result from panel members are indicated by italics. See the complete transcript of the EDMAC meeting posted on the FDA website for details:
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm126136.htm

1. In the JUPITER clinical trial, there were 13 deaths due to gastrointestinal disorders in the treatment arm versus one in the placebo arm. Please comment on the significance of this imbalance.

There was a general consensus from the committee that it's unlikely the gastrointestinal disorders represent an authentic serious adverse event however a prospective study to assess this more definitively would be helpful.

2. In the JUPITER clinical trial, there were 18 patients who reported a confusional state in the treatment arm versus four in the placebo arm. Please comment on the significance of this imbalance.

There was a general consensus from the committee that the imbalance is unlikely related to an authentic safety signal however, a prospective study using more quantitative assessments, at the beginning and throughout the study would more definitively address this question and this is an important question that needs further analysis.

3. In the JUPITER clinical trial, there was a statistically significant increase in investigator-reported diabetes mellitus in the treatment arm versus the placebo arm, 2.8% versus 2.3%, respectively with a hazard ratio of 1.27 (95% CI 1.05, 1.53; p=0.015). Please comment on the significance of this imbalance.

The committee felt that the imbalance in the report of diabetes mellitus in the present study is related and quantified by subjective assessments, but probably represents an authentic increase in the frequency of diabetes and may be a drug class effect. Further studies using statins, should include a quantitative assessment of diabetes in the statistical analyses.

4. Please discuss whether the JUPITER trial has identified an appropriate new target population, defined by LDL-C<130 mg/dL, hsCRP ≥ 2 mg/L, plus at least one additional cardiovascular risk factor, for treatment with rosuvastatin for the primary prevention of major cardiovascular adverse events.

Some committee members agreed that the JUPITER trial has identified a specific population but further discussion and studies need to be performed regarding the age issue and the inter-relationship between age and other traditional risk factors. There was a general consensus by the committee that this may be a separate population that is worthy of additional discussion.

5. Has the applicant established sufficient benefit to offset the observed risks to support the use of rosuvastatin in individuals meeting the following criteria:

- **Men ≥ 50 years, women ≥ 60 years**
- **Fasting LDL-C <130 mg/dL, hsCRP ≥ 2 mg/L, triglycerides <500 mg/dL**
- **Non prior history of cardiovascular or cerebrovascular events or CHD risk equivalent as defined by NCEP ATP-III guidelines.**

Vote: Yes: 12 No: 4 Abstain: 1

Selected comments from the committee:

Although the committee voted twelve to four (and one abstention) in favor of rosuvastatin, the committee suggested that the FDA should be careful with defining the population for the extended use of this drug, in the labeling and marketing materials. There should be warning in the labeling regarding the possible risk factors such as diabetes mellitus (class-effect), confusional state, and weight gain. There were some concerns regarding the short follow-up of the study and the premature stoppage of the study. Most committee members viewed their Yes votes a not to endorse hsCRP as a new risk factor.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21366	SUPPL-16	IPR PHARMACEUTICALS INC	CRESTOR(ROSUVASTATIN CALCIUM)10/20/40/80

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY D ROBERTS
02/05/2010

AMY G EGAN
02/05/2010

TEAM LEADER MEMO

Date:	February 5, 2010
From:	Amy G. Egan, M.D., M.P.H.
NDA #:	21-366/S-016
Submission:	**J**ustification for the **U**se of statins in **P**rimary prevention: an **I**ntervention **T**rial **E**valuating **R**osuvastatin (JUPITER)
Applicant:	AstraZeneca
Date of Submission:	April 8, 2009
PDUFA Goal Date:	February 8, 2010
Proprietary Name/Established Name:	CRESTOR® (rosuvastatin calcium)
Dosage forms/Strength:	5, 10, 20, and 40 mg tablets
Proposed Indication:	In adult patients at (b) (4) risk of cardiovascular disease based on cardiovascular disease risk markers such as age, elevated hsCRP level, hypertension, low HDL-C, smoking or a family history of premature coronary heart disease, CRESTOR is indicated to reduce the risk of total mortality and major cardiovascular events: cardiovascular death, stroke, myocardial infarction, arterial revascularization, unstable angina.

A. INTRODUCTION

This supplemental NDA was submitted on April 8, 2009 for CRESTOR® (rosuvastatin calcium) to support a new indication for the primary prevention of cardiovascular disease based on the results of JUPITER (**J**ustification for the **U**se of statins in **P**rimary prevention: an **I**ntervention **T**rial **E**valuating **R**osuvastatin). JUPITER was a multi-center, double-blind, placebo-controlled cardiovascular outcome trial in ~18,000 adults with no clinically evident cardiovascular disease, LDL-C <130 mg/dL, hsCRP ≥2 mg/L, and at least one other major ATP-III risk factor. This population was not eligible for statin therapy according to the NCEP ATP-III 2001 guidelines, thus representing a novel population for statin treatment. In developing the trial, AstraZeneca sought guidance from the Agency in a Special Protocol Assessment. The sponsor was advised at that time that:

> *While this study may identify a population of subjects with high CRP levels who would benefit from therapy with rosuvastatin, this does not identify CRP as a validated surrogate for risk of cardiovascular disease and a specific target of therapy. Several clinical studies have shown that a variety of statins are capable of lowering CRP levels but the clinical benefits of lowering CRP have not been established. It is unlikely that the results of JUPITER will support labeling for CRP as a goal of statin therapy.*

The sponsor was further advised:

> *Assuming the results for the primary efficacy assessment favor drug treatment, the individual components (cardiovascular death, stroke, MI, unstable angina, or arterial revascularization procedures) would need to be evaluated as secondary or tertiary endpoints to determine their contribution to the overall efficacy findings.*

B. BACKGROUND

CRESTOR® (rosuvastatin calcium) is a member of the statin class of lipid-lowering compounds. Initial approval was on 12 August 2003. CRESTOR® is available in 5, 10, 20, and 40 mg tablets and is indicated for:

1. Patients with primary hyperlipidemia (heterozygous familial and non-familial) and mixed dyslipidemia (Fredrickson Type IIa and IIb) as an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, nonHDL-C, and TG levels and to increase HDL-C
2. Patients with hypertriglyceridemia (Fredrickson Type IV) as an adjunct to diet
3. Patients with primary dysbetalipoproteinemia (Type III hyperlipoproteinemia) as an adjunct to diet
4. Patients with homozygous familial hypercholesterolemia to reduce LDL-C, total-C, and ApoB
5. Slowing the progression of atherosclerosis as part of a treatment strategy to lower total-C and LDL-C as an adjunct to diet

6. Pediatric patients 10 to 17 years of age with heterozygous familial hypercholesterolemia (HeFH) to reduce elevated total-C, LDL-C, and Apo B after failing an adequate trial of diet therapy

Please see Dr. Mary Roberts' review for a more comprehensive presentation of the literature and the rationale and implications of the JUPITER trial.

Both ATP-III and Framingham risk scores rely on conventional cardiovascular risk factors. As Dr. Roberts cites in her review, **"Some data suggest** over 50% of patients **with CHD lack conventional risk factors."** This has spawned a great deal of research and debate in the area of emerging risk factors.

High sensitivity CRP is a non-specific biomarker of inflammation. Inflammation contributes to the plaque instability of atherosclerotic disease.[1] Epidemiologic studies have shown an association between hsCRP and increased risk of CHD. This formed the basis for the JUPITER trial design.

Currently, the following statins have an indication for primary prevention of CHD:

- Pravachol: Indication granted in July 1996 based on the results of WOSCOPS (West of Scotland Coronary Prevention Study).
- Mevacor: Indication granted in March 1999 based on the results of AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study).
- Zocor: Indication granted in April 2003 based on a sub-population of HPS (Heart Protection Study).
- Lipitor: Indication granted in July 2004 based on the results of ASCOT-LLA (Anglo-Scandinavian Cardiac **Outcomes Trial – Lipid Lowering Arm) and** expanded in September 2005 based on the results of CARDS (Collaborative Atorvastatin Diabetes Study).

The sponsor is seeking the following indication based on the results of JUPITER:

> *In adult patients at* (b) (4) *risk of cardiovascular disease based on cardiovascular disease risk markers such as age, elevated hsCRP level, hypertension, low HDL-C, smoking or a family history of premature coronary heart disease, CRESTOR is indicated to reduce the risk of total mortality and major cardiovascular events: cardiovascular death, stroke, myocardial infarction, arterial revascularization, unstable angina.*

C. CMC/DEVICE

The sponsor was granted a categorical exclusion from preparing an environmental assessment based on an expected environmental concentration of (b) (4) μg/L (ppb) which **is below the EA threshold of 1 ppb. Please see Dr. Janice Brown's review.**

---

[1] **Ross et al. Atherosclerosis – an inflammatory disease.** *NEJM.*1999;340:115-126.

D. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

There are no new nonclinical pharmacology/toxicology issues to be reviewed in this supplemental application.

E. CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS

There are no new clinical pharmacology issues to be reviewed in this supplemental application.

F. CLINICAL MICROBIOLOGY

Not applicable.

G. CLINICAL/STATISTICAL - EFFICACY

Please refer to Dr. Mary Roberts' and Dr. David Hoberman's clinical and statistical reviews for more detailed information.

JUPITER was a randomized, double-blind, placebo-controlled trial. Its primary objective was to investigate whether long-term treatment with rosuvastatin 20 mg compared with placebo would decrease the time to first major cardiovascular event (MCE), a composite of cardiovascular death, non-fatal stroke, non-fatal myocardial infarction, hospitalization for unstable angina, or arterial revascularization among men ≥ 50 years and women ≥ 60 years with LDL-C <130 mg/dL who are at high vascular risk on the basis of a hsCRP ≥2 mg/L. Secondary objectives were to investigate the safety of long-term treatment with rosuvastatin compared to placebo through comparisons of total mortality, non-cardiovascular mortality, and adverse events; and to investigate whether rosuvastatin reduces the incidence of diabetes mellitus, venous thromboembolic events, and bone fractures.

The study was composed of two screening visits, a four-week placebo run-in period, followed by a randomized treatment period. Initial screening for study eligibility could not occur within two weeks of a major viral or bacterial illness. High sensitivity CRP and lipid levels drawn at the initial screening visit determined eligibility for a second screening visit. A second hsCRP level was drawn two weeks after the initial screening visit at the second screening visit. Baseline hsCRP was considered the average of these two hsCRP values, although the initial hsCRP level determined eligibility.

Pertinent exclusion criteria included:

- 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
- Active liver disease or hepatic dysfunction or elevations of ALT>2x ULN at Screening Visit 2
- Baseline elevations of CK>3x ULN at Screening Visit 2
- Creatinine >2.0 mg/dL
- Diabetes mellitus, defined by fasting serum glucose >126 mg/dL at Screening Visit 2 or by the use of insulin and/or oral hypoglycemic agent

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

It should be noted that clinical inspections were conducted as part of a routine audit to assess data integrity and human subject protection for the JUPITER trial. Three clinical investigator sites were inspected. In general, the findings supported that the trial was conducted appropriately and the data were considered reliable. However, the audit found a systemic clinical trial conduct issue, in that the exclusion criterion, "CHD risk equivalent as defined by NCEP ATP III" **was not determined for any subject in the** clinical trial. This resulted in the enrollment of 1558 subjects (786 on rosuvastatin and 772 on placebo), or 8.8% of the total study population, who were in the Framingham risk **category of 'High'.**

Of the 89,846 subjects screened for the JUPITER trial, 72,044 (80%) failed screening. Of these screen failures, 92% failed due to not meeting inclusion/exclusion criteria. Specifically, 52% were excluded on the basis of LDL-C level ≥130 mg/dL and 36% were excluded on the basis of hsCRP level <2 mg/L.

Of the 17,802 randomized subjects, 22% were from the United States; however, the U.S. provided the greatest number of subjects (n=4,021) of any of the 26 participating countries. It should be noted that a higher proportion of subjects in the U.S. withdrew from JUPITER, 18.5% versus 4.8% of non-U.S. subjects.

Treatment groups were well-balanced with respect to sex, age, race, BMI, BP, smoking history, hypertension, and family history of CHD. The mean Framingham risk score was 11.6% in both treatment groups. The groups were well-balanced in baseline lipoprotein and hsCRP levels. Median baseline CRP was 4.2 mg/L (Range: 1.1-192.0) in the rosuvastatin treatment group and 4.3 mg/L (Range: 0.55-174.5) in the placebo treatment group.

Clinical endpoints for the primary composite were adjudicated by the Duke Clinical Research Institute (CDRI) Clinical Events Classification (CEC) group.

Per the protocol, with the occurrence of a **subject's first cardiovascular event blinded** study medication was discontinued, subjects continued scheduled follow-up assessments and treatment was left to investigator discretion.

The original protocol planned to follow subjects for approximately 3.5 years to accrue 520 clinical endpoints. The study was stopped early (at the second interim analysis, or 390 events) by the Data Safety Monitoring Board due to meeting predefined stopping rules for efficacy in rosuvastatin-treated subjects.

Treatment with rosuvastatin resulted in a 44% relative risk reduction and 1.2% absolute risk reduction in time to first MCE.

Table 1: Summary of analysis for primary composite endpoint

Number of Subjects with any Event		Event rate/1000 patient years		Hazard ratio (95% CI) p-value	Relative risk reduction	Absolute risk reduction	Number needed to treat
Rosuvastatin N=8901 n (%)	Placebo N=8901 n (%)	Rosuvastatin	Placebo	0.56 (0.46, 0.69) <0.001	44%	1.2%	83
142 (1.6)	252 (2.8)	7.6	13.6				

From Dr. Mary Roberts' clinical review

The distribution of the first MCE that contributed to the composite primary endpoint is shown in the table below. As can be seen from the table, the individual components of cardiovascular death and hospitalized unstable angina did not reach statistical significance.

Table 2: Number of events[a] by treatment group for the composite primary endpoint (ITT population)

Endpoint	Rosuvastatin 20 mg N=8901	Placebo N=8901	p-value[b]
First MCE	142	252	<0.001
Cardiovascular death	29	37	0.33
Non-fatal MI	21	61	<0.01
Non-fatal stroke	30	57	<0.01
Hospitalized unstable angina	15	27	0.069
Arterial revascularization	47	70	0.036

Source: Applicant's Table 18, Pg 62, CSR JUPITER

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

[b]p-values except for First MCE calculated by FDA statistician, Dr. David Hoberman

For the three pre-specified secondary outcomes (a) cardiovascular death/MI/stroke, (b) non-fatal MI/MI, and (c) non-fatal stroke/stroke, treatment with rosuvastatin resulted in relative risk reductions of 48%, 54%, and 48%, respectively.

Table 3: Other cardiovascular efficacy endpoints (ITT population)

	Rosuva 20 mg N=8901 n(%)	Placebo N=8901 n(%)	HR (95% CI)	p-value
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

Source: Applicant's Table 22, Pg 67, CSR; Table 11.2.1.35.1, Pg 2929 CSR

As Dr. Roberts points out in her review, the majority of events contributing to the statistical significance of these 'mini-composite' secondary endpoints were non-fatal

events. In the above analysis, there were nine fatal MIs in the rosuvastatin group and six fatal MIs in the placebo group which contributed to the fatal/nonfatal MI composite. There were three fatal strokes in the rosuvastatin group and six fatal strokes in the placebo group which contributed to the fatal/nonfatal stroke composite.

Of the pre-specified secondary endpoints, the sponsor is seeking to include reduction in total mortality in the indication. It should be noted that total mortality was a pre-specified safety endpoint, the intention of which was to show that if a benefit in cardiovascular death was observed, (b) (4) Time to death (total mortality) was collected from deaths that occurred during the study and through external data sources such as public death records which provided only vital status; these cases were not adjudicated. **According to Dr. Roberts' review, in JUPITER, using all information available on vital** status there were a total of 445 deaths, 198 in rosuvastatin-treated subjects and 247 in placebo-treated subjects. When external data sources were excluded there were a total 372 deaths, 167 in rosuvastatin- and 205 in placebo-treatment groups. The analysis including external data sources reached statistical significance with a nominal p-value of 0.02 and there was a trend towards significance when external vital status was omitted with a nominal p-value of 0.05. This outcome variable was not controlled for type 1 error. Additionally, when one excludes the subjects with a Framingham risk category of **'High' who were inadvertently enrolled in the trial, the nominal p-value including** external data sources is 0.05.

As expected, compared to the placebo group there was a significant increase in HDL-C and decrease in all other lipoproteins and hsCRP levels on rosuvastatin therapy after one year and at the Final visit. After 12 months, mean LDL-C was reduced by 40% in the rosuvastatin group compared to a 5% increase in the placebo group. The median percent reduction from baseline of hsCRP in the rosuvastatin-treated subjects was 47% compared to 20% among placebo-treated subjects after one year.

In general, the treatment effect of rosuvastatin on the primary endpoint was consistent across pre-specified subgroups which included age, sex, race, smoking status, BMI, baseline lipoprotein levels, HTN, and metabolic syndrome. All hazard ratios favored the rosuvastatin-treated group.

The results of the primary composite **endpoint and the secondary 'mini-composite'** endpoints remained robust when the 8.8% of subjects in the high Framingham risk category, who should not have been enrolled in the trial, were removed from the analyses.

Post-hoc subgroup analyses were performed on the primary composite endpoint with regard to baseline hsCRP either ≤3 mg/L or greater than >3 mg/L, number of ATP-III risk factors, either <2 or ≥2, and Framingham cardiovascular risk scores. Subjects with less than 2 ATP risk factors, by nature of the trial design, had only age as their risk factor. In this subgroup the hazard ratio was 0.91 (CI: 0.56-1.46). Approximately 25% of JUPITER subjects had less than 2 risk factors.

Table 1: Time to primary composite endpoint among post-hoc subgroups

	Rosuvastatin		Placebo			
Subgroup	N	# of events (rate/1000 pt years)	N	# of events (rate/1000 pt years	Hazard ratio (95% CI)	p-value for interaction
Baseline CRP						
≤3 mg/L	2649	31 (5.6)	2564	70 (13.0)	0.43 (0.28, 0.66)	0.141
>3 mg/L	6252	111 (8.5)	6337	182 (13.9)	0.62 (0.49, 0.78)	
Number of risk factors						
<2	2199	33 (7.1)	2080	35 (7.9)	0.91 (0.56, 1.46)	0.034
≥2	6702	109 (7.8)	6821	217 (15.5)	0.51 (0.40, 0.64)	
Framingham risk scores						
<10% (low risk)	3615	29 (4.0)	3602	43 (6.0)	0.67 (0.42, 1.07)	0.945
10-20% (intermediate risk)	4485	83 (8.6)	4516	171 (17.6)	0.49 0.38, 0.64)	
>20% (high risk)	786	29 (17.2)	772	38 (24.1)	0.70 (0.43, 1.14)	
Applicant's Table 12.1.9.1.4.2, Pg 710, Appendix 12.1.9						

In addition, a post-hoc subgroup analysis of 1405 subjects (725 on rosuvastatin and 680 on placebo), which represented 8% of the JUPITER study population, with zero traditional cardiovascular risk factors (after adjustment for HDL-C ≥60 mg/dL) experienced no significant treatment benefit with rosuvastatin: HR of 1.54 (95% CI 0.26, 1.60).

H. SAFETY

The safety profile for CRESTOR has been established in clinical trials in over 60,000 rosuvastatin-treated patients cumulatively through 31 October 2009 and post-marketing exposure in approximately (b) (4) patients. It is established that treatment with statins, including CRESTOR, is associated with an increase in liver transaminases in a small percentage of subjects, and muscle-related adverse events have been consistently demonstrated in patients treated with statins, including CRESTOR. At the time of initial approval of CRESTOR there were additional concerns regarding hematuria; however, this has not been shown to be clinically significant nor led to impairment in renal function.

The safety population was defined as subjects receiving at least one dose of study medication. The mean exposure to study drug was 1.9 years for both the rosuvastatin and placebo treatment groups.

During the JUPITER trial, mortality was an efficacy endpoint. Any adjudicated cardiovascular death was classified as an efficacy endpoint and not an AE if it occurred before 31 March 2008. Deaths during the randomized treatment phase were adjudicated by the CEC; however, if a death was not considered to be cardiovascular no organ-specific causality was adjudicated.

There were 141 (1.6%) rosuvastatin-treated subjects versus 179 (2.0%) placebo-treated subjects with a treatment emergent AE leading to death. These occurred primarily in the Neoplasms benign, malignant and unspecified (includes cysts and polyps) SOC; however, no particular cancer site or type predominated. Of note was an imbalance in fatal TEAEs in the Gastrointestinal disorders SOC with 13 subjects in the rosuvastatin-treated group versus one subject in the placebo-treated group. Dr. Roberts has reviewed all of the relevant case narratives, case report forms, and source documents. Based on her review she believes this to be a chance finding. I concur. There is no discernible pattern to these cases.

Treatment-emergent non-fatal SAEs occurred in 1269 (14.3%) rosuvastatin-treated patients versus 1269 (14.3%) placebo-treated patients. Slight imbalances were noted in the Gastrointestinal disorders SOC (184 [2.1%] rosuvastatin-treated subjects versus 171 [1.9%] placebo-treated subjects). Again, there is no apparent pattern to the site or type of gastrointestinal SAE.

There was also noted a slight imbalance in the occurrence of treatment-emergent non-fatal SAEs in the Psychiatric disorders SOC (0.3% versus 0.2% in rosuvastatin-treated and placebo treated subjects, respectively) which was attributed to the preferred terms of depression (8 [0.1%] versus 4 [<0.1%]) and confusional state (7 [0.1%] versus 1 [<0.1%]). It should be noted, however, that two of the subjects reporting confusional state were not on study medication at the time and others had concurrent medical conditions and/or medications confounding the event.

A higher percentage of rosuvastatin-treated subjects discontinued study medication due to an adverse event, 6.6% versus 6.2% in the placebo group. The most common adverse reaction that led to study medication discontinuation was myalgia.

Overall hepatic, skeletal, and renal-related AEs occurred with similar frequencies between treatment groups. A higher percentage of rosuvastatin-treated subjects experienced an ALT >3x ULN (1.4% versus 1.0% for placebo-treated subjects) and a small percentage of rosuvastatin-treated subjects experienced an ALT >3x ULN on 2 consecutive occasions (0.3% versus 0.2% for placebo-treated subjects). There were two subjects with bilirubin >2x ULN, AST >3x ULN, and alkaline phosphatase <2x ULN. One was a placebo-treated subject and the other was a rosuvastatin-treated subject with a **concurrent AE of hepatitis C. No Hy's law cases were observed in a rosuvastatin-treated** subject.

Muscle-related AEs occurred at a higher incidence in the rosuvastatin treatment group compared to the placebo group, 16% versus 15.4%, respectively. Myalgia was the most commonly reported preferred term in the rosuvastatin (8.0%) and placebo groups (7.2%). There was one case of rhabdomyolysis in JUPITER in a rosuvastatin-treated subject, a 90 year-old man with influenza and inability to arise from the floor for ~24 hours, secondary to weakness. CK >10x ULN occurred in 2 rosuvastatin-treated subjects and 1 placebo-treated subject.

Hematuria and proteinuria were the most commonly-occurring Renal and Urinary Disorder SOC AEs with a higher incidence in the rosuvastatin treatment group (4.4%) than in the placebo treatment group (3.7%). Acute, chronic, and unspecified renal failure occurred with similar frequency in the 2 treatment groups, 0.8% for both.

With regard to neurocognitive AEs, there were 18 rosuvastatin-treated subjects versus 4 **placebo-treated subjects who experienced an AE of "confusional state". Six of the 18** confusional states in rosuvastatin-treated subjects were considered as a SAE and were discussed above.

A pre-specified, unadjudicated secondary endpoint was time to investigator-reported diabetes which was assessed for every 3 months. In JUPITER there were 251 (2.8%) rosuvastatin-treated subjects with investigator-reported diabetes as compared to 205 (2.3%) placebo-treated subjects.

Table 4: JUPITER: Summary and time to development of investigator-reported diabetes mellitus (without 30 March 2008 cutoff)

	Number of events (% of subjects having an event)						
	Rosuvastatin 20 mg N=8901		Placebo N=8901				
	n	%	n	%	HR	95% CI	p-value
Investigator reported diabetes	251	2.8	205	2.3	1.27	1.05, 1.53	0.015
Source: Applicant's Table 11.3.6.1.2.7 and 11.3.6.1.2.8, Pg 31998 and 31999, CSR							

Criteria used to qualify as new-onset diabetes was new use of insulin or an oral hypoglycemic agent, a positive glucose tolerance test, a random glucose level over 200 mg/dL with symptoms of diabetes, or repeated fasting glucose levels >126 mg/dL. Overall there was a trend of increasing fasting glucose levels (increase of 3% mean change from baseline) in both treatment groups. HbA1c levels rose in both groups, with a significantly different change from baseline of 0.1% between the two treatment groups.

As summarized by Dr. Roberts:

> *Based on the available clinical evidence it appears that as a drug class statins increase the incidence of diabetes mellitus, although there have been no prospective clinical trials with an adjudicated pre-defined endpoint of diabetes incidence examining the relationship between statin use and diabetes incidence or its effect on microvascular disease and its complications. It is well established that people with diabetes are at high risk for major cardiovascular events and are more likely to die due to a cardiovascular event. Large clinical trials have demonstrated that with and without clinically evident cardiovascular disease statins provide a significant treatment benefit in people with diabetes.*[2,3] *In*

[2] Collins et al. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomized placebo-controlled trail.*Lancet.*2003;361:2005-16.
[3] Calhoun et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicenter randomized placebo-controlled trial. *Lancet.*2004; 364:685-96.

JUPITER, 31% of study subjects were diagnosed with impaired fasting glucose at baseline and within this subgroup a treatment benefit was observed (HR 0.66 [95% CI 0.47, 0.93]).

There was a similar frequency of AEs between the rosuvastatin and placebo groups in subjects ≤65 years and >65 years.

Approximately 1.6% of the overall JUPITER study population reported Asian ethnicity. The overall frequency of AEs was similar for Asian subjects in the rosuvastatin and placebo groups (64.6% versus 64.0%, respectively). There was a slightly higher proportion of AEs leading to death and serious AEs in rosuvastatin-treated Asian subjects compared to placebo-treated Asian subjects. There were seven (4.8%) AEs leading to death versus two (1.5%) in the rosuvastatin and placebo groups, respectively. There were 21 (14.3%) SAEs versus eight (5.9%) in the rosuvastatin and placebo groups, respectively.

The safety profile was similar in subjects who had a LDL-C <50 mg/dL at any point during JUPITER. Of subjects with a LDL-C <50 mg/dL, rosuvastatin-treated subjects had 630 (15.2%) treatment emergent SAE versus 51 (22%) in placebo-treated subjects.

To address the concern regarding the achievement of low LDL-C levels on statins and cancer incidence, it is noted that in subjects with an on-study LDL-C less than 50 mg/dL, 2.5% (102/4154) in the rosuvastatin group and 3.9% (9/232) in the placebo group experienced a treatment-emergent serious adverse event in the Neoplasm SOC. Of subjects with a LDL-C less than 50 mg/dL, 7.2% (300/4154) in the rosuvastatin group and 7.2% (18/232) in the placebo group experienced a TEAE in the Neoplasm SOC group, as compared to an overall incidence of 6.8% in the rosuvastatin-treated group and 7.6% in the placebo-treated group.

I. ADVISORY COMMITTEE MEETING

An Advisory Committee meeting was held on 15 December 2009 to discuss the major efficacy and safety findings of the JUPITER trial. No specific discussions with respect to labeling were included as part of **the Advisory Committee's charge.**

Specifically, the committee was asked to comment on the significance of the following safety concerns seen with rosuvastatin treatment in the JUPITER trial:

- Deaths due to gastrointestinal disorders
- Confusional state
- Diabetes mellitus

Please see Dr. Roberts' review for more detailed information regarding the committee's recommendations. The committee members, in general, did not feel that the imbalances in deaths due to GI disorders or imbalance in the occurrence of confusional state among patients treated with rosuvastatin versus those treated with placebo were authentic safety signals.

The committee felt that the imbalance in the reports of diabetes mellitus in the JUPITER trial was related to rosuvastatin treatment, but that it is likely a class effect of statins.

The sponsor will be asked to provide analyses **on the above adverse reactions as "adverse events of special interest" in PSURs which** will need to be submitted semi-annually for the next 2 years.

One voting question was addressed to the committee:
Has the applicant established sufficient benefit to offset the observed risks to support the use of rosuvastatin in individuals meeting the following criteria:

- **Men ≥ 50 years, women ≥ 60 years**
- **Fasting LDL-C <130 mg/dL, hsCRP ≥ 2 mg/L, triglycerides <500 mg/dL**
- **No prior history of cardiovascular or cerebrovascular events or CHD risk equivalent as defined by NCEP ATP-III guidelines.**

The committee voted: 12 'yes', 4 'no', with 1 member abstaining. The committee advised the Agency, however, to carefully define the population for the extended use of CRESTOR in the label and in marketing.

J. PEDIATRICS
A full waiver of the pediatric study requirement under PREA was requested and granted because necessary studies are impossible or highly impracticable. This is because the indication is for an adult-related condition.

K. LABELING
The sponsor's revised indication request is stated below:
1.6 Prevention of Cardiovascular Disease

- Adult patients at (b) (4) risk of cardiovascular disease based on cardiovascular disease risk markers such as age, elevated hsCRP level, hypertension, low HDL-C, smoking or a family history of premature coronary heart disease, CRESTOR is indicated to reduce the risk of total mortality and major cardiovascular events: cardiovascular death, stroke, myocardial infarction, arterial revascularization, unstable angina.

It was the opinion of the clinical and statistical review team that such a claim was unwarranted for several reasons:

- (b) (4)

(b) (4)

- The indication implies benefit across all components of the primary composite endpoint, while analyses of the individual components revealed statistical significance for stroke, MI, and arterial revascularization only. Dr. Roberts has extensively reviewed the statin labels with indications for primary prevention of cardiovascular disease based on composite endpoint trials and has determined that they provide precedent for granting indications for only the statistically significant components of a composite endpoint, even when the overall composite endpoint has achieved **statistical significance. Please see Dr. Roberts' review for further details.**
- Total mortality was a secondary safety endpoint, was not adjudicated, was not corrected for Type I error, and was of nominal statistical significance (p=0.02). As conveyed previously, the intent of studying total mortality in statin trials is to exclude an increase in mortality due to non-cardiovascular causes. It is not biologically plausible that statins reduce all-cause mortality and such information has no place in an indication of efficacy.

The final agreed upon indication is as follows:

1.6 Primary Prevention of Cardiovascular Disease

In individuals without clinically evident coronary heart disease but with an increased risk of cardiovascular disease based on age ≥ 50 years old in men and ≥ 60 years old in women, hsCRP ≥ 2 mg/L, and the presence of at least one additional cardiovascular disease risk factor such as hypertension, low HDL-C, smoking, or a family history of premature coronary heart disease, CRESTOR is indicated to:

- **reduce the risk of stroke**
- **reduce the risk of myocardial infarction**
- **reduce the risk of arterial revascularization procedures**

One of the key issues to resolve in the Clinical Studies section of the labeling was the appropriateness of inclusion of the mini-composite secondary endpoints (fatal and non-fatal MI; fatal and non-fatal stroke; and cardiovascular death, or nonfatal stroke, or nonfatal MI). These mini-composites were all highly statistically significant in favor of rosuvastatin, but because the composites were driven almost exclusively by the non-fatal events, it was felt that the results, unless broken out by the absolute number of events, could lead to misinterpretation of the data with respect to a mortality benefit. It was resolved that the following information could be included in the clinical study results portion of the label:

Rosuvastatin significantly reduced the risk of myocardial infarction (6 fatal events and 62 nonfatal events in placebo-treated subjects vs. 9 fatal events and 22 nonfatal events in rosuvastatin-treated subjects) and the risk of stroke (6 fatal events and 58

nonfatal events in placebo-treated subjects vs. 3 fatal events and 30 nonfatal events in rosuvastatin-treated subjects).

The important safety concern of diabetes will be conveyed in the Warnings & Precautions section of the label, under 5.5 Endocrine Effects. Given that this is likely a class effect of statins[4], the Division will be addressing the need to update all statin labels with regard to this adverse reaction.

The imbalance in the incidence of 'confusional state' will not be labeled at this time. The Office of Surveillance and Epidemiology (OSE) is in the process of reviewing post-marketing data with respect to the association between statin use and acute confusional states which similarly is felt to be a class effect of statins. Pending the OSE review, consideration will be given to updating all statin labels with regard to this adverse reaction.

L. RECOMMENDATIONS/RISK BENEFIT ASSESSMENT

I recommend approval of this efficacy supplement and I concur with Drs. Roberts and Hoberman in their recommendations for revisions in the proposed labeling.

I concur with Dr. Roberts that there is no need for a Risk Evaluation and Mitigation Strategy based on the safety results of the JUPITER trial, nor is there any recommendation for a post-marketing required study or trial. Rather, the sponsor will be asked to submit semi-annual PSURs for the next two years and to provide analyses in those PSURs of all clinical trial and post-marketing reports of the following adverse events of special interest:

- diabetes-related adverse events
- neurocognitive impairment events
- serious gastrointestinal events

It is important, however, to convey to healthcare providers and the media a balanced interpretation of the data than might be gleaned from the recent publications in the medical literature pertaining to the JUPITER trial, and what will ultimately be conveyed to them and the public by the sponsor. This will be accomplished by a Question and Answer document for Healthcare Providers which will be posted on the FDA web site, as well as a press release.

Information to be conveyed should include:

- The absence of data supporting any purported benefit in men < age 50 and women < age 60.
- The absence of data supporting any purported benefit in individuals with only age and an elevated hsCRP as risk factors.

[4] Rajpathak SN et al. Statin therapy and Risk of Developing Type 2 Diabetes: A Meta-Analysis. *Diabetes Care.*2009;32:1924-1929.

- The failure of the study design to establish the validity of hsCRP as a surrogate marker for cardiovascular disease due to the exclusion of individuals with a hsCRP < 2 mg/L.
- The failure of the study design to determine therapeutic goals for hsCRP.

The JUPITER trial does not suggest that mass screening of individuals for elevated hsCRP should be undertaken. In fact, of the approximately 90,000 individuals screened to participate in the JUPITER trial, approximately 26,000, or 28%, were excluded because their hsCRP was <2 mg/L. Furthermore, JUPITER cardiovascular event rates were very low, 2.8% for individuals receiving placebo, and 1.6% for individuals receiving CRESTOR. So, purely from a cost-benefit perspective, such an approach is unwarranted.

What JUPITER did demonstrate is that a subset of patients at intermediate risk for **cardiovascular events based on Framingham risk assessment may be 're-classified' to a** higher risk category on the basis of an elevated hsCRP. The NCEP ATP IV guidelines are due to issue this year. It is hoped that these guidelines will elucidate the clinical utility of hsCRP in identifying a broader population of patients who may benefit from statin therapy.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21366	SUPPL-16	IPR PHARMACEUTICALS INC	CRESTOR(ROSUVASTATIN CALCIUM)10/20/40/80

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMY G EGAN
02/05/2010