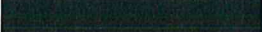

Clinical Study Report Synopsis

Drug Substance Rosuvastatin calcium
 Study Code D3560L00030 (4522US/0011)
 Edition Number
 Date 26 February 2009

JUPITER

**Justification for the Use of statins in Primary prevention: an Intervention Trial
 Evaluating Rosuvastatin**

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

Study dates:	First subject enrolled: 05 February 2003 Last subject completed: 20 August 2008
Phase of development:	Therapeutic confirmatory (III)
International Co-ordinating Investigator:	Paul M. Ridker, MD, MPH Director, Centre for Cardiovascular Disease Prevention, Brigham and Women's Hospital Eugene Braunwald Professor of Medicine, Harvard Medical School 900 Commonwealth Avenue Boston, MA 02215 United States of America
Sponsor's Responsible Medical Officer:	 Executive Director Medical Science CRESTOR™

C

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

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

CRESTOR is a trademark of the AstraZeneca group of companies.

Study centre(s)

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

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

Publications

1. Glynn RJ, MacFadyen JG, Ridker PM. Tracking of high-sensitivity C-reactive protein after observation of an initially increased concentration: the JUPITER study. *Clin Chem* 2009;55:305-312.
2. Ridker PM. Rosuvastatin in the primary prevention of cardiovascular disease among patients with low levels of low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein: rationale and design of the JUPITER trial. *Circulation* 2003;108:2292-7.
3. Ridker PM, Fonseca FAH, Genest J, Gotto AM, Kastelein JJP, Khurmi NS, et al on behalf of the JUPITER Trial Study Group. Baseline Characteristics of Participants in the JUPITER Trial, A Randomized Placebo-Controlled Primary Prevention Trial of Statin Therapy Among Individuals With Low Low-Density Lipoprotein Cholesterol and Elevated High-Sensitivity C-Reactive Protein. *Am J Cardiol* 2007;100:1659-64.
4. Ridker PM, Danielson ED, Fonseca FAH, Genest J, Gotto AM, Kastelein JJP, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008;359(21):2195-207.

Objectives

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

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

Study design

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

Target subject population and sample size

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

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

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

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

Table S1 Details of investigational product and any other study treatments

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

Duration of treatment

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

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

Criteria for evaluation - efficacy (main variables)

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

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

Criteria for evaluation - safety (main variables)

Incidence of adverse events (AEs) and abnormal laboratory values

Statistical methods

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

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

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

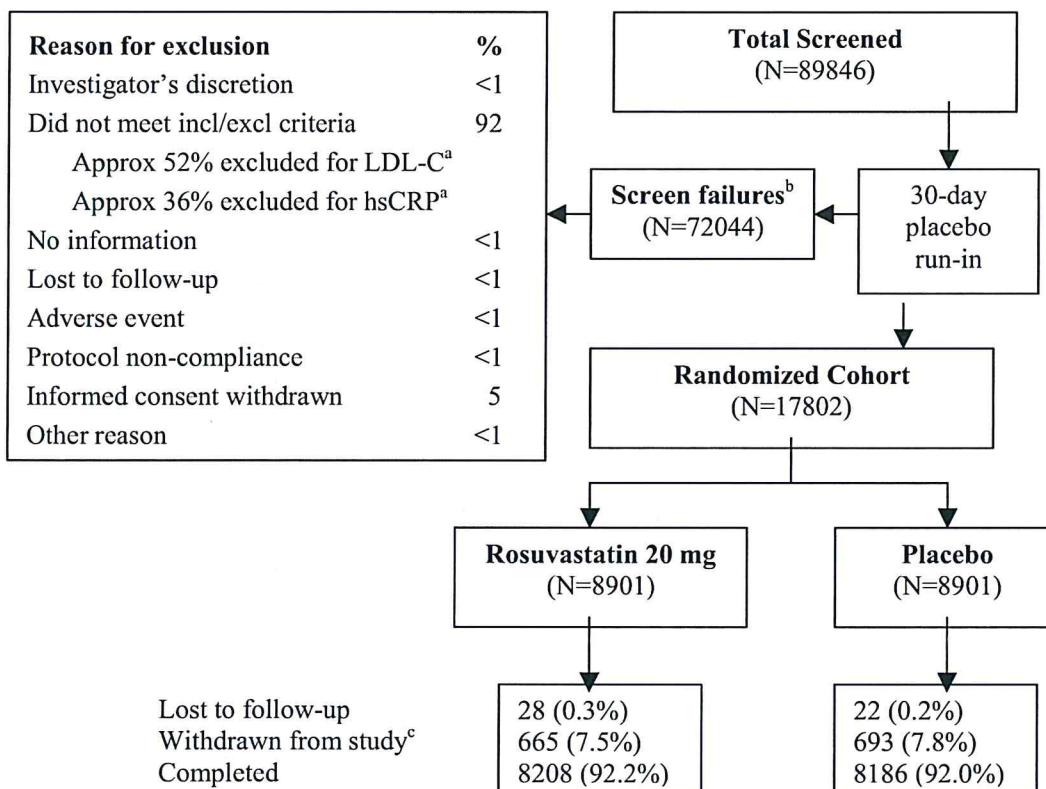
Kaplan-Meier plots were presented for time-to-event variables. Descriptive analyses used the Kaplan-Meier estimates of the probability of remaining free of event for each treatment.

Subject population

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

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

Figure S1 Disposition of JUPITER study subjects



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

^a These numbers reported in Ridker et al 2008.

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

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

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

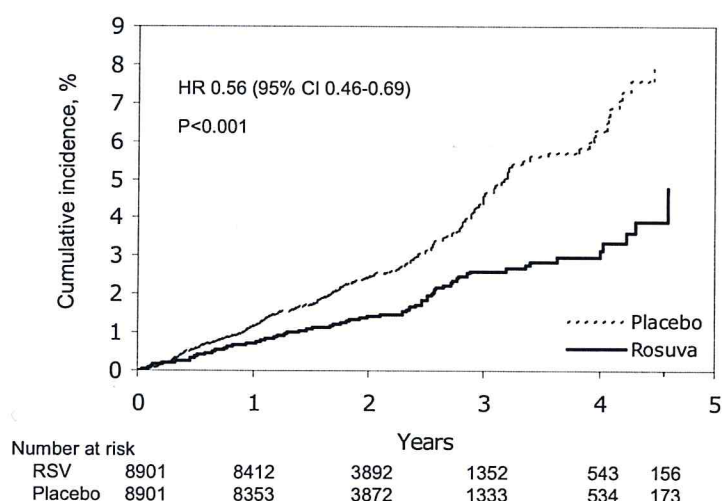
randomized population had low baseline LDL-C levels (mean 104 mg/dL [2.7 mmol/L]). At baseline, the median hsCRP level was 4.3 mg/L. Approximately 70% of subjects had hsCRP >3 mg/L and 30% of subjects had an hsCRP ≤3 mg/L, an “average hsCRP risk” based on CDC/AHA recommendations.

Summary of efficacy results

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

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

Figure S2 Kaplan-Meier plot for the primary composite endpoint



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

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

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

	Number of first events			
	Rosuva 20 mg (N=8901)	Placebo (N=8901)		
	n	n		
First MCE ^a	142	252		
Cardiovascular death	29	37		
Nonfatal MI	21	61		
Non fatal Stroke	30	57		
Hospitalized unstable angina	15	27		
Arterial revascularization	47	70		
Event rate/1000-patient years				
	Rosuva 20 mg	Placebo	HR (95% CI)	P value
First MCE	7.6	13.6	0.56 (0.46, 0.69)	<0.001

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

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

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

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

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

Summary of safety results

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

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

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

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

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

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

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

Conclusion(s)

- Rosuvastatin reduced the risk of MCEs (cardiovascular death, stroke, MI, arterial revascularization, or hospitalized unstable angina) by 44% ($p < 0.001$) and reduced the risk of cardiovascular death/ MI/stroke by [REDACTED] in a population that did not require statin treatment under current guidelines. This was accompanied by a [REDACTED] reduction in LDL-C observed with rosuvastatin treatment.
- Rosuvastatin reduced total mortality by 20% ($p = 0.021$).
- Rosuvastatin 20 mg was safe and well-tolerated in this study of the long-term safety and cardiovascular risk reducing efficacy of rosuvastatin treatment.

- Overall, JUPITER demonstrated a favorable balance of benefits to risks for rosuvastatin 20 mg.
- Data obtained from JUPITER and previously reported statin trials supports the use of rosuvastatin to reduce the risk of atherosclerotic cardiovascular disease events in subjects with an increased risk of cardiovascular disease.

Date of the report

26 February 2009

Clinical Study Report Appendix 12.1.1

Drug Substance Rosuvastatin

Study Code D3560L00030
(4522US/0011)

Appendix 12.1.1
Protocol and Protocol Amendments

VERSION OF PROTOCOL OR PROTOCOL AMENDMENT

Document	Date of issue
First final version of the protocol which includes amendment 1	15 January, 2003
Protocol amendment 2	29 April, 2003
Protocol amendment 3	21 October, 2004
Protocol amendment 4	20 September, 2005
CSP Admin change 1	27 April, 2004
CSP Admin change 2	20 March, 2007

Clinical Study Protocol

Drug Substance	Rosuvastatin
Study Code	4522US/0011
Version No.	2.0
Date	15 January, 2003

JUPITER

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

The following amendment(s) have been made to this protocol since the date of preparation:

Amendment No.	Date of amendment
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01	15 January, 2003
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15 January, 2003

1(53)

Section 5.3.5.1.1 /p.3

PROTOCOL SYNOPSIS

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

Investigator

Paul M Ridker, MD, MPH, FACC

Director, Center for Cardiovascular Disease Prevention

Brigham and Women's Hospital

Harvard Medical School

900 Commonwealth Avenue East

Boston, MA 02215

Study center(s) and number of subjects planned

This study will be conducted in approximately 15,000 male and female subjects recruited from the United States (approximately 500 centers). It is planned to recruit approximately 30 subjects per center.

Study period

Estimated date of first subject
enrolled

February 2003

Estimated date of last subject
completed

December 2007

Phase of development

III

Objectives

Primary objective:

The primary objective of the study is to investigate whether long-term treatment with rosuvastatin 20 mg compared with placebo will decrease the rate (based on time to first event after randomization) of major cardiovascular events (combined endpoint of cardiovascular death, stroke, myocardial infarction, unstable angina, or arterial revascularization) among individuals with low LDL-C (<130 mg/dL [3.36 mmol/L]) who are at high vascular risk on the basis of an enhanced inflammatory response, as determined by elevated levels of CRP (≥ 2.0 mg/L).

Secondary objectives:

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

Study design

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

Target subject population

This study will recruit men aged 55 years and older and women aged 65 years and older, who have no prior history of MI, stroke or arterial revascularization and who, on initial screening, are found to have LDL-C levels <130 mg/dL (3.36 mmol/L) and CRP levels ≥ 2.0 mg/L.

Investigational product, dosage and mode of administration

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

Comparator, dosage and mode of administration

No comparator will be used.

Duration of treatment

After a 4-week run-in period, subjects meeting the study inclusion criteria and having none of the exclusion criteria will be allocated to receive either rosuvastatin 20 mg/day or matching placebo until 520 events have occurred, which is expected to occur after a mean follow-up of approximately 3.5 years.

Endpoints

Primary Endpoint:

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

Secondary Endpoints:

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

- (1) total mortality
- (2) noncardiovascular mortality
- (3) discontinuation of blinded study medication due to adverse effects
- (4) development of diabetes mellitus
- (5) development of venous thromboembolic events (deep vein thrombosis or pulmonary embolism)
- (6) bone fractures

Statistical methods

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

TABLE OF CONTENTS	PAGE
1. INTRODUCTION.....	11
1.1 Background	11
1.2 Rationale for this study	12
2. STUDY OBJECTIVES.....	14
2.1 Primary objective	14
2.2 Secondary objectives.....	15
3. STUDY PLAN AND PROCEDURES	15
3.1 Overall study design and flow chart.....	15
3.2 Rationale for study design, doses and control groups.....	23
3.3 Selection of study population.....	23
3.3.1 Study selection record.....	23
3.3.2 Inclusion criteria	23
3.3.3 Exclusion criteria	24
3.3.4 Discontinuation of subjects from treatment or assessment.....	25
3.3.4.1 Criteria for discontinuation	25
3.3.4.2 Voluntary discontinuation by a subject.....	25
3.3.4.3 Incorrectly enrolled or randomized subjects	26
3.3.4.4 Procedures for discontinuation.....	26
3.3.4.5 Procedures for lost-to-follow-up	26
3.3.5 Restrictions	26
3.4 Treatments.....	27
3.4.1 Investigational products	27
3.4.1.1 Identity of investigational product and comparators.....	27
3.4.1.2 Labeling	28
3.4.1.3 Storage	28
3.4.1.4 Accountability.....	28
3.4.2 Doses and treatment regimens	28
3.4.3 Method of assigning subjects to treatment groups.....	29
3.4.3.1 Interactive Voice Response System (IVRS)	29
3.4.4 Blinding and procedures for unblinding the study	30
3.4.4.1 Methods for ensuring blinding.....	30
3.4.4.2 Methods for unblinding the study	30
3.4.5 Pre-study, concomitant and post-study treatments.....	30
3.4.6 Treatment compliance.....	31
4. STUDY MEASUREMENTS AND ENDPOINTS.....	31
4.1 Primary endpoint.....	31

4.2 Screening and demographic measurements	34
4.3 Efficacy and pharmacodynamic measurements and endpoints	34
4.3.1 Summary of efficacy and pharmacodynamic objectives and endpoints	34
4.4 Safety measurements and endpoints	34
4.4.1 Summary of safety objectives and endpoints	34
4.4.2 Adverse Events	34
4.4.2.1 Definitions.....	34
4.4.2.2 Recording of adverse events	35
4.4.2.3 Reporting of serious adverse events.....	36
4.4.2.4 Reporting of Endpoints	37
4.4.2.5 Reporting of Serious Adverse Events, and Primary and Secondary Endpoints to Independent Data Monitoring Board.....	37
4.4.3 Laboratory safety measurements and variables.....	37
4.4.3.1 Methods of assessment	37
4.4.3.2 Calculation or derivation of endpoints.....	38
4.4.4 Other safety measurements and variables	38
4.5 Health Economic Evaluation	39
4.5.1 Data Collection	39
4.5.2 Cost Analysis of Clinical Endpoints	39
4.5.3 Cost-Per-Life-Year-Saved.....	40
5. DATA MANAGEMENT.....	40
6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE.....	40
6.1 Determination of sample size.....	40
6.2 Statistical evaluation	43
6.2.1 Methods of statistical analysis	43
6.2.2 Study endpoints.....	43
6.2.3 Statistical analyses	43
6.2.4 Interim analyses	44
6.3 Independent Data Monitoring Board	45
6.4 Steering Committee	45
6.5 Endpoint Committee	45
7. STUDY MANAGEMENT	46
7.1 Monitoring	46
7.2 Audits and inspections	46
7.3 Training of staff	47
7.4 Changes to the protocol.....	47
7.5 Study agreements	47

7.6 Genetic sampling and storage	47
7.7 Volume of blood sampling and handling of biological samples.....	48
7.8 Study timetable and termination	48
8. ETHICS.....	48
8.1 Ethics review.....	48
8.2 Ethical conduct of the study.....	49
8.3 Subject information and consent.....	49
8.4 Subject data protection.....	49
9. EMERGENCY PROCEDURES.....	50
9.1 AstraZeneca emergency contact procedure.....	50
9.2 Procedures in case of medical emergency.....	50
9.3 Procedures in case of overdose	50
10. REFERENCES	50

Index of Tables

Table 1 Abbreviations and specialist terms	9
Table 2 Event rates, relative risks (RR) and the number needed to treat (NNT) associated with statin allocation among AFCAPS/TexCAPS participants, according to baseline levels of LDL-C and CRP.....	13
Table 3 Event rates, relative risks (RR) and the number needed to treat (NNT) associated with statin allocation among AFCAPS/TexCAPS participants, according to baseline levels of the TC:HDL-C ratio and CRP.....	14
Table 4 Study plan	22
Table 5 Trial Medication.....	27
Table 6 Alternative event rates, trial designs and required study size for evaluation of Rosuvastatin therapy with 90% power.....	41
Table 7 Volume of blood to be drawn from each subject	48

Index of Figures

Figure 1 Study Flow Chart.....	21
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APPENDICES

Appendix A	Signature pages
Appendix B	Sample written informed consent form
Appendix C	Declaration of Helsinki
Appendix D	Investigator(s) and study administration structure
Appendix E	Insurance and Indemnity
Appendix F	Additional safety information
Appendix G	Management of Elevated Liver Enzymes
Appendix H	Management of Increased Creatine Kinase (CK)
Appendix I	Disallowed Concomitant Medications

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1 Abbreviations and specialist terms

Abbreviation or specialist term	Explanation
AE	Adverse event (see definition in Section 4.4.2.1).
AFCAPS/TexCAPS	Airforce/Texas Coronary Atherosclerosis Prevention Study
ALT	Alanine aminotransferase
Apo (A-1, B-100)	Apolipoprotein (A-1, B-100)
AST	Aspartate aminotransferase
ATP III	Adult Treatment Panel III
β-HCG	β-human chorionic gonadotropin
CABG	Coronary artery bypass graft
CDCP	Center for Disease Control and Prevention
CI	Confidence interval
CK	Creatine kinase
CK-MB	Creatine kinase MB band isoenzyme
CRF	Case report form
CRP	C-reactive protein
CSR	Clinical Study Report
CT	Computed tomography
IDMB	Independent Data Monitoring Board
DM	Diabetes Mellitus
ECG	Electrocardiogram
FSG	Fasting serum glucose
GCP	Good Clinical Practice
HbA _{1c}	Glycosylated hemoglobin
HDL-C	High-density lipoprotein cholesterol
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
HRT	Hormone replacement therapy
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	International normalized ratio

Abbreviation or specialist term	Explanation
IRB	Institutional Review Board
ITT	Intention-to-treat
IVRS	Interactive Voice Response System
LDL-C	Low-density lipoprotein cholesterol
MI	Myocardial Infarction
MRI	Magnetic resonance imaging
NCEP	National Cholesterol Education Program
NHLBI	National Heart, Lung and Blood Institute
NNT	Number needed to treat
OAE	Other significant adverse event (ie, an adverse event of special interest in this clinical development; see definition in Section 4.4.2.1). The classification of OAEs will be performed by AstraZeneca drug safety physicians after the study is complete.
Pap	Papanicolaou cervical smear
Principal investigator	The investigator who leads the study conduct at an individual study center. Every study center has a principal investigator.
PTCA	Percutaneous transluminal coronary angioplasty
PTI	Percutaneous transluminal intervention
RR	Relative risks
SAE	Serious adverse event (see definition in Section 4.4.2.1).
SAP	Statistical analysis plan
TC	Total cholesterol
TG	Triglycerides
TLC	Therapeutic Lifestyle Changes
TPD	Therapeutic Products Directorate
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
WOSCOPS	West of Scotland Coronary Prevention Study

1. INTRODUCTION

1.1 Background

Completed randomized studies of statin therapy indicate that 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibition (statin) is associated with reduced rates of myocardial infarction (MI), stroke, and other cardiovascular events among individuals with established coronary disease or with overt hyperlipidemia (Downs et al 1998, Shepherd et al 1995, 4S Survival Study Group 1994, Sacks et al 1996, LIPID Trial Group 1998). In aggregate, use of statin therapy in these trials has been associated with an approximately 30% reduction in the relative risk of developing future cardiovascular events. This is also likely to have been the case in the Heart Protection Study (HPS Collaborative Group 2002) in which a 24% relative risk reduction was observed despite the fact that over one third of those allocated to placebo were taking active lipid-lowering therapy at trial completion. In the HPS trial, the compliance adjusted relative risk reduction has been reported to exceed 33%.

Largely on the basis of these cholesterol reduction trials, current National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) Guidelines strongly endorse statin therapy in secondary prevention, and encourage use of statins in primary prevention among individuals with overt hyperlipidemia (NCEP-ATP III 2001). However, almost half of the future vascular events occur among apparently healthy individuals with normal low-density lipoprotein cholesterol (LDL-C) levels (Ridker et al 2001). Thus, very large numbers of patients are at substantive risk for future vascular disease and might well benefit from prophylactic statin therapy. Performing placebo-controlled studies of statin therapy among such patients is likely to be difficult unless (a) a high-risk group without hyperlipidemia can be identified, and (b) there is evidence that statin therapy is likely to be effective among such patients.

Research from several groups (Ridker et al 1997, 1998, 1998, 2000, 2001, 2001; Danesh et al 2000; Tracy et al 1997; Koenig et al 1999; Kuller et al 1996; and Haverkate 1997) has shown that C-reactive protein (CRP), a marker of low grade systemic inflammation, is a strong predictor of vascular risk among apparently healthy men and women, even in the absence of hyperlipidemia. Moreover, in studies of over 8000 patients it has been shown that statin therapy lowers CRP in a lipid-independent fashion (Ridker et al 1999, 2001; Albert et al 2001) and that the magnitude of benefit of statin therapy is greater in the presence of high CRP levels (Ridker et al 1998, 1998).

Finally, concerning the critical issue of primary prevention, it has been demonstrated in a hypothesis-generating setting that the absolute risk of a future cardiovascular event among those with low to normal LDL-C levels but above normal CRP levels is just as high as in those with overt hyperlipidemia, and that statin therapy is highly effective in this group (Ridker 2001).

Based on these observations, it is probable that many individuals are at substantial risk for coronary disease and are likely to benefit from prophylactic statin therapy, but do not currently

qualify for treatment. It is thus the primary aim of this study to determine whether long term therapy with rosuvastatin will be effective in reducing the risk of first ever acute coronary events among apparently healthy men and women with low to normal levels of LDL-C but elevated CRP levels. As half of all heart attacks and stroke occur in the United States among individuals without overt hyperlipidemia, this study is likely to have major public health importance and, if successful, will result in far broader use of statin therapy in primary prevention than is currently accepted. Indeed, the estimated target population in the United States alone is 25 to 30 million individuals.

1.2 Rationale for this study

Two landmark clinical trials, the Airforce/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS, Downs et al 1998) and the West of Scotland Coronary Prevention Study (WOSCOPS, Shepherd et al 1995), clearly demonstrate that HMG-CoA reductase inhibition reduces the risk of first cardiovascular events. However, use of statins in the primary prevention of cardiovascular disease has not been widely adopted in part because the number of individuals who need to be treated to prevent 1 clinical event is relatively large, at least in comparison to secondary prevention (Goldman et al 1991).

A method to distinguish high from low risk patients in the setting of primary prevention might allow better targeting of statin therapy. For example, restricting statin use to those with overt hyperlipidemia appears to improve the cost-effectiveness of these agents in primary prevention (Jacobson et al 1998; Garber 2000) and current NCEP guidelines suggest that statins be initiated in this setting when LDL-C levels exceed 160 mg/dL (4.14 mmol/L) (NCEP-ATP III 2001). Unfortunately, half of all acute coronary events occur among apparently healthy individuals without such overt hyperlipidemia. Thus, lipid screening alone may fail to identify all high-risk subgroups likely to benefit from statin therapy.

Over the past 5 years, interest has increased in the use of inflammatory markers such as CRP as a novel method to detect vascular risk among apparently healthy men and women, particularly when lipid levels are low (Ridker et al 1997, 1998, 1998, 2000, 2001, 2001; Danesh et al 2000; Tracy et al 1997; Koenig et al 1999; Haverkate et al 1997). These data are intriguing as it has also been shown that statin therapy reduces CRP levels (Ridker et al 1999, 2001, 2001; Albert et al 2001) and both experimental and clinical studies have suggested that statins have direct anti-inflammatory effects (Farmer 2000). However, while the addition of CRP evaluation to lipid screening has been shown to improve risk prediction for those with low as well as high lipid levels (Ridker 1998, 2000), until recently no clinical data have been available which demonstrate that CRP levels can be used to identify specific patient subsets more or less likely to benefit from statin therapy.

To address this issue, an hypothesis-generating study was recently completed in which CRP levels were measured at baseline among 5742 participants enrolled in AFCAPS/TexCAPS, a randomized, double-blind, placebo-controlled trial of lovastatin in the primary prevention of acute cardiovascular events conducted among men and women with average cholesterol levels (Ridker 2001). The main findings of that study are presented in Tables 2 and 3 (Table 2:

Event rates, relative risks [RR] and the number needed to treat [NNT] associated with statin allocation among AFCAPS/TexCAPS participants, according to baseline levels of LDL-C and CRP; Table 3: Event rates, relative risks [RR] and the number needed to treat [NNT] associated with statin allocation among AFCAPS/TexCAPS participants, according to baseline levels of the TC:HDL-C ratio and CRP).

In brief, as expected among study participants with above median LDL-C levels, statin therapy was clinically effective in reducing cardiovascular events regardless of CRP levels (relative risk = 0.53, 95% confidence interval (CI) 0.37 - 0.77, NNT = 42).

However, as also shown in Table 2, baseline CRP levels had a major effect on determining the efficacy of statin therapy among those with below median LDL-C levels. Specifically, among those with below median LDL-C levels who had above median CRP levels (low LDL-C/high CRP), lovastatin significantly reduced the risk of cardiovascular events (relative risk = 0.58, 95% CI = 0.34 - 0.98). Thus, the NNT among individuals with low LDL-C but high CRP levels was 48, an estimate almost identical to that observed among those high LDL-C levels.

In marked contrast, among AFCAPS/TexCAPS participants with below median LDL-C and below median CRP levels (low LDL-C/low CRP), there was no evidence that statin therapy reduced the risk of future cardiovascular events (relative risk = 1.08, 95% CI 0.56 - 2.08).

Table 2 Event rates, relative risks [RR] and the number needed to treat [NNT] associated with statin allocation among AFCAPS/TexCAPS participants, according to baseline levels of LDL-C and CRP.

Study Group	Statin		Placebo		RR	95 % CI	NNT*
	N	rate	N	rate			
low LDL-C, low CRP	19/726	0.026	17/722	0.024	1.08	0.56-2.08	-----
low LDL-C, high CRP	22/718	0.031	37/710	0.052	0.58	0.34-0.98	48
high LDL-C, low CRP	15/709	0.021	37/711	0.052	0.38	0.21-0.70	33
high LDL-C, high CRP	29/741	0.039	40/705	0.057	0.68	0.42-1.10	58

* Number needed to treat (NNT) calculated based on 5 patient-years

To address the robustness of these findings, these analyses were repeated stratifying study participants into low and high risk groups based upon the total cholesterol (TC):high-density lipoprotein cholesterol (HDL-C) ratio and found almost identical results.

Specifically, as shown in Table 3, the relative risk of future cardiovascular events associated with statin therapy was 0.47 (95% CI 0.27 to 0.85) among those with below median levels of the TC:HDL-C ratio who had above median levels of CRP (low TC:HDL-C/high CRP), such that the NNT in this group was 43. However, statin therapy was minimally effective among those with below median levels of the TC:HDL-C ratio who also had below median levels of

CRP (low TC:HDL-C/low CRP), a group in which the NNT to avoid 1 cardiovascular event was 983.

Table 3 Event rates, relative risks [RR] and the number needed to treat [NNT] associated with statin allocation among AFCAPS/TexCAPS participants, according to baseline levels of the TC:HDL-C ratio and CRP.

Study Group	Statin		Placebo		RR	95 % CI	NNT*
	N	rate	N	rate			
low TC:HDL-C, low CRP	19/762	0.025	20/763	0.026	0.88	0.47-1.67	983
low TC:HDL-C, high CRP	17/650	0.026	35/696	0.050	0.47	0.27-0.85	43
high TC:HDL-C, low CRP	15/673	0.022	34/670	0.051	0.42	0.23-0.77	35
high TC:HDL-C, high CRP	34/809	0.042	42/719	0.058	0.72	0.46-1.13	62

* Number needed to treat (NNT) calculated based on 5 patient-years

As clearly demonstrated in both Tables 2 and 3, the absolute event rate in the low lipid/high CRP subgroups was just as high as the absolute event rate in the high lipid groups. **As such, these hypothesis-generating data strongly suggest that (a) CRP screening can be used to identify high risk populations even in the absence of hyperlipidemia; and (b) that such patients are just as likely to benefit from statin therapy as are those with evidence of hyperlipidemia.** It is critical to recognize, however, that the total number of events in the low LDL/high CRP stratum of the AFCAPS/TexCAPS trial was only 37 on placebo and 22 on statin therapy. Thus, a large-scale, prospective test of this primary prevention hypothesis is now critical, since a positive finding would have major public health implications and lead to far wider use of prophylactic statin therapy than is currently accepted.

In addition to the primary aim of the study, the unique structure of this study in which enrollment is based upon the presence of an elevated CRP level, will also allow for prospective test of whether or not rosuvastatin therapy reduces incident diabetes mellitus. This hypothesis is of particular interest, as it has recently been shown that elevated levels of CRP are a strong independent risk factor for incident diabetes mellitus among apparently healthy individuals with no baseline evidence of glucose intolerance or abnormal levels of glycosylated hemoglobin (HbA_{1c}) (Pradhan et al 2001).

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of the study is to investigate whether long-term treatment with rosuvastatin 20 mg compared with placebo will decrease the rate (based on time to first event after randomization) of major cardiovascular events (combined endpoint of cardiovascular

death, stroke, myocardial infarction, unstable angina, or arterial revascularization) among individuals with low LDL-C (<130 mg/dL [3.36 mmol/L]) who are at high vascular risk on the basis of an enhanced inflammatory response, as determined by elevated levels of CRP (≥ 2.0 mg/L).

2.2 Secondary objectives

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

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design and flow chart

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

Approximately 15,000 subjects, men 55 years or older and women 65 years or older, will be randomized and followed for a period of approximately 3.5 years to accrue the 520 clinical endpoints upon which the study is powered (see Section 6.1). Subjects will be recruited from the United States (approximately 500 centers); each center will recruit approximately 30 subjects.

Following Screening Visit 1, all potentially eligible study subjects will come back for Screening Visit 2 to enroll in a 4-week run-in phase; during this time, they will receive placebo therapy. The purpose of this run-in phase is to select subjects who will be compliant for study drug. All subjects who are found to be compliant during the 4-week run-in phase (defined as taking $>80\%$ of all study tablets) and who meet all of the study inclusion/exclusion criteria, will be randomized, in a double-blind manner, to either 20 mg oral rosuvastatin daily or to matching placebo.

At Week 13, all randomized study subjects will return for an initial Safety Visit; at this time a safety blood sample will be obtained. Throughout the study, subjects will be seen for study assessments at 6-month intervals (see Table 4) until they reach either the study endpoint or study completion.

Any randomized individual for whom alanine aminotransferase (ALT) levels are elevated to $>3 \times$ upper limit of normal (ULN) on 2 consecutive measurements will be asked to discontinue

study medication. However, such subjects will continue to be followed for the study duration, as they have completed the randomization process and thus are full participants in the study.

All randomized study subjects will be followed over an estimated 3.5 year period for the occurrence of a first ever acute cardiovascular event, defined as cardiovascular death, stroke, myocardial infarction, unstable angina, or arterial revascularization. At the time of the subject's first cardiovascular event, blinded study therapy will be discontinued. The subject will continue to follow scheduled study assessments until study completion and will be treated as deemed appropriate by the investigator.

For subjects with ≥ 2 CHD risk factors, whose LDL levels rise to ≥ 130 mg/dL during the study, the following procedure will be followed, in accordance with NCEP ATP III guidelines.

- a) The site will be notified by the central lab of the rise
- b) An additional visit should be scheduled to repeat fasting lipid profile in 6 weeks
- c) If the repeat LDL-C level is < 130 mg/dL, no changes are instituted and subject should return for the next scheduled visit per protocol
- d) If the repeat LDL-C level is ≥ 130 mg/dL, the Framingham risk is calculated by the central lab and the subject should be initiated on Therapeutic Lifestyle Changes (TLC), as defined by NCEP ATP III. In addition, subjects whose 10-year risk is $\geq 10\%$, are asked to return for an additional fasting lipid profile in 3 months; subjects whose 10-year risk is $< 10\%$ are asked to return for the next scheduled visit per protocol
- e) *After 3 months of TLC* the site is notified of subjects whose 10-year risk is $> 10\%$ and LDL-C level is ≥ 130 mg/dL
- f) *These subjects* should be evaluated by the investigator for the appropriateness of initiation of lipid-lowering drug therapy. If this is deemed necessary, it is recommended that a bile-acid sequestrant (eg. colestipol) or cholesterol absorption inhibitors (ezetimibe) are considered as first-line therapy. However, if in the opinion of the investigator, an HMG CoA reductase inhibitor is indicated, the subject should discontinue the blinded study medication before treatment initiation
- g) *If blinded medication is discontinued, the subject should return for all subsequent follow-up visits.*

There are a minimum of 10 study visits planned. Visits 1 and 2 occur during the placebo run-in period and Visits 3-10 occur during the randomized treatment period. Until the study closes, subjects who have completed Visit 10 but have not reached a study endpoint will be asked to return at six-month intervals to repeat the assessments conducted at Visit 9. If these additional visits are required, they will be numbered Visit 10.1, 10.2, etc. Once the study completes, all subjects will attend the clinic for their final visit (Visit F).

For Visits 2 and 3, the allowed visit window will be ± 3 days. For Visits 4 and 5, the allowed visit window will be ± 9 days. For Visits 6 onwards, the allowed visit window will be ± 10 days. If the date of an individual visit does not conform to the study plan and is therefore outside of the permitted visit window, the timing of subsequent visits should be planned to maintain the visit schedule relative to Visit 3, the Randomization Visit.

Assessments planned at each visit are detailed below:

Screening Visit 1 (Week -6)

- Full informed consent taken before any assessments; this includes the addendum to the informed consent for those subjects who agree to have their samples stored for future genetic analyses
- Subject eligibility assessed
- Fasting blood sample taken for analysis of total cholesterol (TC), LDL-C, HDL-C, triglycerides (TG) and CRP

Screening Visit 2 (Week -4)

- Inclusion/exclusion eligibility confirmed
- Fasting blood sample taken for analysis of CRP, ALT, CK, Apolipoprotein (Apo) A-1 and Apo B-100, creatinine, TSH, fasting serum glucose (FSG), HbA_{1c} and complete blood count (CBC)
- Urinalysis

NOTE: Plasma and buffy coat samples obtained at Visit 2, in addition to being used for cholesterol, CRP, and safety evaluations, will also be stored for future use in genomic and proteomic analyses relating to lipid metabolism, inflammatory function, and statin therapy. Samples for genetic analyses will be retained only for those subjects who have signed the addendum to the informed consent at Visit 1. To ensure participant confidentiality, these additional study samples will be coded with separate participant identifiers during the course of the study and will be rendered fully anonymous after the study has been completed.

- Physical exam performed
- Waist circumference taken
- Screening medical history obtained concerning cardiovascular risk factors, family history of premature coronary disease, and co-morbid conditions
- Prior/current medications recorded

- Run-in study medication dispensed to subject
- Subjects who do not meet the entry criteria should be considered screen failures and a Screen Fail Case Report Form (CRF) should be completed

Randomization Visit 3 (Week 0)

- Inclusion/exclusion eligibility confirmed
- Run-in study medication compliance checked
- Adverse experiences assessed
- Concomitant medications recorded
- Endpoint and diabetes mellitus (DM) assessed
- Randomized study drug dispensed

Safety Visit 4 (3-Month Visit)

- Fasting blood samples taken for CRP and ALT
- Urinalysis
- Study medication compliance checked
- Endpoint and DM assessed
- Adverse experiences assessed
- Concomitant medications recorded
- Randomized study drug dispensed

Visits 5, 7, 9 (6-, 18-, 30-Month Visits)

- Study medication compliance checked
- Endpoint and DM assessed
- Adverse experiences assessed
- Concomitant medications recorded
- Blood samples taken for analysis of ALT

- Urinalysis
- Study medication dispensed

Visit 6 (12-Month Visit)

- Study medication compliance checked
- Endpoint and DM assessed
- Adverse experiences assessed
- Concomitant medications recorded
- Fasting blood samples taken for analysis of TC, LDL-C, HDL-C, TG, Apo A-1 and Apo B-100, CRP, and ALT
- Urinalysis
- Study medication dispensed

Visits 8, 10 (24-, 36-Month Visits)

- Study medication compliance checked
- Endpoint and DM assessed
- Adverse experiences assessed
- Concomitant medications recorded
- Fasting blood samples taken for analysis of TC, LDL-C, HDL-C, TG, CRP, ALT, and FSG and HbA_{1c}
- Urinalysis
- Study medication dispensed

Visits 10.1, 10.2, . . . etc. (if required)

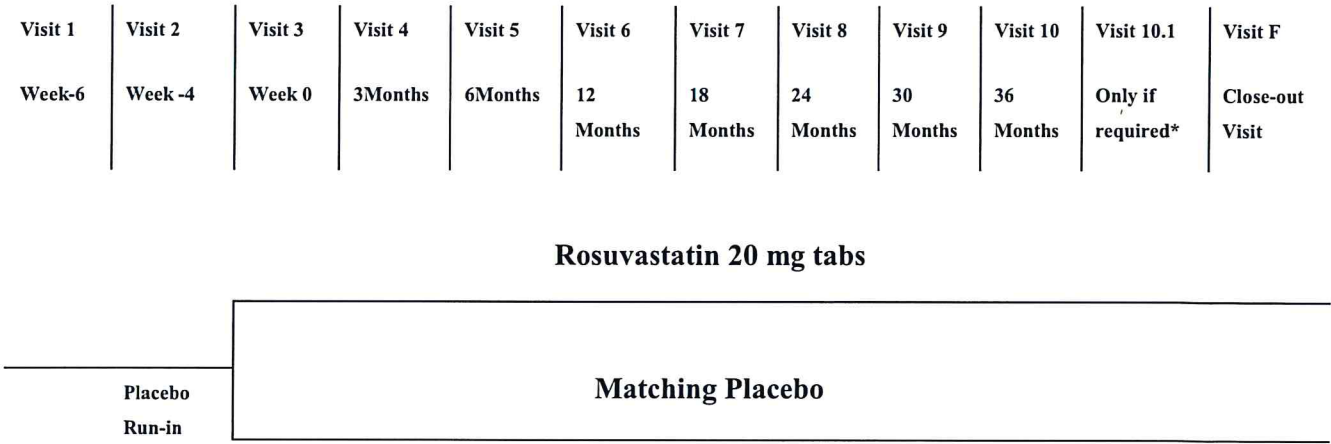
Only for subjects who require prolonged follow-up. Assessments from Visit 9 repeated.

Visit F (Close Out Visit)

- Final study medication compliance checked
- Endpoint and DM assessed

- Adverse experiences assessed
- Concomitant medications recorded
- Physical exam performed
- Waist circumference taken
- Fasting blood samples taken for analysis of TC, LDL-C, HDL-C, TG, CRP, ALT, CK, Apo A-1 and Apo B-100, creatinine, FSG, HbA_{1c}, and CBC
- Urinalysis

Figure 1 Study Flow Chart



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

Table 4 Study plan

Visit Number	1	2	3	4	5	6	7	8	9	10	F
Week No.	-6	-4	0	13	26	52	78	104	130	156	182
	Screen Visit 1	Screen Visit 2	Randomization Visit	Safety Visit	Six-Month Visit	12 Month Visit	18 Month Visit	24 Month Visit	30 Month Visit	36 Month Visit	Close Out Visit
Eligibility Questionnaire	✓	✓	✓								
Informed Consent	✓										
Physical Exam		✓									✓
Waist Circumference		✓									✓
Screening Medical History		✓									
Fasting Lipid Panel	✓					✓	✓	✓		✓	✓
C-reactive Protein ^a	✓	✓		✓		✓	✓	✓		✓	✓
ALT		✓		✓	✓	✓	✓	✓		✓	✓
CK		✓									✓
TSH		✓									
Serum Creatinine		✓									✓
Apo A-1/Apo B-100		✓				✓					✓
Fasting Serum Glucose		✓						✓		✓	✓
HbA _{1c}		✓						✓		✓	✓
Hematology		✓									✓
Urinalysis		✓				✓	✓	✓	✓	✓	✓
Drug		P ^b	P/R ^c	P/R ^c	P/R ^c	P/R ^c	P/R ^c	P/R ^c	P/R ^c	P/R ^c	✓
Endpoint and DM Assessment			✓	✓	✓	✓	✓	✓	✓	✓	✓
Prior/Concomitant Medications		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse Event Assessment			✓	✓	✓	✓	✓	✓	✓	✓	✓
Compliance Check			✓	✓	✓	✓	✓	✓	✓	✓	✓

^aC-reactive protein (CRP) to be measured at Visit 1 must be ≥2.0 mg/L

^bAll potential participants to receive single-blind placebo therapy during 4 week compliance run-in

^cP = placebo, R = rosuvastatin

3.2 Rationale for study design, doses and control groups

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

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

3.3 Selection of study population

3.3.1 Study selection record

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

3.3.2 Inclusion criteria

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

1. Written informed consent to participate in the study (See Appendix B)
2. Men aged 55 years and over; women aged 65 years and over
3. Fasting LDL-C value <130 mg/dL (3.36 mmol/L) at Screening Visit 1
4. CRP value ≥ 2.0 mg/L at Screening Visit 1
5. TG <500 mg/dL (5.65 mmol/L) at Screening Visit 1

3.3.3 Exclusion criteria

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

1. Treatment with any HMG-CoA reductase inhibitors or other lipid lowering therapies including fibric acid derivatives (fibrates), niacin (>50 mg per day), and bile acid sequestrants within 6 weeks of Screening Visit 1
2. History of serious hypersensitivity (including myopathy) reactions to other HMG-CoA reductase inhibitors
3. Prior history of cardiovascular or cerebrovascular events such as MI, unstable angina, prior arterial revascularization, or stroke, or CHD risk equivalent as defined by NCEP ATP III
4. Current use of postmenopausal oral hormone replacement therapy (HRT)
5. Current treatment with cyclosporin, tacrolimus, azathioprine, or other immunosuppressants including chronic use of oral glucocorticoids (See Appendix I)
6. Active liver disease or hepatic dysfunction or elevations of ALT >2 x ULN at Screening Visit 2
7. Baseline elevations of CK >3 x ULN at Screening Visit 2
8. Diabetes mellitus, as defined by FSG >126 mg/dL (7.0 mmol/L) at Screening Visit 2 or by the use of insulin and/or an oral hypoglycemic agent
9. Uncontrolled hypertension, defined as systolic blood pressure >190 mmHg or a diastolic blood pressure >100 mmHg at Screening Visit 2.
10. History of malignancy within the past 5 years, with the exception of basal cell or squamous cell carcinoma of the skin (women with a history of cervical dysplasia should be excluded unless 3 consecutive normal cervical smears, Papanicolaou (Pap) smears, have been recorded subsequently before entry)
11. Uncontrolled hypothyroidism defined as a thyroid stimulating hormone (TSH) >1.5 x ULN at Screening Visit 2 or subjects whose thyroid replacement therapy was initiated or modified within the last 3 months.
12. Chronic inflammatory condition such as severe arthritis, lupus, or inflammatory bowel disease
13. History of alcohol or drug abuse within the past 1 year

14. 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
15. Prior participation in this study
16. Serious or unstable medical or psychological conditions that, in the opinion of the investigator, would compromise the subject's safety or successful participation in the study

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

3.3.4 Discontinuation of subjects from treatment or assessment

3.3.4.1 Criteria for discontinuation

Subjects may be discontinued from study treatment and assessments at any time, at the discretion of the investigator(s). Specific reasons for discontinuing a subject from this study are:

1. Withdrawal of informed consent
2. If, at any time, the subject's CK measures >10 x ULN and is accompanied by unexplained muscle pain, tenderness or weakness
3. If persistent ALT levels >3 x ULN are demonstrated
4. If there is deterioration in the subject's condition which, in the opinion of the investigator, warrants study medication withdrawal
5. If there is the occurrence of an adverse event which, in the opinion of the investigator, warrants study medication withdrawal
6. At the investigator's discretion

3.3.4.2 Voluntary discontinuation by a subject

Subjects are free to discontinue their participation in the study at any time, without prejudice to further treatment. Subjects who discontinue from the study should always be asked about the reason(s) for their discontinuation and about the presence of any adverse events. If possible, they should be seen and assessed by an investigator(s). Adverse events should be followed up and investigational products should be returned by the subject.

3.3.4.3 Incorrectly enrolled or randomized subjects

Incorrectly enrolled subjects will continue to receive study treatment and assessments if, in the opinion of the investigator and/or study team physician, this is not considered to involve any risk or discomfort to the subject. There should be no attempt to switch treatment or change randomization numbers.

In all other instances, incorrectly enrolled subjects will be discontinued from further study treatment and assessments.

3.3.4.4 Procedures for discontinuation

The reason for discontinuation and the date of discontinuation from the study or from study medication must be documented on the CRF provided. The effect of discontinuation will be considered in the analysis to minimize potential bias. For all discontinuations, the full assessments that are specified in Visit F should be carried out wherever possible. All adverse events must be reported, but in particular any adverse event leading to discontinuation from the study. All discontinuations due to a serious adverse event must be reported to AstraZeneca within 24 hours. **It is important that subjects who discontinue study medication continue to follow scheduled study assessments for the remainder of the study, on a six-month visit interval, to ensure that subsequent cardiovascular events are identified and recorded.**

3.3.4.5 Procedures for lost-to-follow-up

If a randomized subject stops taking study drug or misses a scheduled study visit, all remaining study visits must be completed, and, unless contraindicated, re-start of study drug should be encouraged. Therefore, every randomized subject's drug supply must be maintained by the site for re-start unless death, an adverse event or a contraindication requires permanent discontinuation.

To allow for re-start of study drug, unblinding should not occur unless an AstraZeneca physician agrees that a safety issue requires unblinding.

For subjects who miss a scheduled study visit, there should be 3 separate attempts of contacting the subject. All attempts at trying to contact study participants should be well documented by the investigative site including search of National Death Index.

3.3.5 Restrictions

The following restrictions should be applied to subjects in this study:

1. Subjects should not be scheduled for Screening Visit 1 within 2 weeks of a major viral or bacterial illness
2. Subjects who are blood donors should not donate blood during the study and for 3 months following their last dose of study treatment

3. Subjects will fast (water is permitted) and refrain from alcohol consumption for 8 hours before each visit
4. Subjects should be advised to maintain their normal physical activities or exercise routines during the study

3.4 Treatments

It is the investigator/institution's responsibility to establish a system for handling study treatments, including investigational medicinal products, to ensure that:

1. Deliveries of such products from AstraZeneca are correctly received by a responsible person (eg, a pharmacist)
2. Such deliveries are recorded
3. Study treatments are handled and stored safely and properly
4. Study treatments are only dispensed to study subjects in accordance with the protocol
5. Any unused products are accounted for and returned to a designated facility or AstraZeneca for destruction

At the end of the study, it must be possible to reconcile delivery records with records of usage and returned stocks. Any discrepancies must be accounted for. Certificates of delivery and return must be signed, preferably by the investigator or a pharmacist.

3.4.1 Investigational products

The study medication will be supplied to the investigator by AstraZeneca. The study medication will be supplied as tablets for oral use as specified in Table 5.

Table 5 Study Medication

Treatment	Dose	Formulation number
Rosuvastatin tablets	20 mg	F12673
Placebo to match 20 mg rosuvastatin tablets	0 mg	F12832

3.4.1.1 Identity of investigational product and comparators

AstraZeneca will pack blinded clinical study material into tamper-evident high density polyethylene (HDPE) bottles; each bottle will have a label with a reference number and storage conditions. Each bottle will contain 100 tablets. Each subject will be given 1 bottle of

placebo (single-blind) medication at Visit 2. Subjects will then receive 1 bottle of study medication (double-blind) at Visits 3 and 4 and then 2 bottles at each subsequent visit.

3.4.1.2 Labeling

All bottles will be labeled with at least a study reference number, a bottle reference number, administrative instructions, and storage conditions. This label will have a detachable tear-off portion, which will be attached to the appropriate case report form (CRF) at the time of dispensing. The label will also contain a space for subject number, subject initials, visit number and the date dispensed.

3.4.1.3 Storage

All investigational products must be kept in a secure place under appropriate storage conditions.

All study drugs are to be stored in their original containers in a lockable storage facility until dispensed to the study subjects. Study medications should not be frozen but should be protected from light and moisture at temperatures between 68 and 77°F (20 and 25°C).

3.4.1.4 Accountability

It is essential that all medication be accounted for by the investigator or institution, and that any discrepancies are explained and documented.

The study treatments must be used only as directed in the protocol. The investigator must maintain accurate records accounting for the receipt of the investigational products and for the disposition of the material. This record keeping consists of a dispensing record including the identification of the person to whom the drug is dispensed, the quantity and the date of dispensing, and any unused drug returned to the investigator. This record is in addition to any drug accountability recorded on the CRF.

Subjects must return all unused medication and empty containers to the investigator. The number of tablets returned must be checked against the number dispensed to determine subject compliance.

The investigator will retain the returned medication until authorized AstraZeneca personnel collect it, along with any study treatments not dispensed. At the termination of the study or at the request of the sponsor, the investigator must return any unused supplies to AstraZeneca. This return will be documented by using an Investigational Product Return Invoice or equivalent document supplied by AstraZeneca.

3.4.2 Doses and treatment regimens

Study medication will be taken orally, with water if required, once daily. One dose will consist of 1 tablet.

Following Screening Visit 1, all potentially eligible subjects will come back for Screening Visit 2 to be enrolled in the initial 4-week run-in phase and will receive placebo therapy. If found eligible for the main study on the basis of appropriate levels of baseline LDL, CRP, and run-in phase compliance (>80% of pills taken), participants will be randomized to active or placebo therapy at the Randomization Visit (Visit 3). 1 bottle of study medication will be dispensed to each study subject at Visit 3 and then again at Visit 4. At Visit 5 and at each subsequent visit, 2 further study bottles will be dispensed to each study participant.

3.4.3 Method of assigning subjects to treatment groups

A preliminary identifying number (a screening ID number) will be assigned sequentially by the site to each subject at Screening Visit 1, so that subjects can be identified without making assumptions about their subsequent eligibility for the main study. Subjects who do not meet the eligibility requirements for the treatment phase, will be considered screening failures and will keep their identifying number assignment. These subjects will not be able to re-enter the study at a later date.

At the end of the run-in phase (Visit 3), subjects who successfully complete the run-in phase and satisfy all the entry criteria will enter into the treatment phase of the study. Each subject will be assigned by the IVRS, according to the randomization scheme generated by the Biostatistics Department of AstraZeneca or its delegate, to 1 of the following treatment groups: rosuvastatin 20mg, or matching placebo. The randomization ratio between rosuvastatin and placebo will be 1:1, stratified by center.

The study medication will be blinded by providing rosuvastatin and placebo tablets, which are indistinguishable in appearance. Subject numbers will be allocated strictly sequentially as subjects are determined to be eligible for enrollment/randomization. Once a number has been assigned, no attempt should be made to use that number again if, for example, a subject is withdrawn from the study. No subject should be randomized into the study more than once.

If a subject number is allocated incorrectly, study personnel should be informed immediately and the investigator will be instructed on appropriate procedures to be followed.

If a subject discontinues from the study, the subject number will not be reused, and the subject will not be allowed to re-enter the study.

3.4.3.1 Interactive Voice Response System (IVRS)

IVRS will be used for subject registration, study medication assignment, allocation of subject numbers as subjects are randomized, and emergency code breaks. The IVRS technology will be managed and maintained by Perceptive Informatics, Inc. The system is accessible by telephone 24 hours a day, 7 days a week via a toll free number. The IVRS manual, which has full details of the operation and use of the IVRS, will be provided to each site. Training on the use of IVRS will also be given.

3.4.4 Blinding and procedures for unblinding the study

3.4.4.1 Methods for ensuring blinding

Blinded study medication will be allocated by the IVR System.

3.4.4.2 Methods for unblinding the study

The treatment code must not be broken except in medical emergencies when the appropriate management of the subject necessitates knowledge of the treatment randomization. The investigator(s) must document and report to AstraZeneca any breaking of the treatment code. AstraZeneca retains the right to break the code in order to report serious adverse events to regulatory authorities.

When possible, the investigator will consult with the study team physician to ascertain whether the situation warrants breaking the code. **The code may be broken only after a decision has been made to withdraw the subject from the study and if immediate knowledge of the study medication is needed to optimize the clinical management of the subject.**

Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual subject have been made and documented.

3.4.5 Pre-study, concomitant and post-study treatments

Concomitant drug therapy which is deemed necessary by the treating physician to control concomitant diseases is acceptable, except for protocol-disallowed medications. Other medication, which is considered necessary for the subject's safety and well being, may be given at the discretion of the investigator(s). All concomitant therapies will be documented at all study visits. The administration of all medication (including investigational products) must be recorded in the appropriate sections of the CRF.

Current use of lipid lowering drugs, insulin, oral hypoglycemic agents, chronic steroid therapy are not allowed at study entry. Additionally, oral HRT for postmenopausal women is not permitted. Disallowed drugs at both study entry and during follow-up include cyclosporin, tacrolimus, azathioprine, and other potent immunosuppressants, since the use of these agents may increase the risk of adverse events during rosuvastatin treatment.

Warfarin (also warfarin derivatives and coumadin)

In 2 clinical studies, 1 in normal volunteers and the other in subjects receiving a coumadin anticoagulant, rosuvastatin modestly potentiated the effect of the coumadin anticoagulant. With other reductase inhibitors such as simvastatin, clinically evident bleeding and/or increased prothrombin time has been reported in a few subjects taking coumadin anticoagulants concomitantly.

For these reasons, careful monitoring of International Normalized Ratio (INR) is required when warfarin and study medication are co-administered at any time during the subject's

participation in this study. It is suggested that the investigator should, in accordance with usual practice, measure INR frequently (at a local laboratory) until warfarin dose stabilization is achieved, and periodically thereafter in the following situations:

- when **starting warfarin therapy** in a randomized subject,
- when a **subject already receiving warfarin begins randomized study treatment**

In order that up-to-date information and advice can be provided, investigators should telephone their study monitor to discuss the situation with the relevant AstraZeneca Study Team Physician or the physician's delegate.

3.4.6 Treatment compliance

Subjects will be asked to return all unused medication and empty containers. The number of tablets issued minus the number of tablets returned will be used to calculate the tablets taken. From this information compliance will be calculated over previous period.

$$\text{Compliance} = (\text{number of tablets taken} / \text{tablets that should have been taken}) \times 100$$

Any subject taking <80% of the prescribed study medication during the run-in phase will be considered non-compliant. Compliance will be checked at each visit after enrollment to the treatment period.

4. STUDY MEASUREMENTS AND ENDPOINTS

4.1 Primary endpoint

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

Cardiovascular Death

All deaths will be reported in the study. However, only those deaths considered by the endpoints committee to be cardiovascular or cerebrovascular in origin will be included in the primary study endpoint.

Deaths due to MI will be confirmed when the fatal event fulfills the diagnostic criteria for nonfatal MI as outlined below, or if MI is specifically stated in hospital discharge records or on the death certificate, or can be based upon autopsy evidence demonstrated on post-mortem examination. Deaths from heart failure which cannot be classified as due to MI and in which there is no other obvious cause, such as septic shock, will be classified as cardiovascular in origin.

Deaths due to stroke will be confirmed when the fatal event fulfills the diagnostic criteria for nonfatal stroke as outlined below, or if the diagnosis of stroke is specifically stated in hospital discharge records or on the death certificate, or can be based upon autopsy evidence demonstrated on post-mortem examination.

Sudden cardiac deaths will be confirmed as being of cardiovascular origin if the event cannot otherwise be classified as being due to MI or stroke using the above criteria and if the event is either instantaneous or occurs within 12 hours of the onset of acute chest pain, syncope, pulmonary edema, cardiogenic shock, or other cardiovascular or cerebrovascular symptoms. Non-witnessed deaths without other identifiable cause will be reviewed by the Endpoints Committee for consideration as cardiovascular deaths.

Cause-specific mortality for non-cardiovascular deaths will be recorded. In all cases, a single cause of death must be stated by the Endpoints Committee.

Nonfatal Stroke

The diagnosis of nonfatal stroke will be confirmed if there are unequivocal signs of a focal or global neurologic deficit with sudden onset and of duration >24 hours. Computed tomography (CT) and/or magnetic resonance imaging (MRI) scans, as well as clinical reports, will be used to classify stroke types as hemorrhagic, thromboembolic, or other.

Nonfatal Myocardial Infarction

The diagnosis of nonfatal MI will be confirmed if at least 2 of the following criteria are fulfilled:

1. 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
2. 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
3. development or disappearance of localized ST elevation ≥ 1 mm, combined with the development of persistent T-wave inversion in at least 2 anatomically contiguous standard ECG leads or development of new left bundle branch block (LBBB)

Unstable Angina

The diagnosis of unstable angina will be confirmed if there is evidence of ischemic chest pain at rest or with minimal exertion which represents a change in the participant's usual symptom pattern, which occurs **within the preceding 48 hours, and requires hospitalization**, and presence of objective evidence of ischemia. In addition, the diagnosis of unstable angina will

be confirmed only if there is objective evidence of myocardial ischemia as defined by at least 1 of the following criteria:

1. new and/or dynamic ST depression (>0.5 mm), elevation (>1 mm) or T wave inversion (≥ 3 mm) on resting ECG
2. a definite persistent or reversible wall motion abnormality or scintigraphic perfusion defect demonstrated either spontaneously or by stress testing
3. 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
4. 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

The diagnosis of arterial revascularization will be confirmed when there are hospital records demonstrating either coronary artery bypass graft (CABG) surgery or bypass grafting of any peripheral artery or carotid or the performance of at least 1 percutaneous transluminal intervention (PTI) including either angioplasty, stent placement, or other intravascular procedure involving coronary carotid or peripheral arteries.

Secondary Endpoints

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

- (1) total mortality
- (2) noncardiovascular mortality
- (3) discontinuation of blinded study medication due to adverse effects
- (4) development of diabetes mellitus
- (5) development of venous thromboembolic events (deep vein thrombosis or pulmonary embolism)
- (6) bone fractures

The diagnosis of incident diabetes mellitus will be based upon physician diagnosis, confirmed either by the new use of insulin or an oral hypoglycemic agent, or evidence of a positive glucose tolerance test, or evidence of a repeated fasting glucose in excess of 126 mg/dL (7.0 mmol/L). Analyses of incident diabetes mellitus will include all study participants as well as those in whom the baseline HbA_{1c} measurement was $<6.5\%$. Additional analyses will be

done looking at the development of diabetes mellitus as reflected by plasma levels of fasting glucose and HbA_{1c} measured during study follow-up.

4.2 Screening and demographic measurements

The following data will be collected in the CRF:

- date of birth, sex and race
- significant medical and surgical history
- physical examination (including height, weight, vital signs, waist circumference)
- Coronary Heart Disease Risk Factors

4.3 Efficacy and pharmacodynamic measurements and endpoints

4.3.1 Summary of efficacy and pharmacodynamic objectives and endpoints

The study objectives are described in Section 2 and the study endpoints are described in Section 4 with an exact correspondence between objectives and endpoints. Full descriptions of the statistical analyses to be used for each endpoint are given in Section 6.2.3.

4.4 Safety measurements and endpoints

4.4.1 Summary of safety objectives and endpoints

The safety objective is to compare rosuvastatin and placebo with respect to the incidence and severity of adverse events and abnormal laboratory values. The safety evaluation will be determined by the incidence of adverse events and abnormal laboratory data during treatment with rosuvastatin or placebo.

The methods for collecting safety data are described below.

4.4.2 Adverse Events

4.4.2.1 Definitions

The definitions of adverse events (AEs), serious adverse events (SAEs) and other significant adverse events (OAEs) are given below. It is of the utmost importance that all staff involved in the study are familiar with the content of this section. The principal investigator is responsible for ensuring this.

(a) Adverse Event

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition

can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

(b) Serious Adverse Event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), and at any dose of the investigational product, comparator or placebo, that fulfills 1 or more of the following criteria:

- results in death
- is immediately life-threatening
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity
- is a congenital abnormality or birth defect
- is an important medical event that may jeopardize the subject or may require medical intervention to prevent 1 of the outcomes listed above

The causality of SAEs (ie, their relationship to study treatment) will be assessed by the investigator(s) who, in completing the relevant CRF must answer “yes” or “no” to the question, “Do you consider that there is a reasonable possibility that the event may have been caused by the drug?” For further guidance on the definition of a SAE and a guide to the interpretation of the causality question, see Appendix F.

(c) Other significant adverse event

An AstraZeneca expert will identify OAEs during the evaluation of safety data for the Clinical Study Report (CSR). Significant adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the subject from study treatment, will be classified as OAEs. Examples of these are marked hematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment. For each OAE, a narrative will be written and included in the CSR.

4.4.2.2 Recording of adverse events

Adverse events will be identified by means of a standard question such as, “Have you had any health problems since the previous visit?” The question will be asked of each subject at all study visits following randomization. All adverse events must be recorded in the CRF provided.

The subjects will be asked to provide a description of the event, the dates of onset and resolution, and to assess the intensity of the reported adverse event according to the following scale:

1. Mild: awareness of sign or symptom, but easily tolerated
2. Moderate: discomfort sufficient to cause interference with normal activities
3. Severe: incapacitating, with inability to perform normal activities

The investigator should make a causality assessment of the relationship of the event to the study drug and whether it constitutes a SAE or not.

If a diagnosis of the subject's condition has been made, then the diagnosis should be recorded as the adverse event (eg, fever, runny nose, cough can be recorded as "flu"). However if a diagnosis of the subject's condition has not been made, or only if the individual symptoms are not well recognized, then the individual symptoms should be recorded separately.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 4.4.2.1 b. An AE of severe intensity need not necessarily be considered serious. For example, nausea which persists for several hours may be considered severe nausea, but not an SAE.

AstraZeneca will classify adverse events using an appropriate medical coding dictionary.

Clinically significant laboratory values, such as ALT, will be recorded as adverse events and will be followed up (See Appendix G).

Subjects will be followed for 30 days after the final dose of study medication and/or discharge from the study in case they should develop new serious adverse events. Any adverse events or serious adverse events which are unresolved when the subject completes or discontinues the study will be followed until resolution or until they return to baseline, as decided by the investigator.

4.4.2.3 Reporting of serious adverse events

Investigators and other site personnel must inform appropriate AstraZeneca representatives of any SAE that occurs in the course of the study within 1 day (ie, immediately, but no later than the end of the next business day) of when he or she becomes aware of it.

The AstraZeneca representative will work with the investigator to compile all the necessary information and ensure that the appropriate AstraZeneca Drug Safety Department receives a report by **Day 1** for all fatal and life-threatening cases and by **Day 5** for all other SAEs.

Follow-up information on SAEs must also be reported by the investigator within the same time frames.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca within 1 day, as described above.

Serious adverse event data will be collected during the study period and within 30 days after the last dose of study medication.

The investigator is responsible for informing the Ethics Committee and/or Regulatory Authority of the serious adverse events, as per local requirements.

Physicians who perform serious adverse event assessments will be blinded to treatment assignment.

4.4.2.4 Reporting of Endpoints

All primary endpoint events (cardiovascular death, nonfatal stroke, nonfatal myocardial infarction, hospitalization for unstable angina, arterial revascularization) will not be reported as SAEs, but as endpoints. A waiver to this effect will be obtained from the appropriate regulatory agency. The IDMB will review and evaluate all SAEs and endpoints in an unblinded fashion, and will make recommendations to the Steering Committee on terminating the study if stopping rule criteria have been met. An Endpoint Committee will review all endpoints for final determination. Clinical endpoints should be reported in accordance within the procedure documented in the 'Clinical Endpoint Reporting Guidelines'.

Secondary endpoints will be reported in accordance with the usual SAE reporting procedures outlined in Section 4.4.2.3.

4.4.2.5 Reporting of Serious Adverse Events, and Primary and Secondary Endpoints to Independent Data Monitoring Board

The IDMB will receive 6-monthly tables of cumulative serious adverse events and primary and secondary endpoints from data management. Data for the IDMB will be unblinded to treatment group. The Steering Committee and AstraZeneca will not be permitted access to unblinded data.

4.4.3 Laboratory safety measurements and variables

4.4.3.1 Methods of assessment

All analyses of laboratory samples detailed in this section, will be performed by a central laboratory selected by AstraZeneca. This central laboratory will be responsible for all lipid, clinical chemistry, and hematology analyses. This laboratory is certified for standardization of lipid analysis as specified by the Standardization Program of the Center for Disease Control and Prevention (CDCP) and the National Heart, Lung and Blood Institute (NHLBI).

When blood is to be taken for lipid assays as well as safety assessment, subjects must fast for at least 8 hours and have been sitting for at least 5 minutes before blood samples are taken. In these instances, if a subject attends for a study visit without having fasted (from 8 hours before) then they must be asked to return within 10 days for their study visit.

A tourniquet may be applied, but for no longer than 2 minutes, and it must be removed before blood is collected. Full details of sampling, sample preparation, and storage methods to be used are given in the investigator laboratory manual.

Samples for evaluation from all investigational sites in this study will be delivered by courier within 24 hours of blood drawings to the central laboratory, Medical Research Laboratories International (MRLI).

At Screening Visit 1, a fasting lipid profile (TC, LDL-C, HDL-C, & TG) and CRP levels will be measured to determine each subject's eligibility for participation in the study.

A complete blood count will be performed at Screening Visit 2 and Visit F, and will include the following: erythrocyte cell count, hemoglobin concentration, hematocrit, leukocyte cell count, platelet count, red cell distribution width, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration and percentage differential leukocyte count.

A clinical chemistry profile will be performed at Visit 2 and will measure the following: CK, creatinine, ALT, TSH and FSG. Thereafter, FSG will be measured at Visit 8, 10, and Visit F; ALT levels will be measured from Visit 4 through Visit F. In addition, CK and creatinine will be measured at Visit F.

All subjects will have HbA_{1c} measured at Visits 2, 8, 10 and Visit F.

A fasting lipid profile and CRP measurement will also be done at Visits 6, 8, 10, and Visit F. In addition, Apo A-1 and Apo B-100 will be assessed at Visits 2, 6, and Visit F.

At Visit 6, a blood sample will be taken for storage of plasma for future long-term analysis of cardiac inflammatory markers and/or safety issues.

Urinalysis will be performed at Visit 2 and Visit 4 through Visit F. This will consist of, but not limited to: a dipstick test (protein, glucose, ketones, bilirubin, urine reaction pH, occult blood and specific gravity) and microscopy (red blood cells, white blood cells, bacteria, casts and crystals).

4.4.3.2 Calculation or derivation of endpoints

Adverse events which are based upon abnormal findings on laboratory tests and on other objective measurements will be recorded and reported as delineated in Section 4.4.2.2 and 4.4.2.3.

4.4.4 Other safety measurements and variables

Adverse events based upon other safety measurements and variables, including physical examination and vital signs, will be reported and recorded as described in Section 4.4.2.2 and Section 4.4.2.3.

If a liver test (ALT) is increased, see Appendix G for Management of Elevated Liver Enzymes.

4.5 Health Economic Evaluation

The objective of the health economic evaluation is to determine the impact of treatment with rosuvastatin on subsequent healthcare resource utilization and costs associated with the occurrence of protocol defined clinical endpoints. The hypothesis is that comparative reduction in endpoint clinical events in the rosuvastatin 20mg arm will lead to a reduction in the healthcare resource utilization associated with these events.

The primary analysis will be a comparison of rosuvastatin 20mg versus placebo in terms of costs of medical care, including drug treatment, procedures, and inpatient stays related to the treatment of endpoint clinical events. The inpatient cost data may be combined with survival analysis to enable a cost per life year saved to be calculated for the two study arms.

4.5.1 Data Collection

For the economic analysis, the protocol defined clinical endpoints are cardiovascular death, stroke, myocardial infarction, unstable angina requiring hospitalization, and arterial revascularization. Most data elements required for the economic analysis are routinely collected as part of the study protocol. Resource utilization related to the cardiovascular endpoint hospitalization will be recorded on specific Case Report Forms (CRF) at the study sites. Health economic items to be collected in the CRF are (1) hospital admission indicator (tick-box); (2) admission and discharge dates; (3) length of stay; (4) critical care unit stay indicator (tick-box); (5) critical care step-down unit stay indicator (tick-box); (6) and length of stay in the critical care unit, or step-down unit, if such a stay was indicated. Investigators and site study coordinators will use hospital discharge records, progress notes, and/or any other ancillary document within the patient chart to complete the health economic CRF items. Mortality and time of death, to be used in a cost-per-life-year-saved analysis, are collected as part of the protocol.

Resource data, collected as described above, may be supplemented by resource data collected from secondary data sources outside the trial, in a separate, independent retrospective study. These supplementary data will facilitate development of normative care pathway and a comprehensive resource utilization profile for each of the defined endpoint events (e.g., average resource utilization incurred for the cardiovascular patient outside the acute care setting, such as long-term care).

4.5.2 Cost Analysis of Clinical Endpoints

A detailed data analysis plan for the health economic evaluation will be formulated before the last patient is enrolled in the study. At that time, conventions will be determined for statistical evaluation of differential values for basic units of use, assigning standard costs to the units, and for sensitivity testing, to provide a cost analysis as well as a standard description of healthcare utilization. Appropriate unit costs (US costs in USD) will be applied to the

resource use data to enable a comparison between the rosuvastatin and placebo arms in the form of a cost effectiveness analysis. The Diagnostic Related Group (DRG) code may be assigned retrospectively, in a blinded fashion, to each endpoint event, in order to arrive at a common average unit cost and relative weight for each endpoint event.

4.5.3 Cost-Per-Life-Year-Saved

Data on healthcare resource use related to each cardiovascular endpoint will be collected retrospectively, and cost-valued, as described. In addition, mortality rates and times of death will be collected. Cost data may be combined with survival analysis to enable a cost effectiveness analysis to be performed in terms of cost-per-life-year-saved in each study arm.

5. DATA MANAGEMENT

Case Report Forms (CRFs) will be provided for the recording of data. Data will be recorded legibly on the record forms, preferably in ballpoint pen. If any data are not available, omissions will be indicated on the record forms. Corrections should be made legibly and initialed. Correction fluid or covering labels must not be used. CRFs will be collected and returned to AstraZeneca or its designee and copies will be retained by the investigator.

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

6.1 Determination of sample size

Estimates of required study sample size have been based on several considerations including expected event rate in the placebo group, anticipated relative risk reductions with rosuvastatin therapy, rates of non-study statin use, potential rates of annual losses to follow-up, and varying the length of study follow-up. In all calculations, required sample size has been based on a group-sequential design with an early stopping rule, an overall type 1 error probability of $\alpha = 0.05$ based on a 2-sided test of the equality of event rates in the 2 treatment groups, and a study power of 90%. Data that show alternative numbers of subjects required under alternative assumptions about event rates and effect size are provided in Table 6. The tables are based on the log-rank test under the additional assumption that subjects are recruited uniformly over a 1 year period.

Table 6 Alternative event rates, study designs and required study size for evaluation of rosuvastatin therapy with 90% power

Placebo event rate	Relative rate	1 year accrual plus 3 year follow-up				1 year accrual plus 4 year follow up	
		No losses to follow-up		5% annual losses*		No losses to follow up	
		Total N	Expected events	Total N	Expected events	Total N	Expected events
1.00	.75	17060	514	18598	514	13326	514
	.70	11504	337	12542	337	8986	337
	.65	8200	233	8940	233	6406	233
1.20	.75	14260	514	15544	514	11150	514
	.70	9616	337	10482	337	7518	337
	.65	6854	233	7472	233	5358	233
1.35	.75	12706	514	13848	514	9940	514
	.70	8568	337	9338	337	6702	337
	.65	6106	233	6656	233	4776	233
1.50	.75	11462	514	12492	514	8974	514
	.70	7728	337	8422	337	6050	337
	.65	5508	233	6004	233	4310	233
1.70	.75	10144	514	11056	514	7948	514
	.70	6840	337	7454	337	5358	337
	.65	4874	233	5312	233	3818	233
1.85	.75	9344	514	10182	514	7326	514
	.70	6300	337	6864	337	4938	337
	.65	4490	233	4892	233	3518	233

*Losses include non-cardiovascular deaths plus drop-outs and lost to follow-up

The observed event rate in the placebo group is a major determinant of the power of the study. In analyses of primary prevention patients with low LDL-C and high CRP in the AFCAPS/TexCAPS study, the observed placebo event rate was just above 1 major cardiovascular event per 100 person-years of follow-up. However, this number is likely to be low for several reasons. First, the primary AFCAPS/TexCAPS endpoint did not include arterial revascularization procedures, an endpoint clearly reduced by statin therapy in other studies and a critical component of this study's endpoint; when these events from AFCAPS/TexCAPS are included, the base rate increases to 1.5 events/100 person-years of follow-up. Second, unlike AFCAPS/TexCAPS that enrolled men over age 45 and women over age 55, the current study includes only men over age 55 and women over age 65, a feature that should substantially increase absolute event rates. Similarly, and again in contrast with AFCAPS/TexCAPS, there is no upper age limit for eligibility in the current study. Third, the AFCAPS/TexCAPS study excluded individuals with markedly elevated body mass index. The inclusion of such subjects in this study should further increase absolute event rates in the placebo group. Last, the exclusion of women taking oral HRT will reduce the potential for misclassification bias on the basis of spurious CRP elevation. For all of these reasons, it is anticipated that the rate of event accrual should be 1.7 to 1.85 events/100 person years, a rate above that observed in the AFCAPS/TexCAPS study. However, for the purposes of sample size determination, the study has been powered for a more conservative range of 1.35 to 1.50 events/100 person-years in the placebo arm.

A second key component of the sample size calculation is the expected relative risk reduction likely to be seen with daily oral rosuvastatin 20 mg. To date, with the sole exception of the Heart Protection Study, statin studies have generally reported 30 to 35% reductions in rates of acute coronary events in both secondary and primary prevention settings. In particular, in the AFCAPS/TexCAPS study, the overall relative risk reduction was 37%, while that observed in the hypothesis-generating subgroup with low LDL-C/high CRP was 42%. It is important to note that this level of relative risk reduction was achieved despite the fact that the agent tested was lovastatin, a first generation HMG-CoA reductase inhibitor with far less LDL reducing capacity than expected for rosuvastatin. By contrast, in the Heart Protection Study, the observed relative risk reduction was 24%. Although, when corrected for compliance it was equal to 33%. However, in that study which included many secondary prevention subjects, there was substantial crossover to active statin therapy in the placebo group. Despite these findings, for the purposes of sample size estimation, we have again taken a conservative view, and assumed a worst-case relative risk reduction for rosuvastatin of 25%.

Noncompliance and drop in/drop out are major challenges to the validity of any randomized study, and this third component of the sample size calculations also needs consideration. For example, in the AFCAPS/TexCAPS study, study drug regimens were maintained over the mean follow-up of 5.2 years in 71% of actively treated patients and 63% of placebo treated patients. The observed 37% reduction in the primary endpoint occurred in spite of this level of non-compliance. Several design features of the proposed study, including the use of a pre-randomization compliance check in all potentially eligible study participants, should greatly reduce non-adherence throughout the follow-up period. In addition, in marked contrast to the Heart Protection Study, this study is focused on subjects well outside current NCEP ATP III

guidelines for statin therapy and thus drop-in rates in the placebo group should be low. Specifically, while the Heart Protection Study included large numbers of subjects with known coronary disease, the current study is strictly of primary prevention subjects where medical community standards for statin prescription are much less aggressive. Second, entry criteria of an LDL-C <130 mg/dL (3.36 mmol/L) greatly reduces ethical concerns about placebo usage either at study initiation or during the estimated 3.5 year follow-up period. Finally, excluding those with diabetes helps ensure that cross-over will not occur in this controversial high risk subgroup.

The sample size tables show that across the range of reasonable event rates in the placebo group, the study must observe 514 events to have 90% power to detect a 25% reduction in this rate based on a 2-sided alpha of 0.05. We round this required number of events up to 520 total primary events. On the basis of these issues, we believe a total sample size of 12,000 participants would be adequate to detect with 90% power a relative risk reduction as small as 25% for an absolute placebo rate of 1.50 in a study with 3.5 year mean follow-up and a 5% annual loss rate (see Table 6). However, if the sample size is increased to 15,000, then almost all “worst-case” scenarios are covered, since such a study would be capable of detecting a relative risk reduction as small as 25% in a 4 year mean follow-up even if the placebo event rate is as low as 1.0 events per 100 person-years, a level below that observed in the AFCAPS/TexCAPS study which enrolled substantially younger patients.

6.2 Statistical evaluation

6.2.1 Methods of statistical analysis

A comprehensive Statistical Analysis Plan (SAP) will be prepared before unblinding of the data, or in instances where the data are not blinded, database lock.

6.2.2 Study endpoints

Full description of study endpoints are presented in Section 4.

6.2.3 Statistical analyses

The main analysis will use a likelihood ratio test based on a proportional hazards model to test the null hypothesis of no association between rosuvastatin treatment and risk of the primary endpoint. This analysis will include all randomized patients as randomized (Intention to Treat population). Some study subjects are expected to have multiple primary endpoints, but only the first such endpoint will contribute to the primary analysis. This is because occurrence of a non-fatal primary endpoint is expected to lead to unblinded statin therapy. The estimated relative hazard in the rosuvastatin group compared to the placebo group with an accompanying 95% CI will quantify the treatment effect.

The validity of the proportional hazards assumption will be tested through evaluation of a trend over time in the scaled Schoenfeld residuals. A violation of this assumption is unlikely because previous statin studies have found fairly uniform effects over time and the expected duration of follow-up in this study is 3.5 years. If a significant ($P < 0.01$) violation of the

proportional hazards assumption is found, then estimates of the effects of rosuvastatin will be obtained from proportional hazards models fitted to data from each year of follow-up. However, the overall estimate from a single model fitted to all years of follow-up will continue to serve as the best single estimate of the treatment effects, especially in light of the low prior expectation of a changing effect over time.

Additional descriptive analyses will use the method of Kaplan and Meier to quantify the probability of remaining free of a primary study endpoint by time within each of the 2 treatment groups. Additional proportional hazards models will determine whether simultaneous control for baseline cardiovascular risk factors has any effect on the relative risk associated with treatment. Further, the distributions of major cardiovascular risk factors will be compared between treatment groups using the Wilcoxon rank-sum test for continuous variables and Chi-square tests for categorical variables.

The clinical significance of any observed benefit associated with rosuvastatin therapy will be quantified by the number needed to treat. This measure has the advantage of quantifying the absolute, as compared to the relative treatment effect. If P_r is the 3-year cumulative incidence of a primary cardiovascular endpoint among those receiving rosuvastatin and P_p is the comparable rate among those receiving placebo, the number needed to treat is $1/(P_p - P_r)$.

Proportional hazards models will also be used to examine relative rates of discrete safety and secondary endpoints in the study. Pre-specified secondary endpoints include total mortality, cardiovascular mortality, non-cardiovascular mortality, myocardial infarction, unstable angina, arterial revascularization, stroke and diabetes mellitus.

All subjects who take at least 1 dose of study drug will be included in the safety analysis. Summaries and descriptive statistics will be provided.

AEs will be listed for each subject by treatment received. AE incidence will be summarized by the body system and preferred term assigned to the event using the MedDRA dictionary.

Hematology and clinical chemistry data will be listed for each subject and summarized by treatment group. Hematology and clinical chemistry values outside the laboratory reference range will be highlighted.

6.2.4 Interim analyses

To achieve the desired power, the study requires accrual of 520 primary endpoints. Thus, the study is designed to continue until both this number of primary outcomes is observed and the last randomized subject is followed for at least 3 years. However, 2 interim analyses are planned and the study will be terminated early if the early stopping rule is met and both the IDMB and the Steering Committee concur. A group sequential design will be used to preserve the overall type 1 error probability of 0.05.

Planned interim analyses will be performed when 37.5% of primary events have occurred (195 confirmed primary endpoints) and again when 75% of primary events have occurred (390

confirmed primary events). The final analysis is scheduled when 520 primary events have occurred. The group sequential boundaries for these 3 scheduled analyses are 2.947, 2.411, and 2.011, which correspond to nominal p-values of 0.003, 0.016, and 0.044, respectively. These boundaries are based on an alpha spending function that approximates an O'Brien-Fleming boundary in the setting of unequal analysis times. These information times were used, for example, in the AFCAPS/TexCAPS, study which was terminated early on the basis of a significant benefit found at the second interim analysis.

6.3 Independent Data Monitoring Board

An IDMB will review unblinded safety data approximately twice a year and will include evaluations of all laboratory data, quality assurance reports, and serious adverse experiences defined as those (1) requiring or prolonging hospitalization, (2) resulting in a permanent or substantial disability, and (3) deaths. At appropriate time points, the IDMB will also consider unblinded data with regard to potential study efficacy and, following a pre-specified analysis plan as set out in the Manual of Operations, make recommendations to the Steering Committee on whether or not to continue the study. The IDMB will be comprised of 5 fully independent members.

6.4 Steering Committee

A steering committee will be established. The steering committee will have the scientific responsibility for the study, will meet initially to agree on the final protocol and review the logistical procedures, and will meet periodically thereafter to review study conduct and progress, to consider recommendations from the IDMB and to resolve any other study-related issues. The steering committee will review all proposed ancillary studies and proposed publications, as well as recommendations from the IDMB regarding early termination of the study. The steering committee will be comprised of 9 members including one AstraZeneca clinician and one AstraZeneca statistician as non-voting members of this committee. Steering committee members will remain blinded to study results. The roles and responsibilities of the steering committee will be fully documented in a written charter.

6.5 Endpoint Committee

A clinical event adjudication committee, or Endpoint Committee, independent of the sponsor and investigators and blinded to treatment assignments, will review all deaths and non-fatal cardiovascular events included as primary endpoints.

The Endpoint Committee will ensure consistency of event diagnosis across all subjects throughout the study.

The Endpoint Committee will be responsible for the final adjudication of whether an event meeting the study criteria for an endpoint has occurred.

7. STUDY MANAGEMENT

7.1 Monitoring

Before the study begins, a representative of AstraZeneca will visit the investigational site to

- determine the adequacy of the facilities
- discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives.

During the study, a monitor from AstraZeneca or company representing AstraZeneca will have regular contacts with the investigational site, including visits to

- provide information and support to the investigator(s)
- confirm that facilities remain acceptable
- confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the CRFs, and that investigational product accountability checks are being performed.
- perform source data verification (a comparison of the data in the CRFs with the subject's records at the hospital or practice, and other records relevant to the study). This will require direct access to all original records for each subject (eg, clinic charts).

The monitor or another AstraZeneca representative will be available between visits if the investigator(s) or other staff at the center needs information and advice.

7.2 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the center to perform audits or inspections, including source data verification. The purpose of an AstraZeneca audit or inspection is to systematically and independently examine all study related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements. The investigator should contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at his or her center.

7.3 Training of staff

The principal investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff). He or she will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

7.4 Changes to the protocol

Study procedures will not be changed without the mutual agreement of the principal investigator, the steering committee, and AstraZeneca.

If it is necessary for the study protocol to be amended, the amendment or a new version of the study protocol must be notified to or approved by each IEC or IRB, and in many countries also by the local regulatory authority, before implementation. Local requirements must be followed.

If a protocol amendment requires a change to a particular center's Written Informed Consent Form, then AstraZeneca and the center's IEC or IRB must be notified. Approval of the revised Written Informed Consent Form by AstraZeneca and by the IEC or IRB is required before the revised form is used.

AstraZeneca will distribute amendments and new versions of the protocol to each principal investigator(s), who in turn is responsible for the distribution of these documents to his or her IEC or IRB, and to the staff at his or her center. The distribution of these documents to the regulatory authority will be handled according to local practice.

7.5 Study agreements

The principal investigator at each center must comply with all the terms, conditions, and obligations of the study agreement for this study. In the event of any inconsistency between this protocol and the study agreement, this study agreement shall prevail.

7.6 Genetic sampling and storage

Plasma and buffy coat samples obtained at Visit 2, in addition to being used for cholesterol, CRP, and safety evaluations, will also be stored for future use in genomic and proteomic analyses relating to lipid metabolism, inflammatory function, and statin therapy. Samples for genetic analyses will be retained only for those subjects who have signed the addendum to the informed consent at Visit 1. To ensure participant confidentiality, these additional study samples will be coded with separate participant identifiers during the course of the study and will be rendered fully anonymous after the study has been completed.

7.7 Volume of blood sampling and handling of biological samples

The total volume of blood that will be drawn from each subject in this study will not exceed the following:

Table 7 Volume of blood to be drawn from each subject

Assessment	Sample volume (ml)	Number of samples	Total volume (ml)
Lipid assay	7.5	5	37.5
CRP	7.5	7	52.5
HbA _{1c}	3.0	4	12.0
ALT	7.5	9	67.5
Clinical chemistry	7.5	2	15.0
Hematology	3.0	2	6.0
Plasma storage sample	5.0	1	5.0
Genetic testing	5.0	1	5.0
Total			200.0

The total volume of blood collected during the duration of the study is not expected to exceed 200.0 ml.

7.8 Study timetable and termination

The proposed start date for this study is February 2003. As such, recruitment is anticipated to end by July 2004 with an expected study completion by December 2007, barring early termination by the IDMB.

8. ETHICS

8.1 Ethics review

The final study protocol, including the final version of the Written Informed Consent Form, must be approved or given a favorable opinion in writing by an IEC or IRB, as appropriate. The investigator must submit written approval to AstraZeneca before he or she can enroll any subject into the study.

The principal investigator(s) is responsible for informing the IEC or IRB of any amendment to the protocol in accordance with local requirements. In addition, the IEC or IRB must approve all advertising used to recruit subjects for the study. The protocol must be reapproved by the IEC or IRB annually, as local regulations require.

Either the investigator(s) or AstraZeneca must submit progress reports to the IEC or IRB according to local regulations and guidelines. The principal investigator(s) must also provide the IEC or IRB with any reports of serious adverse events from the study site.

The principal investigator(s) is also responsible for providing the IRB with reports of any serious adverse events from any other study conducted with the investigational product. This information will be provided to the principal investigator(s) by AstraZeneca.

8.2 Ethical conduct of the study

The study will be performed in accordance with the ethical principles in the Declaration of Helsinki (see Appendix C), GCP, and applicable regulatory requirements.

8.3 Subject information and consent

The principal investigator(s) at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study.

The principal investigator(s) must store the original, signed Written Informed Consent Form. A copy of the Written Informed Consent Form must be given to the subject.

A sample Written Informed Consent Form is attached (Appendix B). If modifications are made according to local requirements, the new version has to be approved by AstraZeneca.

8.4 Subject data protection

The Written Informed Consent Form will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. The subjects' names will not be recorded in this database. The Written Informed Consent Form will also explain that for data verification purposes, authorized representatives of AstraZeneca, a regulatory authority, an IEC or IRB may require direct access to parts of the hospital or practice records relevant to the study, including subjects' medical history.

9. EMERGENCY PROCEDURES

9.1 AstraZeneca emergency contact procedure

In case of a medical emergency contact the PPD switchboard at **1-888-483-7729** and request to be put in contact with the assigned Medical Monitor for the JUPITER study.

9.2 Procedures in case of medical emergency

The principal investigator(s) is responsible for ensuring that procedures and expertise are available to cope with medical emergencies during the study.

9.3 Procedures in case of overdose

There is no specific antidote to rosuvastatin. Experience of overdose with other statins is limited; a few cases of overdose following simvastatin have been reported. In all cases, there were no sequelae. Monitoring of CK and liver enzymes (ALT, AST) is recommended. Clinical monitoring and general supportive measures should be given as appropriate.

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Clinical Study Protocol: Appendix A

Study Code 4522US/0011

Version No. 2.0

Appendix Date 15 January, 2003

Appendix A**Signatures**

IND No. 56,385

ASTRAZENECA SIGNATURE(S)

Study Title

A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase III Trial 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

I agree to the terms of this study protocol

AstraZeneca Research and Development
site representative

.....
[Redacted Signature] Date
Senior Medical Director
AstraZeneca LP
[Redacted Signature]
725 Chesterbrook Blvd
Wayne, PA 19087

AstraZeneca Marketing Company
representative

.....
<< (Name, title, address and telephone number) >> Date

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SIGNATURE OF PRIMARY INVESTIGATOR

Title of report

A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase III Trial 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

I agree to the terms of this study protocol. I will conduct the study according to the procedures specified herein, and according to the principles of Good Clinical Practice (GCP) and local regulations.

Signature:

.....
Paul M Ridker, MD, MPH, FACC

.....
Date

Director, Center of Cardiovascular Disease Prevention
Brigham and Women's Hospital
Harvard Medical School
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Boston, MA 02215

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