AstraZeneca

Clinical Study Protocol

Drug Substance	Rosuvastatin
Study Code	D356FC00003
Date	

A 12-week Open-label, Randomised, Parallel-group, Multicentre, Phase IIIb Study to Compare the Efficacy and Safety of Rosuvastatin (CRESTOR™) 10 mg and 20 mg in Combination with Ezetimibe 10 mg and Simvastatin 40 mg and 80 mg in Combination with Ezetimibe 10 mg (fixed dose combination) in Patients with Hypercholesterolaemia and Coronary Heart Disease (CHD) or a CHD Risk Equivalent, Atherosclerosis or a 10-year CHD Risk of >20%

GRAVITY – Gauging the lipid effects of **R**osuv**A**statin plus ezetimibe **V**ersus s**I**mvastatin plus ezetimibe **T**herap**Y**

Sponsor:

AstraZeneca AB, 151 85 Södertälje, Sweden.

The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change

PROTOCOL SYNOPSIS

A 12-week Open-label, Randomised, Parallel-group, Multicentre, Phase IIIb Study to Compare the Efficacy and Safety of Rosuvastatin (CRESTOR™) 10 mg and 20 mg in Combination with Ezetimibe 10 mg and Simvastatin 40 mg and 80 mg in Combination with Ezetimibe 10 mg (fixed dose combination) in Patients with Hypercholesterolaemia and Coronary Heart Disease (CHD) or a CHD Risk Equivalent, Atherosclerosis or a 10-year CHD Risk of >20%

GRAVITY – Gauging the lipid effects of **R**osuv**A**statin plus ezetimibe **V**ersus s**I**mvastatin plus ezetimibe **T**herap**Y**

Investigator

of patients planned

This study requires approximately 800 randomised patients (200 patients per arm) with approximately 50% of patients from the US, 25% from Latin America and 25% from Europe. Centres may be discontinued from the study if recruitment rates are poor and new centres will be added if necessary to achieve recruitment goals. Recruitment will be competitive and centres will stop enrolment once the projected total number of patients is recruited.

Study period	**Phase of development**
Estimated date of first patient enrolled	IIIb
Estimated date of last patient completed	

Objectives

The primary objective of this study is to evaluate the LDL-C lowering efficacy of rosuvastatin (CRESTOR™) 10 mg and 20 mg in combination with ezetimibe relative to that of simvastatin in a fixed dose combination with ezetimibe. This objective has 3 specific components:

1. Percentage change from baseline in LDL-C for rosuvastatin 20mg in combination with ezetimibe 10mg vs simvastatin 40mg in combination with ezetimibe 10mg after 6 weeks combination therapy (mean value of 4 and 6 weeks of combination therapy will be used)

2. Percentage change from baseline in LDL-C for rosuvastatin 10mg in combination with ezetimibe 10mg vs simvastatin 40mg in combination with ezetimibe 10mg after 6 weeks combination therapy (mean value of 4 and 6 weeks of combination therapy will be used)

3. Percentage change from baseline in LDL-C for rosuvastatin 20mg in combination with ezetimibe 10mg vs simvastatin 80mg in combination with ezetimibe 10mg after 6 weeks combination therapy (mean value of 4 and 6 weeks of combination therapy will be used)

To address the apparent multiple comparisons of rosuvastatin/ezetimibe combinations to simvastatin/ezetimibe fixed dose combinations, the primary objective is constructed of 3 components. There will be a 'family of tests' approach using the Hochberg procedure to adjust for the multiple comparisons.

If statistical significance is reached for any of the components of the primary objective, the following secondary objectives (1 to 6) will be formally tested (secondary objectives 7 and 8 and the exploratory objective will be tested even if statistical significance is not reached):

1. To assess and compare the effects of rosuvastatin 10 mg in combination with ezetimibe 10 mg vs simvastatin 80 mg in combination with ezetimibe 10 mg on percentage LDL-C reduction after 6 weeks combination therapy (mean value of 4 and 6 weeks of combination therapy will be used)

2. To assess and compare the effects of rosuvastatin 10 mg and 20 mg in combination with ezetimibe 10 mg vs simvastatin 40 mg and 80 mg in combination with ezetimibe 10 mg on percentage change in HDL-C, TC, TG, nonHDL-C, ApoB, apolipoprotein A-I (ApoA-I); TC/HDL-C, LDL-C/HDL-C, nonHDL-C/HDL-C, ApoB/ApoA-I and high sensitivity C-reactive protein (hs-CRP) from baseline after 6 weeks of combination therapy (mean value of 4 and 6 weeks of combination therapy will be used)

3. To assess the efficacy of rosuvastatin 20 mg in combination with ezetimibe 10 mg vs simvastatin 40 mg in combination with ezetimibe 10 mg on the proportion of patients achieving lipid goals (American and European guideline) after 6 weeks

combination therapy (mean value of 4 and 6 weeks of combination therapy will be used)

4. To assess the efficacy of rosuvastatin 10 mg in combination with ezetimibe 10 mg vs simvastatin 40 mg in combination with ezetimibe 10 mg on the proportion of patients achieving lipid goals (American and European guideline) after 6 weeks combination therapy (mean value of 4 and 6 weeks of combination therapy will be used)

5. To assess the efficacy of rosuvastatin 20 mg in combination with ezetimibe 10 mg vs simvastatin 80 mg in combination with ezetimibe 10 mg on the proportion of patients achieving lipid goals (American and European guideline) after 6 weeks combination therapy (mean value of 4 and 6 weeks of combination therapy will be used)

6. To assess the efficacy of rosuvastatin 10 mg in combination with ezetimibe 10 mg vs simvastatin 80 mg in combination with ezetimibe 10 mg on the proportion of patients achieving lipid goals (American and European guideline) after 6 weeks combination therapy (mean value of 4 and 6 weeks of combination therapy will be used)

7. To assess the effects of rosuvastatin 10 mg and 20 mg in combination with ezetimibe 10 mg vs the same dose of rosuvastatin 10 mg and 20 mg alone on percentage change in LDL-C, HDL-C, TC, TG, nonHDL-C, ApoB, ApoA-I; TC/HDL-C, LDL-C/HDL-C, nonHDL-C/HDL-C, ApoB/ApoA-I and hs-CRP from baseline and on current American and European guideline lipid goal achievement after 6 weeks monotherapy and 6 weeks of combination therapy (mean value of 4 and 6 weeks of combination therapy will be used)

8. To assess the safety and tolerability of rosuvastatin in combination with ezetimibe vs simvastatin in combination with ezetimibe by observing adverse events, changes in laboratory safety variables and discontinuations over 6 weeks of combination therapy

The exploratory objective of this study is as follows:

- To assess and compare the effects of rosuvastatin 10 mg and 20 mg in combination with ezetimibe 10 mg vs simvastatin 40 mg and 80 mg in combination with ezetimibe 10 mg on change in biomarkers (sitosterol, lanosterol, C4 and lipoprotein-associated phospholipase A2 (LpPLA2). An additional sample will also be drawn for possible other biomarkers and lipid fractions that are related to atherosclerosis

Study design

This is a 12-week open-label, randomised, parallel-group, multicentre, phase IIIb study to compare the efficacy and safety of rosuvastatin 10 mg and 20 mg in combination with

ezetimibe 10 mg and simvastatin 40 mg and 80 mg in fixed dose combination with ezetimibe 10 mg in patients with hypercholesterolaemia and CHD or a CHD risk equivalent, atherosclerosis or a 10-year CHD risk of >20%. Patients will undergo 6 weeks of monotherapy followed by 6 weeks of combination therapy.

Target patient population

Male and female patients, 18 years of age or older, with hypercholesterolaemia and CHD or a CHD risk equivalent, clinical evidence of atherosclerosis or a Framingham 10-year CHD risk score of >20%.

Investigational product, dosage and mode of administration

Monotherapy

- Rosuvastatin 10 mg or 20 mg once daily (od) in single oral tablet form

Combination therapy

- Rosuvastatin 10 mg or 20 mg and ezetimibe 10 mg od provided as 2 oral tablets

Comparator, dosage and mode of administration

Monotherapy

- Simvastatin 40 mg or 80 mg od in single oral tablet form

Combination therapy

- Simvastatin 40 mg or 80 mg and ezetimibe 10 mg od in a fixed dose combination provided as a single oral tablet

Duration of treatment

The length of the study is 18 weeks. Patients will initially undergo a 6-week dietary lead-in. At the end of the dietary lead-in phase, eligible patients will be randomised to the monotherapy phase, when they will receive either rosuvastatin (10 mg or 20 mg) or simvastatin (40 mg or 80 mg) for 6 weeks. At the end of the monotherapy phase, patients will begin the 6-week combination therapy phase, when they will receive ezetimibe 10 mg in combination with the rosuvastatin or simvastatin dose that they received during the monotherapy phase.

Outcome variables

- Primary outcome variable:
    - The primary efficacy variable is the change in LDL-C relative to the baseline value. The change can be expressed as a percentage change. The primary variable is assessed after 6 weeks of combination treatment (mean of Visit 6 (Week 10) and Visit 7 (Week 12)) relative to the baseline (mean of Visit 2 (Week -2) and Visit 3 (Week 0)) value

- Secondary outcome variables:

The secondary outcome variables include:

  - LDL-C, HDL-C, TC, TG, nonHDL-C, ApoB, ApoA-I, TC/HDL-C, LDL-C/HDL-C, nonHDL-C/HDL-C and ApoB/ApoA-I, hs-CRP; and the corresponding measures of effects are the respective changes from baseline

  - Therapeutic lipid goals as described in American and European guidelines, with the corresponding measures of effect being the proportions of patients achieving goal

- Exploratory outcome variables

  - Change in biomarkers (sitosterol, lanosterol, C4 and LpPLA2). An additional sample will also be drawn for possible other biomarkers and lipid fractions that are related to atherosclerosis

- Patient reported outcomes (PROs)

  - There are no PROs for this study

- Health economics

  - There are no health economic outcomes for this study

- Pharmacokinetic

  - There are no pharmacokinetic outcomes for this study

- Pharmacodynamic

  - As listed under efficacy

- Safety

  - Adverse events (AEs)

  - Vital signs (blood pressure and pulse rate)

  - Clinical chemistry

  - Haematology

  - Urinalysis

  - Discontinuations

- Genetics

    - Genetic sampling is planned for the randomisation visit but can be taken at a subsequent visit. This sampling is optional and may only be performed in certain countries

Statistical methods

The primary analysis will be on the last observation carried forward (LOCF) in the intention to treat (ITT) population.

Formal analysis of lipids will be by analysis of co-variance (ANCOVA) with terms for baseline LDL-C, centre and treatment as covariates. For treatment to goal measures, analysis will be by logistic regression with baseline LDL-C, centre and treatment in the model.

Baseline for calculating percentage change in lipids and lipoproteins will be the mean of values from Visits 2 and 3 (Weeks -2 and 0). The effect of monotherapy will be assessed with the mean from Visits 4 and 5 (Weeks 4 and 6), and the effect of combination therapy will be assessed with the mean from Visits 6 and 7 (Weeks 10 and 12).

The estimates of the additional effects on lipids and lipoproteins of adding ezetimibe 10 mg to rosuvastatin 10 mg or 20 mg and simvastatin 40 mg and 80 mg will be estimated in the same way using the geometric mean of the 2 monotherapy visits as baseline. Corresponding 95% confidence intervals (CIs) will be computed.

Analysis of hs-CRP will be done by the non-parametric Kruskal-Wallis test. The median score will be used. In the case of pairwise comparisons, a Wilcoxon test will be used.

All AEs will be categorised by body system and medical dictionary for regulatory activities (MedDRA) preferred term and listed for each patient. In the randomised safety population, treatment emergent events will be reported as frequencies in each treatment group.

Haematology and clinical chemistry data will be listed for each patient and summarised for each treatment group at each visit. Values outside laboratory reference ranges will be highlighted.

Shift tables for haematuria and proteinuria data will show numbers and percentages of patients with categories of urinary protein and blood (none, trace, +, ++, +++ and ++++) at Week 12 against baseline (Week 0) and Visit 5 (Week 6).

TABLE OF CONTENTS PAGE

LIST OF TABLES PAGE

LIST OF FIGURES PAGE

LIST OF APPENDICES

LIST OF SUPPLEMENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ACC	American College of Cardiology
AE	Adverse Event (see definition in Section 4.7.1.1)
AHA	American Heart Association
ALT	Alanine Aminotransferase (also known as SGPT, serum glutamic pyruvic transaminase)
ANCOVA	Analysis of Co-Variance
Apo (A-I, B)	Apolipoprotein (A-I, B)
AST	Aspartate Aminotransferase (also known as SGOT, serum glutamic oxaloacetic transaminase)
ATP	Adult Treatment Panel
BMI	Body Mass Index
β-HCG	β-Human Chorionic Gonadotrophin
BP	Blood Pressure
°C	Degrees Celsius
CABG	Coronary Artery Bypass Graft
CDCP	Standardisation Program of the Centre for Disease Control and Prevention
CHD	Coronary Heart Disease
CI	Confidence Interval
CK	Creatine Kinase
eCRF	Electronic Case Report Form
CRO	Contract Research Organisation
CRP	C-Reactive Protein
CSA	Clinical Study Agreement/Investigator contract
CSP	Clinical Study Protocol
CSR	Clinical Study Report
DAE	Adverse event leading to discontinuation of the study drug
DOB	Date of Birth

Abbreviation or special term	Explanation
ECLIPSE	An Evaluation to Compare Lipid lowering effects of rosuvastatin and atorvastatin In force titrated subjects: a Prospective Study of Efficacy and tolerability
EDTA	Ethylenediamine Tetra-acetic Acid
ECG	Electrocardiogram
Ethics Committee	Synonymous to Institutional Review Board and Independent Ethics Committee
EU	European Union
EXPLORER	Examination of Potential Lipid-modifying effects Of Rosuvastatin in combination with Ezetimibe versus Rosuvastatin alone
°F	Degrees Fahrenheit
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
HDL-C	High-Density Lipoprotein Cholesterol
HDPE	High-Density Polyethylene
HMG-CoA	3-Hydroxy-3-Methylglutaryl-Coenzyme A
HRT	Hormone Replacement Therapy
hs-CRP	High Sensitivity C-Reactive Protein
IB	Investigator Brochure
ICH	International Conference on Harmonisation
INR	International Normalised Ratio
International co-ordinating investigator	If a study is conducted in several countries the international co-ordinating investigator is the investigator co-ordinating the investigators and/or activities internationally
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intention-To-Treat
IVRS	Interactive Voice Response System
LDL	Low-Density Lipoprotein
LDL-C	Low-Density Lipoprotein Cholesterol
LOCF	Last Observation Carried Forward
Lp(a)	Lipoprotein (a)
LpPLA2	Lipoprotein-associated phospholipase A2
MCH	Mean Cell Haemoglobin

Abbreviation or special term	Explanation
MCHC	Mean Cell Haemoglobin Concentration
MCV	Mean Cell Volume
Measurement	An observation made on a variable using a measurement device
MedDRA	Medical Dictionary for Regulatory Activities
NCEP	National Cholesterol Education Program
NDC	National Drug Code
NHLBI	National Heart, Lung and Blood Institute
NYHA	New York Heart Association
OAE	Other Significant Adverse Event (ie, adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient from study treatment; see definition in Section 4.7.1.1).
OCT	Oral Contraceptive Therapy
od	Once Daily
Outcome variable	A variable (usually a derived variable) specifically defined to be used in the analysis of a study objective
Pap	Papanicolaou (smears)
Parameter	A quantity (usually unknown) that characterises the distribution of a variable in a population of patients.
PP	Per-Protocol
Principal Investigator	A person responsible for the conduct of a clinical study at an investigational study site. Every investigational study site has a Principal Investigator.
PR	Pulse Rate
PRO	Patient Reported Outcome
PTCA	Percutaneous Transluminal Coronary Angioplasty
RBC	Red Blood Cell
ROW	Rest of World
SAE	Serious Adverse Event (see definition in Section 4.7.1.1)
SAP	Statistical Analysis Plan
SD	Standard Deviation
SE	Standard Error
SGOT	Serum Glutamic Oxaloacetic Transaminase (= AST)
SGPT	Serum glutamic Pyruvic Transaminase (= ALT)
SOP	Standard Operating Procedure

Abbreviation or special term	Explanation
SUADR	Suspected Unexpected Adverse Drug Reaction
TC	Total Cholesterol
TG	Triglycerides
TIA	Transient Ischaemic Attack
TLC	Therapeutic Lifestyle Change (Diet)
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
US	United States (of America)
Variable	A characteristic or a property of a patient that may vary eg, from time to time or between patients
vs	Versus
WBC	White Blood Cell
WBDC	Web Based Data Capture

1. INTRODUCTION

1.1 Background

Expert groups have identified low-density lipoprotein cholesterol (LDL-C) as the primary target for cholesterol lowering therapy because it is strongly associated with coronary heart disease (CHD) risk but, more importantly, clinical studies document that lowering LDL-C reduces the risk for major CHD events (Expert Panel NCEP ATP III 2001: De Backer et al 2003; American Heart Association (AHA)/American College of Cardiology (ACC): Smith et al 2006). A recent meta-analysis quantified the value of lowering LDL-C and predicted a 20% reduction in the 5-year incidence of major coronary events per 39 mg/dL reduction in LDL-C (Baigent et al 2005). These data from recently conducted clinical studies have spurred guideline committees to set progressively more rigorous, lower LDL-C therapeutic goals, particularly for very high-risk patients (Grundy et al 2004). As a consequence, even with the most effective cholesterol lowering tools, such as the HMG Co-A reductase inhibitors (statins) it can sometimes be difficult to induce the requisite reductions in LDL-C to meet these new goals for a substantial number of patients (Foley et al 2004). To enhance the likelihood that patients will reach these new targets, multiple drug treatment may be necessary; statin dose escalation alone may not be sufficient (Grundy et al 2004). Such combination cholesterol-lowering regimens pose the potential for additive or complementary effects and enhanced cholesterol lowering capabilities.

Recent interest has focused on statins and ezetimibe as a potential combination treatment regimen (Davidson and Toth 2004). Statins pharmacologically inhibit the HMG-CoA reductase enzyme in the endogenous cholesterol synthesis pathway and because of the consequent enhanced hepatic clearance and reduced production, LDL-C plasma levels decline substantially (Olsson, McTaggart and Raza 2002). Ezetimibe inhibits the absorption of cholesterol from the gastrointestinal tract, reducing hepatic cholesterol stores and enhancing LDL-C clearance (Sudhop et al 2002). This then suggests a mechanistic basis for additive cholesterol lowering with statin/ezetimibe combination treatment. This expectation of additive cholesterol-lowering has been borne out by multiple clinical studies (Ballantyne et al 2003, Cruz Fernandez et al 2005, Davidson et al 2004; Kosoglou et al 2004). Ezetimibe predictably adds, by about 15%, to the LDL-C lowering effects of essentially every statin tested to date and at every statin dose level (Ezetimibe Prescribing Information 2005). In fact, there is now a marketed fixed dose combination product of ezetimibe and a statin, simvastatin. The 10 mg dose of ezetimibe is available in combination with the entire range of simvastatin dose levels (10 to 80 mg) and these induce dose related declines in LDL-C of about 45% to 60%.

Rosuvastatin is a potent HMG Co-A reductase inhibitor that is at least equal to and is typically more effective in lowering LDL-C than essentially all statins at all approved dose levels (Jones et al 2003). Clinical study and post-marketing data to date indicate that rosuvastatin is also generally well tolerated, similar to other statins (Shepherd et al 2004). When combined with ezetimibe, rosuvastatin at its top dose (40 mg) has lowered LDL-C by 70% in

hypercholesterolaemic patients with CHD or a high CHD risk which represented a 13% additive reduction (95% confidence interval (CI) -15, -10; p <0.001) relative to rosuvastatin 40 mg monotherapy. This translated into an NCEP ATP III LDL-C target goal attainment rate of 94% (Ballantyne et al 2007). Ezetimibe enhances the cholesterol lowering capacity of rosuvastatin 40 mg whether co-administered as 'initial' treatment as described above or whether ezetimibe is added to rosuvastatin 40 mg in hypercholesterolaemic patients unable to attain NCEP ATPIII LDL-C goal in spite of receiving rosuvastatin 40 mg as a monotherapy (Ose et al 2005, Stein et al 2005a, Stein et al 2005b).

The additivity of ezetimibe co-administered with rosuvastatin has not, however been characterised at lower rosuvastatin doses. Such lower dose combinations could well prove a more effective LDL-C lowering option compared to the 2 top doses of simvastatin (40 mg and 80 mg) in fixed dose combination with ezetimibe 10 mg.

There are principally 3 different ways by which the body may regulate cholesterol homeostasis: through uptake, synthesis and excretion of cholesterol/bile acids. Thus there are 3 major sites of pharmacotherapeutic intervention in cholesterol metabolism: cholesterol synthesis (statins), bile acid absorption (resins, ileal bile acid transporter inhibitors) and cholesterol absorption (ezetimibe). A method to analyse the plasma biomarkers for cholesterol synthesis (lanosterol), cholesterol absorption (β-sitosterol), bile acid synthesis (7-a-hydroxy-4-cholestene-3-one, C4) and lipoprotein-associated phospholipase A2 (LpPLA2) has been established at DMPK&BAC, R&D, Mölndal. Currently there is a lack of knowledge how these 4 biomarkers are related to lipid abnormalities (LDL cholesterol, HDL cholesterol and triglycerides), but also how lipid-lowering treatments modulate the inter-relationships between these 4 biomarkers.

1.2 Rationale

Given the importance of lowering LDL-C and the clinical study data indicating the potential for ezetimibe to enhance the cholesterol lowering properties of statins, this study seeks to characterise the LDL-C lowering potential of an effective statin, rosuvastatin, over a range of doses and to profile the LDL-C lowering properties of these combinations relative to that of the simvastatin/ezetimibe fixed dose combination, including the highest dose of this combination.

With regard to cholesterol absorption, it was recently described that patients having a combination of high LDL-C and high sitosterol levels in plasma also had the highest risk for developing cardiovascular disease. In addition, it has been proposed that cholesterol absorption inhibitors might be most effective in patients being hyperabsorbers (high β-sitosterol levels). Thus, biomarkers for cholesterol absorption (β-sitosterol), cholesterol synthesis (lanosterol) and bile acid synthesis (7-beta-hydroxy-4-cholestene-3-one, C4) will also be analysed.

This study will be conducted in compliance with the protocol and with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP).

2. STUDY OBJECTIVES

2.1 Primary objectives

The primary objective of this study is to evaluate the LDL-C lowering efficacy of rosuvastatin (CRESTOR™) 10 mg and 20 mg in combination with ezetimibe relative to that of simvastatin in a fixed dose combination with ezetimibe. This objective has 3 specific components:

1. Percentage change from baseline in LDL-C for rosuvastatin 20mg in combination with ezetimibe 10mg vs simvastatin 40mg in combination with ezetimibe 10mg after 6 weeks combination therapy (mean value of 4 and 6 weeks of combination therapy will be used)

2. Percentage change from baseline in LDL-C for rosuvastatin 10mg in combination with ezetimibe 10mg vs simvastatin 40mg in combination with ezetimibe 10mg after 6 weeks combination therapy (mean value of 4 and 6 weeks of combination therapy will be used)

3. Percentage change from baseline in LDL-C for rosuvastatin 20mg in combination with ezetimibe 10mg vs simvastatin 80mg in combination with ezetimibe 10mg after 6 weeks combination therapy (mean value of 4 and 6 weeks of combination therapy will be used)

To address the apparent multiple comparisons of rosuvastatin/ezetimibe combinations to simvastatin/ezetimibe fixed dose combinations, the primary objective is constructed of 3 components. There will be a 'family of tests' approach using the Hochberg procedure to adjust for the multiple comparisons and this is detailed in Section 6.

2.2 Secondary objectives

If statistical significance is reached for any of the components of the primary objective, the following secondary objectives (1 to 6) will be formally tested (secondary objectives 7 and 8 and the exploratory objective will be tested even if statistical significance is not reached):

1. To assess and compare the effects of rosuvastatin 10 mg in combination with ezetimibe 10 mg vs simvastatin 80 mg in combination with ezetimibe 10 mg on percentage LDL-C reduction after 6 weeks combination therapy (mean value of 4 and 6 weeks of combination therapy will be used)

2. To assess and compare the effects of rosuvastatin 10 mg and 20 mg in combination with ezetimibe 10 mg vs simvastatin 40 mg and 80 mg in combination with ezetimibe 10 mg on percentage change in HDL-C, TC, TG, nonHDL-C, ApoB, apolipoprotein A-I (ApoA-I); TC/HDL-C, LDL-C/HDL-C, nonHDL-C/HDL-C, ApoB/ApoA-I and high sensitivity C-reactive protein (hs-CRP) from baseline after 6 weeks of combination therapy (mean value of 4 and 6 weeks of combination therapy will be used)

3. To assess the efficacy of rosuvastatin 20 mg in combination with ezetimibe 10 mg vs simvastatin 40 mg in combination with ezetimibe 10 mg on the proportion of patients achieving lipid goals (American and European guideline) after 6 weeks combination therapy (mean value of 4 and 6 weeks of combination therapy will be used)

4. To assess the efficacy of rosuvastatin 10 mg in combination with ezetimibe 10 mg vs simvastatin 40 mg in combination with ezetimibe 10 mg on the proportion of patients achieving lipid goals (American and European guideline) after 6 weeks combination therapy (mean value of 4 and 6 weeks of combination therapy will be used)

5. To assess the efficacy of rosuvastatin 20 mg in combination with ezetimibe 10 mg vs simvastatin 80 mg in combination with ezetimibe 10 mg on the proportion of patients achieving lipid goals (American and European guideline) after 6 weeks combination therapy (mean value of 4 and 6 weeks of combination therapy will be used)

6. To assess the efficacy of rosuvastatin 10 mg in combination with ezetimibe 10 mg vs simvastatin 80 mg in combination with ezetimibe 10 mg on the proportion of patients achieving lipid goals (American and European guideline) after 6 weeks combination therapy (mean value of 4 and 6 weeks of combination therapy will be used)

7. To assess the effects of rosuvastatin 10 mg and 20 mg in combination with ezetimibe 10 mg vs the same dose of rosuvastatin 10 mg and 20 mg alone on percentage change in LDL-C, HDL-C, TC, TG, nonHDL-C, ApoB, ApoA-I; TC/HDL-C, LDL-C/HDL-C, nonHDL-C/HDL-C, ApoB/ApoA-I and hs-CRP from baseline and on current American and European guideline lipid goal achievement after 6 weeks monotherapy and 6 weeks of combination therapy (mean value of 4 and 6 weeks of combination therapy will be used)

8. To assess the safety and tolerability of rosuvastatin in combination with ezetimibe vs simvastatin in combination with ezetimibe by observing adverse events, changes in laboratory safety variables and discontinuations over 6 weeks of combination therapy

2.3 Exploratory objective

The exploratory objective of this study is as follows:

- To assess and compare the effects of rosuvastatin 10 mg and 20 mg in combination with ezetimibe 10 mg vs simvastatin 40 mg and 80 mg in combination with ezetimibe 10 mg on change in biomarkers (sitosterol, lanosterol, C4 and LpPLA2). An additional sample will also be drawn for possible other biomarkers and lipid

fractions that are related to atherosclerosis. Biomarker results will be reported separately from the clinical study report (CSR)

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design and flow chart

This is a 12-week open-label, randomised, parallel-group, multicentre, phase IIIb study to compare the efficacy and safety of rosuvastatin 10 mg and 20 mg in combination with ezetimibe 10 mg and simvastatin 40 mg and 80 mg in fixed dose combination with ezetimibe 10 mg in patients with hypercholesterolaemia and CHD or a CHD risk equivalent, atherosclerosis or a 10-year CHD risk of >20%. Patients will undergo 6 weeks of monotherapy followed by 6 weeks of combination therapy.

This study requires approximately 800 randomised patients (200 patients per arm) with approximately 50% of patients from the US, 25% from Latin America and 25% from Europe. An approximate screen failure rate of 65% is anticipated based on previous studies (eg, ECLIPSE (Faergeman et al 2006) at 62%; EXPLORER (Ballantyne et al 2007) at 61%). It is therefore anticipated that it will be necessary to screen approximately 2285 patients in order to achieve the requisite number of randomised patients. Centres may be discontinued from the study if recruitment rates are poor and new centres will be added if necessary to achieve recruitment goals. Recruitment will be competitive and centres will stop enrolment once the projected total number of patients is recruited.

The study requires a population of male and female patients, 18 years of age or older, with hypercholesterolaemia and CHD or a CHD risk equivalent, clinical evidence of atherosclerosis (see Appendix G) or a Framingham 10-year CHD risk score of >20% (Appendix J).

Potentially eligible patients undergo screening procedures (Week –6; Visit 1) which include a fasting lipid analysis, discontinuation of previous dyslipidemia treatments and enter a 6-week dietary lead-in period (in which they will follow the Therapeutic Lifestyle Change (TLC) diet), during which they have another lipid analysis (at Week –2; Visit 2). Those who fulfil all eligibility criteria (Week -6; Visit 1) and have qualifying lipid values at Visit 2 (LDL-C 130 to 220 mg / dL; triglyceride < 400 mg / dl) are randomly allocated (1:1:1:1) to 1 of 4 treatments (at Week 0; Visit 3):

- Rosuvastatin 10 mg for 6 weeks followed by rosuvastatin 10 mg plus ezetimibe 10 mg for an additional 6 weeks
- Rosuvastatin 20 mg for 6 weeks followed by rosuvastatin 20 mg plus ezetimibe 10 mg for and additional 6 weeks
- Simvastatin 40 mg for 6 weeks followed by simvastatin 40 mg plus ezetimibe 10 mg fixed dose combination for an additional 6 weeks

- Simvastatin 80 mg for 6 weeks followed by simvastatin 80 mg plus ezetimibe 10 mg fixed dose combination for an additional 6 weeks

Patients return for clinic visits at Week 4 (Visit 4), Week 6 (Visit 5), Week 10 (Visit 6), and then at Week 12 (Visit 7) for the end-of-study procedures. Accordingly, the patient participation time is 18 weeks (see Figure 1 and Table 1).

All visits are related to Visit 3 (Week 0), the randomisation visit, which is referred to as the reference visit. The visit windows for all other visits will be ±4 days (see Table 2). It is important that investigators adhere to the study plan as closely as possible. If the date of an individual visit does not conform to the study plan, the timing of subsequent visits should be planned to maintain the visit structure relative to baseline.

Throughout the treatment phase of the study, from randomisation until final visit, the results of all blood lipid and lipoprotein levels will not be revealed to the study centre personnel. The results can then be provided following last patient completed, data base lock and formal unblinding.

During the course of the study, investigators are encouraged to manage of other cardiovascular risk factors such as hypertension and diabetes according to criteria specified in established guidelines and/or good medical practices, including a diet and exercise advice.

Once patients have completed participation in the study, their subsequent clinical management, including dyslipidemia treatment will be left to the discretion/clinical judgement of the Investigator. Investigators are encouraged to defer post-study lipid analyses until after the patient has instituted post-study dyslipidemia treatment.

There is a proposed optional genetics component to the study (please refer to Appendix K for details). In addition, the biomarkers research is not mandatory for participating patients.

6-week dietary lead-in phase (Visits 1 and 2, Weeks -6 to 0)

Patient eligibility will be assessed and written informed consent must be obtained prior to any visit procedures, including for the biomarker and genetic components of the study. Patients entering the dietary lead-in phase will follow the TLC diet (Appendix I) and are required to discontinue any current lipid-lowering therapy at Visit 1 (Week -6) to ensure that no residual effect on lipids will be carried forward in to the randomised treatment period. As part of the screening procedures, fasting blood samples will be taken for lipid analysis at Visits 1 and 2 (Weeks -6 and -2). In addition, evidence of atherosclerosis/CHD risk will be assessed, along with clinical chemistry, haematology and β-HCG. Medical and surgical history/demography will be recorded, as will concomitant medication and a physical examination, including vital signs, weight, height and waist circumference, will be performed. Dietary counselling will also be provided during the whole study.

12-week randomised treatment phase (Visits 3 to 7, Weeks 0 to 12)

Eligible patients will be randomised to the treatment phase to 1 of 4 treatment groups: rosuvastatin10 mg, rosuvastatin 20 mg, simvastatin 40 mg or simvastatin 80 mg. Treatment of 1 oral tablet will be administered once daily (od) for 6 weeks. After 6 weeks of monotherapy, patients will begin combination therapy, continuing on their previous treatment in combination with ezetimibe 10 mg. Patients randomised to rosuvastatin and ezetimibe combination therapy will receive 2 oral tablets od. Patients randomised to simvastatin and ezetimibe fixed dose combination therapy will receive a single oral tablet od. Tablet bottles will be dispensed at Visit 3 (Week 0) and at Visit 5 (Week 6) and compliance will be checked at Visits 4 to 7 (Weeks 4 to 12). Fasting blood samples for lipid and lipoprotein analysis will be taken at each visit during the treatment phase. Clinical chemistry testing will be performed at all visits during the treatment phase, as will urinalysis; haematology will be assessed at Visits 3, 5 and 7 (Weeks 0, 6 and 12). Concomitant medications and AEs will be recorded at each visit. The mean LDL-C values of Weeks 4 and 6 of combination therapy (Visits 6 and 7) will be used for the primary outcome variable. Optional samples for biomarker analysis will be taken at all visits during the treatment phase and a genetic sample will be taken at Visit 3 (Week 0), if applicable.

Figure 1 Study flow chart

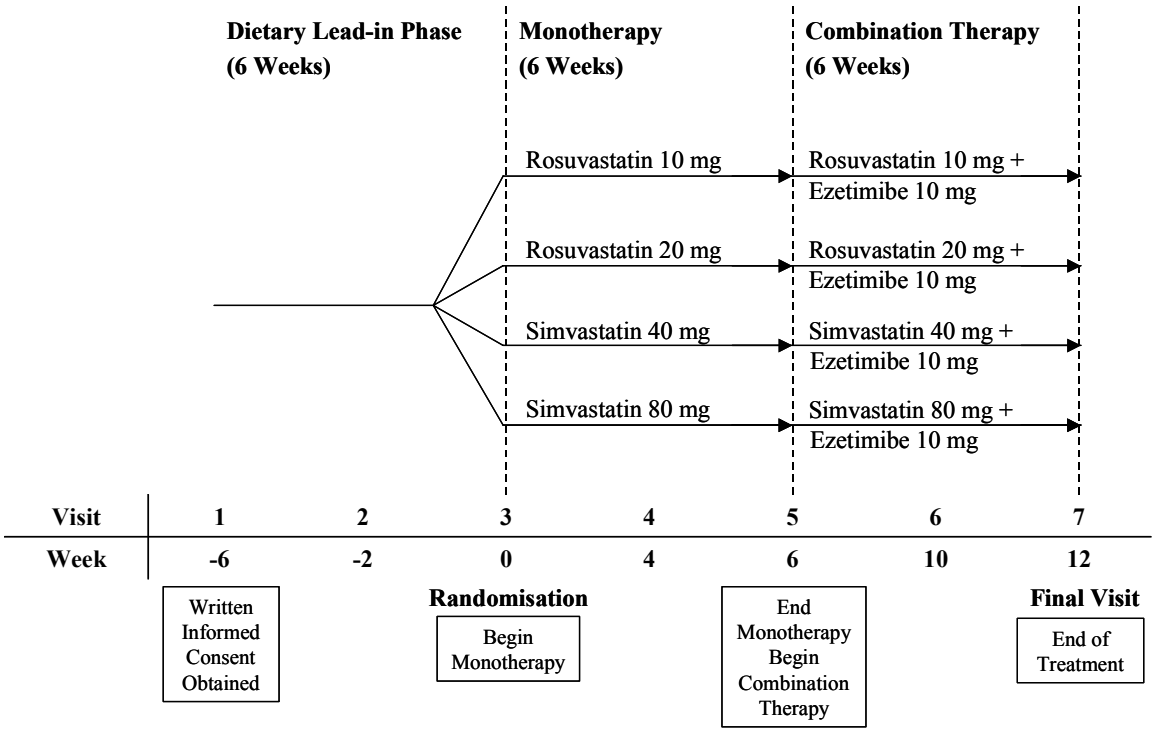

Table 1 Study plan

	Screening Phase		Randomised Phase				
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Visit Description	**Dietary lead-in**		**Statin monotherapy**		**Statin + Ezetimibe**		
No. Weeks	**-6 w**	**-2 w**	**0 w**	**4 w**	**6 w**	**10 w**	**12 w**
Written informed consent	X						
Written informed consent for genetic sampling	X						
Written informed consent for biomarker sampling	X						
Medical and surgical history/demography	X						
Evidence of atherosclerosis/CHD risk	X						
Physical examination	X						X
Vital signs/weight/waist circumference	X						X
Height	X						
Concomitant medication	X	X	X	X	X	X	X
Dietary counselling	X	X	X	X	X	X	
Clinical chemistry [a]	X		X		X		X
Abbreviated clinical chemistry [b]		X		X		X	
Haematology [c]	X		X		X		X
Fasting lipids[d]	X	X	X	X	X	X	X
Urinalysis[e]			X	X	X	X	X
β-HCG[f]	X	(X)	(X)	(X)	(X)	(X)	(X)
Genetic sampling[g]			X				
Biomarker sampling[h]			X	X	X	X	X
Eligibility criteria	X	X	X				
Randomisation			X				
Dispense study medication			X		X		
Study drug compliance				X	X	X	X
Adverse events (AEs)[i]		X	X	X	X	X	X

[a] The following clinical chemistry tests are to be performed: albumin, total bilirubin, blood urea nitrogen, CK, serum creatinine, alanine aminotransferase (ALT) (serum glutamic pyruvic transaminase (SGPT)), aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase (SGOT)), fasting glucose, alkaline phosphatase, calcium, phosphate, potassium, sodium, total protein, gamma-glutamyl transferase.

[b] The following abbreviated clinical chemistry tests are to be performed: creatine kinase (CK), serum creatinine, ALT, AST and TSH (TSH only at Visit 2; Week -2).

[c] Haematology is to consist of: platelet count, haemoglobin, haematocrit, red blood cell (RBC) count, RBC indices (mean cell volume (MCV), mean cell haemoglobin (MCH) and mean cell haemoglobin concentration (MCHC)), white blood cell (WBC) count, WBC differential (neutrophils, bands, lymphocytes, monocytes, eosinophils and basophils).

[d] Lipids include: TC, LDL-C, HDL-C, TG, nonHDL-C, LDL-C/HDL-C, TC/HDL-C, nonHDL-C/HDL-C, ApoB, ApoA-I, ApoB/A-I, along with hs-CRP. Only lipids required at Visits 1 and 2 (Weeks -6 and -2); lipids, lipoproteins and hs-CRP at Visits 3 to 7 (Weeks 0 to 12).

[e] For Visits 3, 5 and 7 (Weeks 0, 6 and 12), urinalysis sample is to consist of: visual description (colour and appearance), a dipstick test (specific gravity, pH, protein (qualitative), glucose, ketones, bilirubin and blood), microscopy (RBC, WBC, bacteria, casts and crystals). Quantitative assessment of total protein, albumin and creatinine is to be performed if indicated. For Visits 4 and 6 (Weeks 4 and 10), the following abbreviated urinalysis is to be performed: a dipstick test (specific gravity (if suspected/necessary), protein (qualitative) and blood). Qualitative assessment of total protein, albumin and creatinine is to be performed if indicated.

[f] An assay of serum β-HCG is only to be performed for women of childbearing potential. After Visit 1 (Week -6), an assay of serum β-HCG is only performed if it is suspected that a woman has become pregnant during the study. Assays of serum β-HCG will be performed on blood samples drawn for the clinical chemistry/abbreviated clinical chemistry testing.

[g] If consent is not obtained at Visit 1 (Week -6), as per study plan, it can be obtained at any subsequent visits. The genetic sampling is planned for the randomisation visit, but can be taken at a subsequent visit.

[h] Blood samples for biomarkers, ie, sitosterol, lanosterol, C4 and LpPLA2 will be drawn at randomisation and at the following visits. An additional sample will also be drawn at these visits for other biomarkers and lipid fractions that are related to atherosclerosis. The decision to perform the analyses will be taken after completion of the study.

[i] AEs and serious adverse events (SAEs) will be collected from the time when informed consent is obtained to end of study.

Table 2 Patient visit design with visit windows

Visit	Visit Description	Visit Window
Visit 1 (Week -6)	Screening/dietary lead-in	6 weeks (±4 days) before Visit 3
Visit 2 (Week -2)	Screening/dietary lead-in	2 weeks (±4 days) before Visit 3
Visit 3 (Week 0)	Randomisation/Treatment	Reference Visit (N/A)
Visit 4 (Week 4)	Treatment	4 weeks (±4 days) after Visit 3
Visit 5 (Week 6)	Treatment	6 weeks (±4 days) after Visit 3
Visit 6 (Week 10)	Treatment	10 weeks (±4 days) after Visit 3
Visit 7 (Week 12)	Study completion	12 weeks (±4 days) after Visit 3

Unscheduled visits

Patients may return for evaluation at any time their condition warrants medical attention. Appendices C, D, E and F provide guidance concerning certain laboratory elevations.

3.2 Rationale and risk/benefit assessment

3.2.1 Rationale for study design, doses and control groups

To address the goal of a comparative assessment of rosuvastatin/ezetimibe vs simvastatin/ezetimibe, the study design employs a parallel design with treatment groups formed by randomised allocation so that statistical inferences are valid. To characterise the additivity of ezetimibe and rosuvastatin, a sequential treatment 'before and after' design is incorporated, ie, the incremental contribution of ezetimibe is determined after addition to rosuvastatin. Prior studies with the top dose (40 mg) of rosuvastatin suggest that ezetimibe and rosuvastatin have additive effects on LDL-C lowering whether co-administered as 'initial therapy' or as the sequential addition of ezetimibe (Ballantyne et al 2007, Ose et al 2005, Stein et al 2005a, Stein et al 2005b).

The primary objective is constructed of 3 components. The statistical analytical plan specifies a 'family of tests' approach using the Hochberg procedure to adjust for the multiple comparisons and is detailed in Section 6. The second goal of the study, to characterise the additivity of ezetimibe and rosuvastatin, is a sufficiently independent objective, ie, no further adjustments for the number of comparisons is required.

Plasma LDL-C is an accepted measure for cholesterol lowering therapies and the change from baseline value allows for an approximate quantification of the magnitude of the treatment effect. To minimise variability of the baseline measure, the study design includes a pre-randomisation 6-week dietary lead-in period during which patients are instructed to follow therapeutic life-style measures (TLC diet) and to discontinue potential confounding lipid altering therapies (see Table 4). To minimise variability, the end of study treatment LDL-C measure is derived as the mean of the last 2 measures (after 4 and 6 weeks of combination treatment).

The study is conducted open-label, which allows for treatment with the fixed dose combination simvastatin/ezetimibe tablets (corresponding fixed dose rosuvastatin/ezetimibe tablets are not available). However, investigators and sponsor staff remain blinded to the objective efficacy measures (cholesterol values) as these are maintained by the central laboratory and can only be provided to study centre personnel following last patient completed, database lock and formal unblinding.

The allocation of patients to study treatments is to be by site-level randomisation so that investigators have no for-knowledge of a patient's treatment assignment. Although there are 2 sequential study treatment phases (monotherapy followed by combination treatment), there is only 1 randomisation and that is to the treatment sequence, statin dose followed by the same statin dose plus ezetimibe. The 6-week treatment periods (6 weeks of statin monotherapy followed by 6 weeks of statin/ezetimibe combination treatment) have been shown in prior

studies to be sufficient to attain a relatively stable estimate of the treatment effect and, in fact, a relatively stable level is evident after 4 weeks. Therefore, 6-week treatment periods were considered adequate time to show the relative LDL-C reducing efficacy of the statins and in combination with ezetimibe (Jones et al 2003).

The doses selected for study include 'lower 'doses of rosuvastatin in combination with ezetimibe as the highest dose (40 mg) was previously studied in the EXPLORER study (Ballantyne et al 2007) and the residual interest is in the value of the lower dose combinations with ezetimibe 10 mg. The highest simvastatin (40 and 80 mg) doses in fixed dose combination with ezetimibe 10 mg are chosen to assure that direct comparisons with rosuvastatin and simvastatin are 'fair' (Jones et al 2003, ICH guideline E10). Ezetimibe is available in only 1 dose, 10 mg.

The combination treatments under study in this study are expected to induce substantial reductions in LDL-C. Accordingly, the study evaluates the treatments in a clinically relevant population - patients with or at high risk for CHD and with an LDL-C value exceeding 130 mg/dL.

3.2.2 Risk/benefit and ethical assessment

All the patients in this study are at high CHD risk and are thus candidates for treatments capable of inducing substantial reductions in LDL-C and all receive such a treatment. The agents under study are marketed throughout the world and their efficacy and safety properties have been characterized accordingly. While there is not a marketed fixed dose rosuvastatin/ezetimibe combination product, rosuvastatin at its highest dose has been studied in co-administration with ezetimibe and this combination was generally well tolerated.

Dosing recommendations for statin therapy typically suggest starting at lower doses and escalating the dose as needed and as tolerated. In the clinical study setting the initiation of statin treatment at high doses has, however, generally been well tolerated (Crouse et al 2007, Nissen et al 2006), and the current study incorporates standard clinical and laboratory oversight measures that would support high dose initial statin treatment.

The risks associated with statin and dyslipidemia treatment are well described and include abnormalities in hepatic and renal function as well as myopathy and rhabdomyolysis. The study eligibility criteria and specified safety monitoring measures outlined in the clinical study protocol (CSP) are structured to minimise the risk for these adverse effects.

3.3 Selection of study population

3.3.1 Study selection record

Investigator(s) must keep a record of patients who were considered for enrolment but who were never enrolled in a screening log so as to characterise the population sampled for the study.

3.3.2 Inclusion criteria

At Visit 1 (Week -6)

For inclusion in the dietary lead-in phase, patients must fulfil all of the following criteria at Visit 1:

1. Provision of signed written informed consent

2. Male or female patients aged 18 years of age or older

3. A history of CHD or a CHD risk equivalent, clinical evidence of atherosclerosis (definitions given in Appendix G) or a 10-year Framingham risk score of >20% for CHD, as described in NCEP ATP III guidelines

4. The patient must have a reasonable likelihood of attaining LDL-C values of ≥ 130 mg/dL to <220 mg/dL at Visit 2, in the opinion of the Investigator. Based upon the experience of previous studies, the following guidance can be used in interpreting Visit 1 LDL-C results:

    - ≥ 125 mg/dL (3.24 mmol/L) to <220 mg/dL (5.69 mmol/L) in statin-naïve patients (patients who have not taken any lipid-lowering therapy known to affect LDL-C in the 4 weeks prior to Visit 1)

    - ≥ 90 mg/dL (2.33 mmol/L) to <180 mg/dL (4.66 mmol/L) in patients who have taken lovastatin, fluvastatin, or pravastatin within 4 weeks of Visit 1

    - ≥ 70 mg/dL (1.81 mmol/L) to <160 mg/dL (4.14 mmol/L) in patients who have taken simvastatin, atorvastatin, rosuvastatin or any statin in combination with ezetimibe within 4 weeks of Visit 1

5. Fasting TG concentrations <400 mg/dL (4.52 mmol/L)

6. Patients willing to follow all study procedures including attendance at clinics for scheduled study visits, fasting prior to clinic visits (all visits blood draws) and compliance with study treatment regimen

For inclusion in the biomarker research, patients must fulfil the following criterion:

- Provision of written informed consent for biomarker research

For inclusion in the genetic research, patients must fulfil the following criterion:

- Provision of written informed consent for genetic research. Any additional criteria are provided in Appendix K

If a patient declines to participate in the biomarker or genetic research, there will be no penalty or loss of benefit to the patient. The patient will not be excluded from other aspects of the study described in this CSP, so long as they consent.

Randomised treatment period

For inclusion into the randomised treatment phase of the study, patients must fulfil the following criteria:

1. Fasting LDL-C concentrations of ≥ 130 mg/dL (3.36 mmol/L) to <220 mg/dL (5.69 mmol/L) at Visit 2

2. Fasting TG concentrations <400 mg/dL (4.52 mmol/L) at Visit 2

3.3.3 Exclusion criteria (for dietary lead-in and randomised treatment period)

At Visit 1 (Week -6)

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

1. Use of lipid lowering drugs and other prohibited concomitant medications from Visit 1 (see Section 3.7)

2. History of statin-induced myopathy, or serious hypersensitivity reaction to other HMG-CoA reductase inhibitors (statins), including rosuvastatin, simvastatin and/or a history of hypersensitivity to any components of ezetimibe

3. Pregnant women, women who are breast feeding, and women of childbearing potential who are not using chemical or mechanical contraception or have a positive serum pregnancy test (serum β-HCG analysis)

4. Patients considered to be unstable by the Investigator after the following events (event within 8 to 12 weeks of study entry (Visit 1) at the Investigators discretion): a myocardial infarction, recent episode of unstable angina, myocardial revascularisation [percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass graft (CABG) surgery or another revascularisation procedure] or a transient ischaemic attack (TIA) or stroke. (These patients should be on a statin and should not be entered into a washout phase, therefore they are unsuitable for this study)

5. Severe congestive cardiac failure (New York Heart Association [NYHA] Class IIIb or IV) (see Appendix H). (There is no evidence that these patients benefit from statin therapy)

6. Patients awaiting a planned myocardial revascularisation prior to Visit 1. (These patients require statin therapy and so a washout phase is not appropriate; therefore they are unsuitable for this study)

7. History of malignancy with the exception of resected basal cell or squamous cell carcinoma of the skin. Women with a history of cervical dysplasia will be permitted to enter the study provided they have 3 consecutive clear Papanicolaou (Pap) smears. (So that patients who are at risk of recurrence of malignancy requiring treatment are not included)

8. History of homozygous familial hypercholesterolaemia (the severity of hypercholesterolaemia in these patients usually dictates the need for individualised treatment regimens which can include phoresis)

9. History of alcohol or drug abuse within the last 5 years

10. Current active liver disease [alanine aminotransferase (ALT) (serum glutamic pyruvic transaminase (SGPT)) ≥ 2 x upper limit of normal (ULN)] or severe hepatic impairment

11. Participation in another investigational drug study (including a previous rosuvastatin study) <4 weeks before enrolment in the study, or according to patient's local ethics committee requirements where a longer period is stipulated

12. Patients previously screened for this study

13. Serious or unstable medical or psychological conditions that, in the opinion of the Investigator, would compromise the patient's safety or successful participation in the study

14. Patients whose hormone replacement therapy (HRT) or oral contraceptive therapy (OCT) was initiated or changed within the 3 months prior to enrolment in the dietary lead-in phase. (Changes in female hormones can have an effect on lipid measurements)

At randomisation visit

15. Patients with uncontrolled hypothyroidism within 3 months prior to enrolment in the dietary lead-in phase, defined as a TSH >1.5 x ULN (this is due to the relationship between myopathy and patients with hypothyroidism undergoing statin therapy)

16. Patients with unexplained creatine kinase (CK) within 3 months prior to enrolment in the dietary lead-in phase, defined as >1 x ULN

17. Serum creatinine >176 μmol/L or 2.0 mg/dL at Visit 2. (This is consistent with other statin studies previously performed)

3.3.4 Restrictions

Patients are instructed to adhere to the following restrictions during the study:

1. Avoid blood donation within 3 months of entering the study, during the study and for 3 months following study participation

2. To fast (water is permitted) for 8 hours before each study visit. Refrain from consuming alcohol and cigarette smoking on the morning of each of these clinic visits

3. Maintain their usual physical activities or exercise

4. Follow the NCEP TLC diet for the duration of the study (see Appendix I)

5. Not to take any of the disallowed medications outlined in Section 3.7

3.3.5 Discontinuation of patients from treatment or assessment

3.3.5.1 Criteria for discontinuation

Patients may be discontinued from study treatment and assessments at any time. Specific reasons for discontinuing a patient from this study are:

1. Voluntary discontinuation by the patient who is free at any time to discontinue his/her participation in the study, without prejudice to further treatment

2. Safety reasons as judged by the Investigator and/or AstraZeneca

3. If at any time, the patient experiences muscle pain, tenderness or weakness which is accompanied by CK >10 x ULN, study medication should be discontinued. See management of increased CK in Appendix D

4. If ALT (SGPT) >3 x ULN on 2 consecutive occasions at least 48 hours apart, withdrawal of study medication is recommended (see Appendix B)

5. Severe non-compliance to protocol as judged by the Investigator and/or AstraZeneca

6. Pregnancy

7. Deterioration in the patient's condition which, in the opinion of the Investigator, warrants study medication withdrawal

8. Incorrect enrolment, ie, enrolment in violation of the inclusion/exclusion criteria

9. Incorrect randomisation, ie, randomisation in violation of the inclusion/exclusion criteria, where the evaluation of the Study Team Physician and Investigator did not render it appropriate to allow the patient to continue the study

3.3.5.2 Procedures for discontinuation

Patients who discontinue should always be asked about the reason(s) for their discontinuation and about the presence of any AEs. If possible, they should be seen and assessed by an Investigator(s) and the patient followed according to the study schedule. AEs should be followed-up to obtain a final outcome. Serious adverse events (SAEs) should be followed-up until resolution or until stabilised and no further change is expected. All investigational products (IPs) should be returned to the clinic by the patient.

3.3.5.3 Procedures for handling incorrect enrolled patients

Incorrectly enrolled patients will be discontinued from the study. Patients who are incorrectly randomised, not meeting the inclusion/exclusion criteria should be handled in the following way. First, a discussion must occur between the Study Team Physician and the Investigator regarding whether to continue or discontinue the patient from the study. This discussion should consider if continuation of study treatment or follow-up actions are necessary for the patient's safety and well-being, and the continuation of the study is not expected to be associated with any risk or discomfort for the patient. Once a decision is made, investigators need to ensure they comply with all applicable requirements for human patient protection and ethical review. The Study Team Physician is to ensure all such decisions are appropriately documented. In situations where an agreement cannot be reached with the Investigator in terms of how best to manage the patient going forward, the patient should have their randomised therapy stopped and be discontinued from the study.

3.4 Treatments

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

- Deliveries of such products from AstraZeneca are correctly received by a responsible person (eg, a pharmacist)
- Such deliveries are recorded
- Study treatments are handled and stored safely and properly
- Study treatments are only dispensed to study patients in accordance with the CSP
- Any unused products are accounted for and are destroyed locally (where appropriate procedures exist) or returned to AstraZeneca, or a designated facility 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 Identity of investigational product and comparators

AstraZeneca will provide open-labelled clinical study material, including rosuvastatin 10 mg, rosuvastatin 20 mg, simvastatin 40 mg, simvastatin 80 mg, ezetimibe 10 mg, the combination product of ezetimibe 10 mg/simvastatin 40 mg and the combination product of ezetimibe 10 mg/simvastatin 80 mg. Material will be labelled with a two-panel open tear-off label. The information on dose/form and national drug code (NDC) of each of the products is presented in Table 3.

Table 3 Product, dose/form and NDC

Product	Dose/form	NDC
Rosuvastatin	10 mg tablet	NDC #00310-0751-90
	20 mg tablet	NDC #00310-0752-90
Simvastatin	40 mg tablet	NDC #00006-0749-31
	80 mg tablet	NDC #00006-0543-31
Ezetimibe	10 mg tablet	NDC #66582-0414-31
Ezetimibe/Simvastatin	10/40 mg tablet	NDC #66582-0313-31
	10/80 mg tablet	NDC #66582-0315-31

3.4.2 Doses and treatment regimens

Study medication will be taken orally, with water if required, od at approximately the same time day or night.

At Visit 3 (Week 0) patients will be randomised to 1 of 4 treatment groups for monotherapy:

- Rosuvastatin 10 mg od in single oral tablet form
- Rosuvastatin 20 mg od in single oral tablet form
- Simvastatin 40 mg od in single oral tablet form
- Simvastatin 80 mg od in single oral tablet form

At Visit 5 (Week 6) patients will continue with their original statin dose but in combination therapy with ezetimibe:

- Rosuvastatin 10 mg and ezetimibe 10 mg od provided as 2 oral tablets
- Rosuvastatin 20 mg and ezetimibe 10 mg od provided as 2 oral tablets
- Simvastatin 40 mg and ezetimibe 10 mg od in a fixed dose combination provided as a single oral tablet

- Simvastatin 80 mg and ezetimibe 10 mg od in a fixed dose combination provided as a single oral tablet

Patients receiving combination therapy of rosuvastatin and ezetimibe will receive separate bottles of rosuvastatin and ezetimibe.

3.4.3 Labelling

All study drug supplies will be clearly marked according to local requirements regarding use for clinical study investigation only. The material will be labelled with at least the study reference number, administration instructions and storage conditions. Expiry dates will be on the label of all material as they are commercially available. The tear off label will also contain space for the enrolment code (patient number), visit number and date dispensed.

3.4.4 Storage

All IPs must be kept in a secure place under appropriate storage conditions. All study drugs will be stored in their original containers (as supplied by AstraZeneca) in a lockable storage facility until dispensed to the patients.

Rosuvastatin storage instructions

- Centres to store at controlled room temperature of 20 to 25 degrees Celsius (°C) (68 to 77 degrees Fahrenheit (°F)). Protect from moisture and light

Simvastatin storage instructions

- Centres to store at 5 to 30°C (41 to 86°F). Protect from moisture and light

Ezetimibe storage instructions

- Centres to store at 25°C (77°F). Excursions permitted from 15 to 30°C (59 to 86°F). Protect from moisture

Simvastatin/ezetimibe storage instructions

- Centres to store at 20 to 25°C (68 to 77°F)

3.4.5 Accountability

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

The study treatment(s) must be used only as directed in the CSP. The Investigator must maintain accurate records accounting for the receipt of the IPs 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 in the electronic data capture system.

Patients 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 patient compliance.

The Investigator will retain the returned medication until AstraZeneca authorised 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 (or its designee). This return will be documented by using an IP Return Invoice (or an equivalent form) supplied by AstraZeneca.

3.5 Method of assigning patients to treatment groups

Once a patient has signed the written informed consent, they will be assigned with a unique identifying number (enrolment number). This enrolment number will be used as the identification number throughout the study and once allocated it will not be re-used. The enrolment number will be a combination of the site number and the sequential patient at that site.

Patient eligibility will be established before treatment randomisation. At Visit 3 (Week 0), patients who satisfy the entry criteria will be randomised by blinded randomisation via Interactive Voice Response System (IVRS) to receive either rosuvastatin monotherapy (10 mg or 20 mg) or simvastatin monotherapy (40 mg or 80 mg). After completion of monotherapy, patients will continue with the same dose of rosuvastatin or simvastatin but in combination with ezetimibe 10 mg. The randomisation scheme will be generated by an AstraZeneca representative using the GRand system. A blocked randomisation schedule by site will be produced for the main study. Patients will be randomised strictly sequentially as patients are eligible for randomisation. No one outside the group generating the randomisation scheme and the group adopting it in to the IVRS will have knowledge about the scheme. Hence, investigators will have no knowledge beforehand of the treatment the patient will receive.

If a patient discontinues from the study, the patient will not be allowed to re-enter the study.

If a patient is provided treatment by mistake which is not the treatment assigned by IVRS, no attempt should be made to remedy the error once study medication has been dispensed. The patient should continue with their original statin and dose, as provided, and from Visit 5 (Week 6) onwards in combination with ezetimibe. AstraZeneca or its representative should be notified as soon as the error is discovered.

3.6 Blinding and procedures for unblinding the study

3.6.1 Methods for ensuring blinding

In this study the medication is not blinded, so as to allow the use of the fixed dose simvastatin/ezetimibe tablets (there is no similar rosuvastatin/ezetimibe combination tablet). However, the investigators and sponsor staff remain blinded to the efficacy measures (lipid levels) and are also blinded to the randomisation scheme.

3.6.2 Methods for unblinding the study

As study treatments are not blinded, provisions are not necessary to provide such information to investigators during the study. The results of all blood lipid and lipoprotein levels can be revealed to the study centre personnel following last patient completed, data base lock and formal unblinding.

3.7 Pre-study, concomitant and post-study treatment(s)

Other medication, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the investigators, provided that they do not conflict with the disallowed medication in Table 4. The administration of all medication (including IPs) must be recorded in the appropriate sections of the electronic case report form (eCRF).

All disallowed medications should be stopped on entry to the study and are disallowed while the patient is on study medication.

If a patient is taking antacids then the antacids should be taken 2 hours after administration of study medication, due to antacids reducing rosuvastatin efficacy.

Table 4 Disallowed concomitant medications

CLASS OF DRUG	GENERIC NAME
Lipid lowering agents	niacin/nicotinic acid (includes vitamins/supplements with >50 mg/day niacin/nicotinic acid)
	bile acid sequestrant
	probucol
	clofibrate
	fenofibrate
	gemfibrozil (and other fibrates)
	atorvastatin
	lovastatin
	pravastatin
	rosuvastatin (except for study medication)
	simvastatin (except for study medication)
	fluvastatin
	ezetimibe (except for study medication)
	cholestyramine
	colesevelam
	colestipol hydrochloride
CYP3A4 inhibitors	azole antifungals (itraconazole, ketoconazole)
	erythromycin, clarithromycin, telithromycin
	HIV protease inhibitors
	nefazodone
	large quantities of grapefruit juice (>1 quart daily)
Immunosuppressants	cyclosporine
Synthetic androgen	danazole
Antiarrhythmics	amiodarone
Calcium channel blockers	verapamil

3.7.1 Vitamin K antagonist usage (eg, warfarin, coumarins)

Clinical studies have shown a potentiation of the anticoagulant effect during concomitant administration of rosuvastatin (and other statins) and a vitamin K antagonist. Interactions of this type may be clinically managed by close monitoring of the anticoagulant effect (expressed as international normalised ratio (INR)).

For these reasons, careful monitoring of INR is required and investigators should, in accordance with usual practice, measure INR frequently until vitamin K antagonist dose stabilisation is achieved, and periodically thereafter, particularly in the following situations:

- **when starting vitamin K antagonist therapy in a patient currently receiving study medication**

- **when a patient currently receiving a vitamin K antagonist begins study medication**

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

3.8 Treatment compliance

Patients will be asked to bring their medication bottles to all visits from Visit 4 (Week 4) onwards and to return all unused medication and empty containers. The number of tablets issued minus the number of tablets returned is used to calculate the tablets taken. From this information compliance is calculated:

$$\textbf{Compliance} = \left(\frac{Tablets \cdot taken \cdot during \cdot the \cdot period}{Tablets \cdot which \cdot should \cdot have \cdot been \cdot taken} \right) \textbf{x 100}$$

Any patient taking <80% of any study medication is considered to be non-compliant. Compliance will be checked at Visits 4 to 7.

Those taking <80% of the prescribed study medication will be considered protocol deviators.

4. MEASUREMENTS OF STUDY VARIABLES AND DEFINITIONS OF OUTCOME VARIABLES

4.1 Primary variable

The primary variable is the change in LDL-C from baseline, expressed as a percentage.

4.2 Screening and demographic measurements

The screening and demographic data include:

- Date of birth (DOB), sex and race
- Significant medical (including CHD and atherosclerosis) and surgical history
- Prior and concomitant medication
- Full physical examination including height, weight and vital signs
- Waist circumference

- Fasting blood samples of lipids, haematology and clinical chemistry
- Serum β-human gonadotrophin (β-HCG) for female patients of childbearing potential

4.3 Patient-Reported Outcomes (PROs)

Not applicable.

4.4 Health Economic measurements and variables

Not applicable.

4.5 Pharmacokinetic measurements and variables

Not applicable.

4.6 Efficacy and pharmacodynamic measurement and variables

The primary efficacy variable, change in LDL-C, is determined after 6 weeks of combination treatment (mean of Visit 6 and Visit 7 (Week 10 and Week 12) values) relative to the baseline value (mean of Visit 2 and Visit 3 (Week -2 and Week 0) values). The secondary measures of change in lipid and lipoprotein values are derived in a similar manner.

The secondary measures of proportions at the therapeutic goals are determined as the simple ratio of the number of patients achieving goal and the number of patients randomised.

For the secondary objective of assessing the additive effect of ezetimibe and rosuvastatin, the mean of Visits 2 and 3 (Week -2 and Week 0) serves as baseline for monotherapy treatments and the mean of Visits 4 and 5 (Week 4 and Week 6) as baseline for the rosuvastatin/ezetimibe combination treatments.

The efficacy variables for the study are described below:

- Primary outcome variable:
  - The primary efficacy variable is the change in LDL-C relative to the baseline value. The change can be expressed as a percentage change. The primary variable is assessed after 6 weeks of combination therapy
- Secondary outcome variables:

The secondary outcome variables include:

- LDL-C, HDL-C, TC, TG, nonHDL-C, ApoB, ApoA-I, TC/HDL-C, LDL-C/HDL-C, nonHDL-C/HDL-C and ApoB/ApoA-I, hs-CRP; and the corresponding measures of effects are the respective changes from baseline

  - Therapeutic lipid goals as described in American and European guidelines, with the corresponding measures of effect being the proportions of patients achieving goal

- Exploratory outcome variable

  - Change in biomarkers (sitosterol, lanosterol, C4 and LpPLA2). An additional sample will also be drawn for possible other biomarkers and lipid fractions that are related to atherosclerosis

4.6.1 Lipid assessments

The primary and secondary efficacy variables are based on fasting lipid values collected at the scheduled visits and analysed by a central laboratory.

4.6.1.1 Methods of assessment

Analyses of all laboratory samples will be performed by a central laboratory that is certified by the Standardisation Program of the Centre for Disease Control and Prevention (CDCP) and the National Heart, Lung and Blood Institute (NHLBI). Further details of the central laboratory can be found in the central laboratory manual.

Two blood samples of 5 mL will be drawn at each visit for lipid and lipoprotein assessments from Visit 1 (Week -6) onwards.

Fasting concentrations of LDL-C will be determined by the Friedewald equation, with the exception of those visits where TG level >400 mg/dL (4.52 mmol/L) in which case a β-quantification measurement of LDL-C will be used. The methodologies for the other lipid and lipoprotein measures are included in a separate laboratory manual.

Fasting concentrations of TC, LDL-C, HDL-C, TG, nonHDL-C, LDL-C/HDL-C, TC/HDL-C, nonHDL-C/HDL-C, ApoB, ApoA-I, TC/HDL-C, LDL-C/HDL-C, nonHDL-C/HDL-C and ApoB/ApoA-I will be determined at Visits 3, 4, 5, 6 and 7 (Weeks 0, 4, 6, 10 and 12). Only lipids are required at Visits 1 and 2 (Weeks -6 and -2).

The Friedewald equation is as follows:

<u>For SI units (mmol/L):</u>

$$LDL\text{-}C = TC - \{HDL\text{-}C + {}^{TG}/_{2.2}\}$$

<u>For non-SI units (mg/dL):</u>

$$LDL\text{-}C = TC - \{HDL\text{-}C + {}^{TG}/_{5}\}$$

The results of all blood lipid and lipoprotein levels measured during the treatment period (Visit 3 (Week 0) onwards) can only be revealed to the study centre following last patient completed, data base lock and formal unblinding.

4.6.2 hs-CRP assessments

A secondary outcome variable is the assessment of hs-CRP from samples collected at the scheduled visits and analysed by a central laboratory.

4.6.2.1 Methods of assessment

Analysis of hs-CRP will be performed on blood samples taken as part of the lipid assessments from Visit 1 (Week -6) onwards. The samples for hs-CRP assessment will be assessed by nephelometry and this will be performed by the central laboratory.

4.6.3 Biomarker assessments

An exploratory outcome variable is the assessment of biomarkers from samples collected at the scheduled visits and analysed by a central laboratory.

4.6.3.1 Methods of assessment

Blood samples for biomarkers, ie, sitosterol, lanosterol, C4, LpPLA2 will be drawn from Visit 3 (Week 0) onwards. An additional sample will also be drawn at these visits for possible other biomarkers and lipid fractions that are related to atherosclerosis. At each timepoint, two 5 mL samples of blood will be taken from a peripheral vein into ethylenediamine tetra-acetic acid (EDTA) tubes and centrifuged for 10 minutes at room temperature or lower at 2000 g. The samples will be frozen and stored at -20°C at site for an initial time period and then shipped to the central laboratory for further storage at -70°C. The decision to perform the analyses will be made after completion of the study. This is due to the exploratory nature of these biomarkers and will depend upon the heterogeneity of the efficacy and safety outcome variables and the current scientific interest in their predictive value.

4.6.4 Derivation or calculation of outcome variable

The primary variable, change in LDL-C, is determined after 6 weeks of combination treatment (mean of Visit 6 and Visit 7 (Week 10 and Week 12) values) relative to the baseline value (mean of Visit 2 and Visit 3 (Week -2 and Week 0) values). Percentage change is the difference in the mean of the Visit 6 and Visit 7 (Week 10 and Week 12) value relative to the baseline value multiplied by 100.

The secondary measures of change in lipid and lipoprotein values are derived in a similar manner.

The secondary measures of proportions at the therapeutic goals are determined as the simple ratio of the number of patients achieving goal and the number of patients randomised.

For the secondary objective of assessing the additive effect of ezetimibe and rosuvastatin, the mean of Visits 2 and 3 (Week -2 and Week 0) serves as baseline for monotherapy treatments and the mean of Visits 4 and 5 (Week 4 and Week 6) as baseline for the rosuvastatin/ezetimibe combination treatments.

4.7 Safety measurements and variables

The methods for collecting safety data are described below.

4.7.1 Adverse events

4.7.1.1 Definitions

The definitions of AEs and 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.

Adverse event

An AE 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 (ECG)). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including dietary lead-in periods, even if no study treatment has been administered.

Serious adverse event

A SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), and at any dose of the IP, comparator or placebo, that fulfils 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient 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 case report form 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 any of the following – study medication – other medication?” For further guidance on the definition of a SAE and a guide to the interpretation of the causality question, see Appendix B.

Note that SAEs that could be associated with any study procedure should also be reported. For such events the causal relationship is implied as "yes".

Other significant adverse events

OAEs will be identified by the Study Delivery Team Physician in consultation with the appropriate Global Drug Safety Physician during the evaluation of safety data for the CSR. Significant AEs of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the patient from study treatment, will be classified as OAEs. Examples of these are marked haematological 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, an e-narrative will be generated and included in the CSR.

4.7.1.2 Recording of adverse events

AEs will be identified by means of a standard question, "Have you had any health problems since the previous visit?" The patient will be asked to provide a description of the event, the dates of onset and resolution, and to assess the intensity of the reported AE according to the following scale:

- mild (awareness of sign or symptom, but easily tolerated)
- moderate (discomfort sufficient to cause interference with normal activities)
- 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 an SAE or not.

If a diagnosis of the patient's condition has been made, then the diagnosis should be recorded as the AE (eg, fever, runny nose; cough can be recorded as "flu"). However, if a diagnosis of the patient's condition has not been made, or only if the individual symptoms are not well recognised, 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 4.7.1.1. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

AstraZeneca or representative will classify AEs using the Medical Dictionary for Regulatory Activities (MedDRA).

Should an overdose (accidental or deliberate) occur, it must be reported in accordance with the procedures described in Section 9.3, Procedures in case of overdose, regardless of whether the

overdose was associated with any symptom or not. All symptoms associated with the overdose should be reported as AEs.

Should a pregnancy occur, it must be reported in accordance with the procedures described in Section 9.4, Procedures in case of pregnancy. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an IP may have interfered with the effectiveness of a contraceptive medication.

4.7.1.3 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product or to the study procedure(s). All SAEs will be recorded in the eCRF.

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 not later than the end of the next business day) of when he or she becomes aware of it.

SAE information will be entered and submitted into the Web Based Data Capture (WBDC) system on the relevant eCRF modules. An automated email alert will be sent to the designated AstraZeneca representative who will work with the Investigator to ensure that all the necessary information is available in the system within the required time frames, but taking advantage of the time allocated in those timelines. The AstraZeneca representative will notify the appropriate AstraZeneca Drug Safety department through the WBDC system via email that a completed electronic SAE module and relevant information from other appropriate eCRF modules is available in the WBDC system. If the system is unavailable, the Investigator should fax a paper back-up SAE report to the AstraZeneca representative immediately, recognising that the same reporting time frames still apply. The Investigator is responsible for completing the eCRF as soon as the system becomes available again.

The AstraZeneca representative will work with the Investigator to compile all necessary information and ensure that the appropriate Safety Database Data Entry Site receives a report within the required timeframes, which will be detailed in a study specific Safety Plan. The Investigator must report follow-up information on SAEs 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 the time lines described above.

The Investigator and/or Sponsor are responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE, as per local requirement. For studies in countries implementing the EU Clinical Trials Directive, this will be taken care of by AstraZeneca or their representative (see Section 8.1).

4.7.2 Laboratory safety measurements and variables

4.7.2.1 Methods of assessment

Clinical chemistry testing will be performed at Visits 1, 3, 5 and 7 (Weeks -6, 0, 6 and 12) and will include: albumin, total bilirubin, blood urea nitrogen, CK, serum creatinine, ALT (SGPT), aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase

(SGOT)), fasting glucose, alkaline phosphatase, calcium, phosphate, potassium, sodium, total protein and gamma-glutamyl transferase (GGT). At Visits 2, 4 and 6 (Weeks -2, 4 and 10) abbreviated clinical chemistry tests will be performed, consisting of: CK, serum creatinine, ALT, AST and TSH (TSH only at Visit 2 (Week -2)).

Haematology testing will be performed at Visits 1, 3, 5 and 7 (Weeks -6, 0, 6 and 12), which will include: platelet count, haemoglobin, haematocrit, red blood cell (RBC) count, RBC indices (mean cell volume (MCV), mean cell haemoglobin (MCH), mean cell haemoglobin concentration (MCHC)), white blood cell (WBC) count, WBC differential (neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils).

A 10 mL mid-stream urine sample will be collected at Visits 3, 4, 5, 6 and 7 (Weeks 0, 4, 6, 10 and 12) for analysis at the central laboratory. For Visits 3, 5 and 7 (Weeks 0, 6 and 12), urinalysis sample is to consist of: visual description (colour and appearance), a dipstick test (specific gravity, pH, protein (qualitative), glucose, ketones, bilirubin and blood), microscopy (RBC, WBC, bacteria, casts and crystals). For Visits 4 and 6 (Weeks 4 and 10), the following abbreviated urinalysis is to be performed: a dipstick test (specific gravity (if suspected/necessary), protein (qualitative) and blood). At Visits 4 to 7 (Weeks 4 to 12), for any patients with dipstick protein ++ or greater where this represents a $\geq$ 1 grade shift (eg, from + to ++ or trace to ++) from the baseline visit, the central laboratory will automatically perform a quantitative assessment of total protein, albumin and creatinine.

If the urine protein/creatinine ratio is >0.5 mg protein per mg creatinine (US) or >56 mg protein per µmol creatinine (RoW), the Investigator may stop study medication following consultation with the relevant AstraZeneca personnel (eg, Clinical Study Team Physician).

An assay of serum β-HCG concentration will be performed for women of childbearing potential at Visit 1 (Week -6). If the test is positive for pregnancy, the patient should not enter the study. An assay of serum β-HCG concentration will be performed at all subsequent visits if it is suspected that the patient may have become pregnant. If the test is positive for pregnancy the patient will be withdrawn from the study. Assays of serum β-HCG will be performed on blood samples drawn for the clinical chemistry/abbreviated clinical chemistry testing.

Vital signs (sitting blood pressure (BP) and pulse rate (PR)) will be assessed at Visit 1 (Week -6) and Visit 7 (Week 12).

In the event of elevated liver function tests, see Appendix C for guidance with regards to management of elevated liver enzymes.

In the case of new or increased symptoms of muscle pain/myopathy/elevation of CK to >5x ULN developing after randomisation, see Appendix D for guidance with regards to management of increased CK.

In the event that serum creatinine levels increase >30% from the baseline value, see Appendix E for guidance with regards to elevated serum creatinine.

Additional testing required (unscheduled visits) due to elevated values and/or symptoms (liver enzymes, CK, serum creatinine, see Appendix C, D and E) will be performed at the central laboratory.

Other laboratory tests which are performed outside the CSP will not be analysed by the central laboratory.

4.8 Volume of blood sampling and handling of biological samples

The total volume of blood that will be drawn from each patient in this study is as follows:

Table 5 Volume of blood to be drawn from each patient

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Pharmacodynamic	(Lipid assay including TC, LDL-C, HDL-C, TG, nonHDL-C, LDL-C/HDL-C, TC/HDL-C, nonHDL-C/HDL-C, ApoB, ApoA-I, hs-CRP)	5	14	70
Exploratory	Biomarkers: Refer to Section 2.3; Exploratory objective	5	10	50
Safety	Clinical chemistry	3.5	4	14
	Abbreviated clinical chemistry	3.5	3	10.5
	Haematology	3	4	12
Total				156.5

Note: For patients consenting to the genetic study (Appendix K) an additional 9 - 10 mL will be taken. It should also be noted that additional samples may be required following safety findings (refer to Appendices C, D and E).

4.8.1 Analysis of biological samples

The analyte stability limits defined by the central laboratory will be applied to all analyses performed on behalf of AstraZeneca. The central laboratory will not analyse samples that fall outside these stability limits. Analytical data will not be reported if found to have been derived from a sample that fell outside these stability limits. The standards of procedure followed by the central laboratory may be amended in accordance with its Standard Operating Procedures (SOPS). The central laboratory will inform AstraZeneca of the stability limits relevant to this study before the first patient gives informed consent to take part in the study.

If the central laboratory chooses to sub-contract the analytical work to another laboratory, the central laboratory must assure itself and provide assurance to AstraZeneca that the other laboratory will apply defined stability limits to all analyses performed on behalf of AstraZeneca. Samples falling outside these limits must not be analysed or data reported. The other laboratory will inform AstraZeneca of the stability limits relevant to this study before the first patient gives informed consent to take part in the study.

The central laboratory will provide the investigational sites with all the appropriate materials for specimen collection and sample processing, packaging, and shipping to the central laboratory. An Investigator laboratory manual providing detailed instructions will be provided to each investigational site before the study starts. A tourniquet may be applied, but for no longer than 2 minutes. Full details of sampling, sample preparation, and storage methods to be used are given in the Investigator laboratory manual.

Samples which will be analysed by the central laboratory will be labelled according to the guidelines provided by the central laboratory.

Shipment of samples to the central laboratory will be carried out according to the guidelines provided by the central laboratory. The samples are shipped the day of collection by express courier to ensure receipt at the central laboratory within the period of sample integrity (within 48 hours of blood drawing). The appropriate documentation should accompany the samples.

Analyses of samples from all clinic visits will be carried out as described in the central laboratory methodology manual, a copy of which will be distributed to each centre before any patient is enrolled.

4.9 Genetic measurements and co-variables

4.9.1 Collection of samples for genetic research

Full details of the optional generic research component to this study, including rationale, areas of interest and logistical information are provided in Appendix K.

5. DATA MANAGEMENT

Data will be entered in the WBDC system at the study site. Trained study personnel will be responsible for entering data on the observations, tests and assessments specified in the protocol into the WBDC system and according to the eCRF Instructions. The eCRF Instructions will also provide the study site with data entry instructions. Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. When data have been entered, reviewed, edited and Source Data Verification (SDV) performed the Principal Investigator will be notified to sign the eCRF electronically as per the agreed project process and data will be locked to prevent further editing. A copy of the eCRF will be archived at the study site.

Data collected from the completed eCRFs and laboratory data will be received electronically by an AstraZeneca representative. The processes will be documented in the Data Management Plan and the validation performed under the direction of the responsible Data Manager, according to the Data Validation Manual.

5.1 Reporting of genotypic results

Results from any genetic research performed will be reported separately from the CSR. AstraZeneca will not provide individual genotype results to patients, their family members, any insurance company, an employer, clinical study investigator, general physician or any other third party, unless required to do so by law. The patient's DNA will not be used for any purpose other than those described in the study protocol.

Individual patients will not be identified in any report or publication resulting from this work. The data and results of this study may be reviewed with collaborators and published, but neither the patient's name nor any other personal identifiers will appear in any publication or report.

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

6.1 Statistical evaluation – general aspects

A comprehensive statistical analysis plan (SAP) will be prepared before unblinding of the data, and before database lock.

Experience in previous studies indicates that within-patient fluctuations in LDL-C exhibit autocorrelations lasting a period of several weeks. Thus, overall precision will be increased by using an average of 2 measurements taken at least 2 weeks apart. Since the onset of lipid-lowering treatments is largely complete by 4 weeks, an average of measurements made at 4 and 6 weeks will provide an accurate estimate of the treatment effect throughout this period. In this study, all baseline and on-treatment effects are assessed as the mean of 2

consecutive measurements made 2 weeks apart. For reporting purposes, the average of weeks 4 and 6 is termed the effect after 6 weeks of treatment.

Two-sided tests of statistical significance will be used throughout.

6.2 Description of outcome variables in relation to objectives and hypotheses

Primary outcome variable:

- Percentage LDL-C change from baseline to 6 weeks (mean of weeks 4 and 6) of combination therapy

- Statistical significance of the following 3 comparisons will be tested simultaneously by a Hochberg procedure to control for multiple comparisons:

    1. Rosuvastatin 20 mg + ezetimibe 10mg vs simvastatin 40 mg+ 10 mg ezetimibe

    2. Rosuvastatin 10 mg + ezetimibe 10mg vs simvastatin 40 mg+ 10 mg ezetimibe

    3. Rosuvastatin 20 mg + ezetimibe 10mg vs simvastatin 80 mg+ 10 mg ezetimibe

Secondary outcome variables:

The secondary outcome variables include:

- LDL-C, HDL-C, TC, TG, nonHDL-C, ApoB, ApoA-I, TC/HDL-C, LDL-C/HDL-C, nonHDL-C/HDL-C and ApoB/ApoA-I, hs-CRP; and the corresponding measures of effects are the respective changes from baseline

- Therapeutic lipid goals as described in American and European guidelines, with the corresponding measures of effect being the proportions of patients achieving goal

Exploratory

- Change in biomarkers (sitosterol, lanosterol, C4 and LpPLA2). An additional sample will also be drawn for possible other biomarkers and lipid fractions that are related to atherosclerosis

Safety

- AEs
- Vital signs (blood pressure and pulse rate)
- Clinical chemistry
- Haematology
- Urinalysis

6.3 Description of analysis sets

Efficacy analyses will be performed on intent-to-treat (ITT) last observation carried forward (LOCF), completers only and observed data. Per-protocol (PP) data will be available for subsequent analysis if required, though this is not anticipated.

The ITT population will consist of patients who have baseline and at least 1 post-baseline measurement.

LOCF will be interpreted as follows:

- If no data are available for a particular variable following commencement of therapy, then for that variable, the patient is not included in the ITT analysis
- If a measurement is not available for either Visit 4 or 5 (after 4 and 6 weeks of monotherapy, respectively), then the LOCF for the monotherapy phase will be determined as the last of the on-monotherapy measurements
- If a measurement is not available for either Visit 6 or Visit 7 (after 4 and 6 weeks of combination therapy, respectively), then the LOCF for combination therapy will be determined as the last of the on-combination therapy measurements
- In the case where there are no measurements available in the combination therapy phase, then the monotherapy LOCF will be carried forwards to impute the combination therapy LOCF

Completers are the patients in the ITT population who have had at least 1 measurement made following combination therapy. An analysis of completers will be done specifically to show combination treatment efficacy in the absence of dilution of effect, due to carryover of LOCF data from the monotherapy phase.

Patients will be evaluated using randomised treatment.

There will be 2 safety populations. The dietary lead-in safety population will consist of all patients who entered the dietary lead-in period. The randomised safety population will consist

of all patients who were randomised and took at least 1 dose of study medication. Patients in this safety population will be analysed by treatments and doses actually received as follows:

Table 6 Safety populations

Period	Treatments
Dietary lead-in	Diet
Randomised (0 to 12 weeks)	Rosuvastatin or simvastatin monotherapy followed by combination therapy of rosuvastatin or simvastatin with ezetimibe

6.3.1 Patient characteristics and withdrawals

The total number of patients in the dietary lead-in safety population will be stated together with a summary of basic demographic data and data for other characteristics, including lipids. Patients withdrawn during the dietary lead-in period will be identified as screening failures and numbers will be stated. Similarly, the total number of patients in the randomised safety population will be stated together with a summary of demographic data and data for other characteristics, including pre-treatment lipids, by treatment group. The numbers of patients withdrawn at each visit and reasons for withdrawal will also be summarised by treatment group.

6.4 Method of statistical analysis

The primary analysis will be made on LDL-C as the LOCF in the ITT population. A supportive analysis will be made on the completer ITT population.

Lipids and lipoproteins (as part of the secondary objectives) are: TC, LDL-C, HDL-C, TG, ApoA-I, ApoB, nonHDL-C, ApoB/ApoA-I, TC/HDL-C, LDL-C/HDL-C, nonHDL-C/HDL-C and hs-CRP. Baseline for calculating percentage change in a lipid or lipoprotein will be the mean of values from Visits 2 and 3 (Weeks -2 and 0). Monotherapy will be assessed as the mean of Visits 4 and 5 (Weeks 4 and 6), and combination therapy will be assessed as the mean of Visits 6 and 7 (Weeks 10 and 12).

The effect of combination therapy will be assessed by analysis of co-variance (ANCOVA) using geometric percentage change, where the response variable is the logarithm of the ratio of the treatment value divided by the corresponding baseline value, and treatment and centre are the explanatory variables. Estimates of treatment effect, and their 95% CI, will be exponentiated to produce estimates of percentage change. For comparison with other studies, point estimates and confidence intervals will also be calculated arithmetically on the percentage change from baseline. However, the p-values for specified comparisons will be calculated for the geometric analysis only.

The estimates of the additional effects on lipids and lipoproteins of adding ezetimibe 10 mg to rosuvastatin 10 mg or 20 mg will be calculated in the same way using the geometric mean of the 2 monotherapy visits as baseline. Corresponding 95% CIs will be computed.

Depending on the distribution of patients across centres, it may be sensible to pool some small centres together by region. This will be discussed and agreed by biostatistical personnel and the clinical team at AstraZeneca before database lock.

The numbers and percentages of patients reaching appropriate goals will be summarised. Since the prescribed goals may change over time, the goals used in the evaluation will represent the current regional guidelines for this patient population at the time when the SAP is finalised (prior to database lock).

Formal analysis will be by logistic regression with terms for baseline LDL-C, centre and treatment in the model. Hypothesis testing in logistic regression models will be performed using likelihood ratio tests.

Analysis of hs-CRP will be performed using the non-parametric Kruskal-Wallis test (Hollander and Wolfe 1973). The median score will be used. In the case of pairwise comparisons, a Wilcoxon test will be used.

Lipid data will be analysed geometrically (log transformed). This transformation is preferred for the following reasons:

- Experience with similar data in the EXPLORER study shows that the change in LDL-C data has a rightward skew that increases in severity with increasing treatment efficacy
- A study of STELLAR data found that the arithmetic mean of percentage change from baseline produced estimates of efficacy that were consistently below the median effect. The geometric mean was much closer to the median
- Information collated from other studies suggests that ezetimibe has a multiplicative effect on LDL-C. This effect is better modelled by a geometric analysis
- A Bootstrap analysis of EXPLORER data showed that use of the geometric analysis provided equivalent power to the percentage change from baseline analysis with approximately 30% fewer subjects

AEs can occur in the dietary lead-in phase and the randomised phase of the study. All AEs will be classified according to the following:

- Treatment emergent. This is further categorised as:

  - Ongoing from the dietary lead-in period and subsequently worsening during the randomised period, and;

  - Starting during the randomised period

All AEs will be categorised by body system and MedDRA preferred term and listed for each patient. In the randomised safety population, treatment emergent events will be reported as frequencies in each treatment group. Frequencies of AEs leading to withdrawal from the randomised period will also be tabulated and reported by treatment group. AEs leading to death, SAEs and drug-related AEs and SAEs will be presented similarly. Tests of statistical significance will not be performed.

Haematology and clinical chemistry data will be listed for each patient and summarised for each treatment group at each visit. Values outside laboratory reference ranges will be highlighted.

Shift tables for haematuria and proteinuria data will show numbers and percentages of patients with categories of urinary protein and blood (none, trace, +, ++, +++ and ++++) at Week 12 against baseline (Week 0) and Visit 5 (Week 6).

6.5 Determination of sample size

The size of the study population is based upon the primary endpoint, the percentage reduction in LDL-C after 4 to 6 weeks of combination therapy, and the following treatment comparisons:

- rosuvastatin 10 mg plus ezetimibe 10 mg vs simvastatin 40 mg plus ezetimibe 10 mg

- rosuvastatin 20 mg plus ezetimibe 10 mg vs simvastatin 40 mg plus ezetimibe 10 mg

- rosuvastatin 20 mg plus ezetimibe 10 mg vs simvastatin 80 mg plus ezetimibe 10 mg

These endpoints will be tested sequentially using the Hochberg procedure.

Power is calculated for simultaneously attaining all 3 endpoints. Since the success of the rosuvastatin 20 mg plus ezetimibe 10 mg vs simvastatin 40 mg plus ezetimibe 10 mg is essentially assured when the other 2 comparisons are met, the power calculation is based on those contrasts. In order for the overall power of the study to be 90%, each of the 2 contrasts must have approximately 95% power.

The rosuvastatin/ezetimibe combinations in this study have not been previously studied in large populations and so the effect size of these treatments is not known with certainty. Based

on the relative potencies observed for rosuvastatin and simvastatin monotherapies, and the approximately uniform supplemental effect of ezetimibe used with various statins, it is reasonable to assume an effect size of approximately 5% for the 2 comparisons between the rosuvastatin and simvastatin combinations, with a standard deviation (SD) of mean percentage reduction of 13%. This SD assumes a variance reduction because of the use of averages of replicates. Under these assumptions, a sample size of 177 ITT patients per arm is required.

Further exploratory calculations, based on logarithmic analysis and incorporation of an apparent increase in variation with increasing lipid-lowering effect, supported this conclusion.

It is anticipated that there will be a screen-failure rate of up to approximately 65% during the dietary lead-in phase and a dropout rate of 10% following randomisation.

Using this information, approximately 2285 patients will enter into the dietary lead-in phase, of whom 800 (approximately 200 per arm) will be randomised to receive study treatment.

6.6 Interim analyses

No interim analyses are planned.

6.7 Data monitoring board

Not applicable.

7. STUDY MANAGEMENT

7.1 Monitoring

Before first patient into the study, a representative of AstraZeneca will visit the investigational study 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 CSP adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement (CSA) between AstraZeneca and the Investigator

During the study, a monitor from AstraZeneca or company representing AstraZeneca will have regular contacts with the study 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 CSP, that data are being accurately recorded in the eCRFs, and that IP accountability checks are being performed

- Perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study). This will require direct access to all original records for each patient (eg, clinic charts)

The monitor or another AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the centre need information and advice.

7.2 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, an Ethics Committee may visit the centre to perform audits or inspections, including source and 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, analysed, and accurately reported according to the CSP, GCP, guidelines of the 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 centre.

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.

Before the first patient is entered into the study, the investigational staff will be trained to use the WBDC system by AstraZeneca personnel or delegates.

7.4 Changes to the protocol

Study procedures will not be changed without the mutual agreement of the coordinating Investigator and AstraZeneca.

If it is necessary for the CSP to be amended, the amendment and/or a new version of the CSP (Amended CSP) must be notified to or approved by each Ethics Committee, and if applicable, also the local regulatory authority, before implementation. Local requirements must be followed.

If an administrative change is required, such a change must be notified to or approved by each Ethics Committee according to local requirements.

If a CSP amendment requires a change to a particular centre's Informed Consent Form, then AstraZeneca and the centre's Ethics Committee must be notified. Approval of the revised Informed Consent Form by AstraZeneca and by the Ethics Committee is required before the revised form is used.

AstraZeneca will distribute amendments and new versions of the CSP to each Principal Investigator(s), who in turn is responsible for the distribution of these documents to his or her Ethics Committee, and to the staff at his or her centre. 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 centre must comply with all the terms, conditions, and obligations of the CSA for this study. In the event of any inconsistency between this CSP and the CSA, the CSP shall prevail.

7.6 Study timetable and end of study

Before a patient's enrolment in the study and any study-related procedures are undertaken the following should be fulfilled:

- Signed CSP and other agreements between AstraZeneca and the Principal Investigator/Study Site.
- Approval of the study by the Ethics Committee
- Approval of the study, if applicable, by the regulatory authority.

The timetable for the study is as follows:

Estimated date of first patient enrolled:

Estimated date of last patient enrolled:

Estimated date of last patient completed:

Estimated recruitment period: 8 months

Discontinuation or suspension of the whole study program

If AstraZeneca decides to withdraw or suspend the study, the Principal Investigator/Sub-Investigator, the head of the institution, and regulatory authorities should be informed of the fact in a written form clarifying the reason. The Principal Investigator/Sub-Investigator will immediately notify the decision to the patients, give appropriate medical treatment, take necessary measures, and record treatment or measures provided on the source documents.

Completion of the study

Upon termination of the study, the Principal Investigator/Sub-Investigator will report in writing the completion of the study as well as the summary of the results to the head of the institution in accordance with the institution's rules. The head of the institution who is informed of the termination by the investigator will notify in writing the fact with the summarised results to the institutional review board (IRB) and AstraZeneca.

The end of the study is defined as the date of database lock, which is the timepoint after which no patient will be exposed to study related activities.

8. ETHICS

8.1 Ethics review

AstraZeneca or representative will provide Ethics Committees and Principal Investigators with safety updates/reports according to local requirements.

The final CSP, including the final version of the Informed Consent Form, must be approved or given a favourable opinion in writing by an Ethics Committee as appropriate. The Investigator must submit written approval to AstraZeneca before he or she can enrol any patient into the study.

The Principal Investigator is responsible for informing the Ethics Committee of any amendment to the CSP in accordance with local requirements. In addition, the Ethics Committee must approve all advertising used to recruit patients for the study. The CSP must be re-approved by the Ethics Committee annually, as local regulations require.

The Principal Investigator is also responsible for providing the Ethics Committee with reports of any serious and unexpected adverse drug reactions (SUADRs) from any other study conducted with the IP. AstraZeneca or representative will provide this information to the Principal Investigator.

Progress reports and notifications of SUADRs will be provided to the Ethics Committee according to local regulations and guidelines.

8.2 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the latest version of the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics.

8.3 Informed consent

The Principal Investigator(s) at each centre will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any

time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient'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 Informed Consent Form. A copy of the signed Informed Consent Form must be given to the patient.

The genetic research is optional and the patient may participate in the main study without participating in the genetic component. To participate in the genetic part of the study, the patient must sign and date both the consent form for the main study (non-genetic components of the study) and the genetic component of the study. Copies of both signed and dated consent forms must be given to the patient and the original filed at the study centre. The Principal Investigator(s) is responsible for ensuring that consent is given freely and that the patients understand that they may freely discontinue the genetic aspect of the study at any time. The same applies for the biomarker component of the study.

If modifications are made according to local requirements, the new version has to be approved by AstraZeneca.

8.4 Patient data protection

The Master Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, patients will authorise the collection, use and disclosure of their study data by the Investigator and by those persons who need that information for the purposes of the study.

The Master Informed Consent Form will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. All data computer processed by AstraZeneca will be identified by randomisation code, study code and initials.

The Master Informed Consent Form will also explain that for data verification purposes, authorised representatives of AstraZeneca, a regulatory authority, an Ethics Committee may require direct access to parts of the hospital or practice records relevant to the study, including patients' medical history.

All data protection and confidentiality principles, described in the main CSP, are applicable to the optional genetic research. Reference to participation in the genetic research should not be recorded into the patient's general medical records. All notes should be kept within the clinical study records. Due to the exploratory nature of the genetic research, there will be no routine communication of results to patients. AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician or any third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient (details of the procedure specific to this study are in Appendix K).

9. PROCEDURES IN CASE OF EMERGENCY, OVERDOSE OR PREGNANCY

9.1 ICON emergency contact procedure

In the case of a medical emergency you should contact the ICON Medical Monitor or Drug Safety Associate. Details are provided in Supplement 1 of the CSP.

9.2 Procedures in case of medical emergency

The Principal Investigator(s) is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and should be reported as such, see Section 4.7.1.1.**

9.3 Procedures in case of overdose

Doses of study treatment in excess of that specified in the CSP are considered to be an overdose. The following procedures should be followed in case of overdose:

- Use of study medication in doses in excess of that specified in the CSP should not be recorded in the eCRFs as an AE of 'Overdose' unless there are associated symptoms or signs
- An overdose with associated SAEs should be recorded as the SAE diagnosis/symptoms on the relevant AE forms in the eCRFs
- An overdose with associated non-serious AEs should be recorded as the AE diagnosis/symptoms on the relevant AE forms in the eCRFs. In addition, the overdose should be reported on the separate AstraZeneca "Clinical Study Overdose Report Form"
- An overdose without associated symptoms should not be recorded as an AE in the eCRFs. The overdose should be reported on the separate AstraZeneca "Clinical Study Overdose Report Form"

9.4 Procedures in case of pregnancy

Although it is unlikely that pregnancy will occur in this study, subjects should be instructed to stop study drug immediately if pregnancy is suspected or confirmed, and to notify the site. All pregnancies should be reported to ICON Medical Affairs (Medical Monitor or Drug Safety Associate) within 1 day of the time the site personnel becomes aware of the pregnancy. Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or

congenital abnormality) must be followed up and documented even if the patient was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. All outcomes of pregnancy must be reported on the Pregnancy Outcomes Report Form.

10. REFERENCES

Baigent et al 2005
Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino E, et al. Cholesterol Treatment Trialists' (CCT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomized trials of statins. Lancet 2005;366:1267-1278.

Ballantyne et al 2003
Ballantyne C, Houri J, Notarbartolo A, Melani L, Lipka LJ, Suresh R, et al. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolaemia: a prospective, randomised, double blind trial. Circulation 2003;107:2409-15.

Ballantyne et al 2007
Ballantyne C, Weiss R, Moccetti T, Vogt A, Eber B, Sosef F, et al. Efficacy and safety of rosuvastatin 40 mg alone or in combination with ezetimibe in patients at high risk of cardiovascular disease (results from the EXPLORER study). Am J Cardiol 2007;1;99(5):673-80.

Crouse et al 2007
Crouse JR, Raichlen JS, Riley WA, Evans GW, Palmer MK, O'Leary DH, et al. Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: The METEOR trial. JAMA 2007;297(12):1344-1353.

Cruz Fernandez et al 2005
Cruz-Fernandez JM, Bedarida GV, Adgey J, Allen C, Johnson Levonas AO, Massaad R. Efficacy and safety of ezetimibe co-administered with ongoing atorvastatin therapy in achieving low density lipoprotein goal in patients with hypercholesterolemia and coronary heart disease. Int J Clin Pract 2005;59:619-27.

Davidson and Toth 2004
Davidson MH, Toth PP. Comparative effects of lipid-lowering therapies. Progress In Cardiovascular Diseases 2004;7(2):73-104.

Davidson et al 2004
Davidson MH, Ballantyne CM, Kerzner B, Melani L, Sager P, Lipka LJ, et al. Efficacy and safety of ezetimibe coadministered with statins: randomised, placebo controlled blinded experience in 2382 patients with primary hypercholesterolemia. Int J Clin Pract 2004;58:746-55.

De Backer et al 2003
De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, et al. European guidelines on cardiovascular disease prevention in clinical practice: Third Joint Task Force of European and other Societies on Cardiovascular Disease Prevention in Clinical Practice. European Heart Journal 2003;24:1601-1610.

Faergeman et al 2006
Faergeman O, Sosef F, Duffield E. Efficay and tolerability of rosuvastatin and atorvastatin when force-titrated in high-risk patients: Results from the ECLIPSE Study. Atheroscler Suppl 2006;7(3):580 Abs Th-P16:394.

Foley et al 2004
Foley KA, Massing MW, Simpson, RJ, Alexander CM, Markson LE. Population implications of changes in lipid management in patients with coronary heart disease. Am J Cardiol 2004;93:193–5.

Grundy et al 2004
Grundy SM, Cleeman JI, Merz CNB, Brewer HB Jr, Clark LT, Hunninghake DB, et al. National Cholesterol Education Program report: Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004;110:227-39.

Hollander and Wolfe 1973
Hollander M and Wolfe D. Nonparametric Statistical Methods 1973;114-132.

ICH guideline E10
ICH harmonised tripartite guideline E10: Choice of control group and related issues in clinical trials. Step 4 version: 20 July 2000.

Jones et al 2003
Jones PH, Davidson MH, Stein EA, Bays HE, McKenney JM, Miller E, et al. for the STELLAR Study Group. Comparison of efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR Trial). Am J Cardiol 2003;92:152-160.

Kosoglou et al 2004
Kosoglou T, Statkevich P, Yang B, Suresh R, Zhu Y, Boutros T, et al. Pharmacodynamic interaction between ezetimibe and rosuvastatin. Curr Med Res Opin 2004;20:1185-95.

Nissen et al 2006
Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: The ASTEROID trial. JAMA 2006;295(13):1556-1565.

Olsson, McTaggart and Raza 2002
Olsson AG, McTaggart F, Raza A. Rosuvastatin: a highly effective new HMG-CoA reductase inhibitor. Cardiovasc Drug Rev 2002;20(4):303-328.

Ose et al 2005
Ose L, Tonstad S, Harris S, Marotti M. Ezetimibe added to rsouvastatin for severely hypercholesterolemic patients: effects on lipid measures and c-reactive protein. Submitted to the 75th European Atherosclerosis Society Congress: Prague, Czech Republic; April 23-26, 2005.

Shepherd et al 2004
Shepherd J, Hunninghake DB, Stein EA, Kastelein JJ, Harris S, Pears J, et al. Safety of rosuvastatin. Am J Cardiol 2004;94:882–888.

Smith et al 2006
Smith SC, Allen J, Blair SN, Bonow RO, Brass LM, Fonarow GC, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung and Blood Institute. Circulation 2006;113:2363–2372.

Stein et al 2005a
Stein EA, Harris S, Schleman M, Sager P. Ezetimibe added to rosuvastatin for severly hypercholesterolemic patients: effects on low-density lipoprotein cholesterol and c-reactive protein. American College of Cardiology Annual Scientific Session: Orlando, Florida; March 6-9, 2005.

Stein et al 2005b
Stein EA, Ose L, Retterstol K, Tonstad S, Schleman M, Harris S, et al. Further reduction of low-density lipoprotein cholesterol and c-reactive protein with the addition of ezetimibe to maximum-dose rosuvastatin in patients with severe hypercholesterolaemia. Submitted to the American Heart Association Scientific Sessions: Dallas, Texas; November 13-16, 2005.

Sudhop et al 2002
Sudhop T, Lutjohann D, Kodal A, Igel M, Tribble DL, Shah S, et al. Inhibition of intestinal cholesterol absorption by ezetimibe in humans. Circulation 2002;106:1943–1948.

Clinical Study Protocol Appendix A

Drug Substance	Rosuvastatin
Study Code	D356FC00003
Appendix Edition Number	1.0
Appendix Date	

Appendix A
Signatures

ASTRAZENECA SIGNATURE(S)

A 12-week Open-label, Randomised, Parallel-group, Multicentre, Phase IIIb Study to Compare the Efficacy and Safety of Rosuvastatin (CRESTOR™) 10 mg and 20 mg in Combination with Ezetimibe 10 mg and Simvastatin 40 mg and 80 mg in Combination with Ezetimibe 10 mg (fixed dose combination) in Patients with Hypercholesterolaemia and Coronary Heart Disease (CHD) or a CHD Risk Equivalent, Atherosclerosis or a 10-year CHD Risk of >20%

I agree to the terms of this study protocol.

AstraZeneca Research and Development site representative

SIGNATURE(S)

A 12-week Open-label, Randomised, Parallel-group, Multicentre, Phase IIIb Study to Compare the Efficacy and Safety of Rosuvastatin (CRESTOR™) 10 mg and 20 mg in Combination with Ezetimibe 10 mg and Simvastatin 40 mg and 80 mg in Combination with Ezetimibe 10 mg (fixed dose combination) in Patients with Hypercholesterolaemia and Coronary Heart Disease (CHD) or a CHD Risk Equivalent, Atherosclerosis or a 10-year CHD Risk of >20%

I agree to the terms of this study protocol.

AstraZeneca Research and Development site representative

SIGNATURE OF INTERNATIONAL CO-ORDINATING INVESTIGATOR

A 12-week Open-label, Randomised, Parallel-group, Multicentre, Phase IIIb Study to Compare the Efficacy and Safety of Rosuvastatin (CRESTOR™) 10 mg and 20 mg in Combination with Ezetimibe 10 mg and Simvastatin 40 mg and 80 mg in Combination with Ezetimibe 10 mg (fixed dose combination) in Patients with Hypercholesterolaemia and Coronary Heart Disease (CHD) or a CHD Risk Equivalent, Atherosclerosis or a 10-year CHD Risk of >20%

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.

Centre No.:

Signature:

Clinical Study Protocol Appendix B	
Drug Substance	Rosuvastatin
Study Code	D356FC00003
Appendix Edition Number	1.0
Appendix Date	

Appendix B
Additional Safety Information

ADDITIONAL SAFETY INFORMATION

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the patient was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the patient's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Out-patient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the patient or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Examples of such events are:

- *Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment*
- *Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine*
- *Intensive treatment in an emergency room or at home for allergic bronchospasm*
- *Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation*
- *Development of drug dependency or drug abuse.*

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- Dechallenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Rechallenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a rechallenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

A "reasonable possibility" could be considered to exist for an AE where one or more of these factors exist.

In contrast, there would not be a "reasonable possibility" of causality if none of the above criteria apply or where there is evidence of exposure and a reasonable time course but any dechallenge (if performed) is negative or ambiguous or there is another more likely cause of the AE.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?

- Is there a known mechanism?

Ambiguous cases should be considered as being a "reasonable possibility" of a causal relationship unless further evidence becomes available to refute this. Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Clinical Study Protocol Appendix C	
Drug Substance	Rosuvastatin
Study Code	D356FC00003
Appendix Edition Number	1.0
Appendix Date	

Appendix C
Guidance on Management of Elevated Transaminases and Suspected Liver Disease

GUIDANCE ON MANAGEMENT OF ELEVATED TRANSAMINASES AND SUSPECTED LIVER DISEASE

- ALT and other liver function tests should be measured at baseline and during the study as directed in the trial plan.

- Appropriate liver function tests should be measured at any other time if liver disease is suspected.

- A suitably-experienced physician should be involved in interpreting the results and deciding appropriate management for the subject. The physician should be alerted to the occurrence of any ALT values >3xULN and significantly out-of-range values for other liver function tests. The following questioning and follow-up investigations should be considered:

    - Clarify the nature, duration and intensity of relevant symptoms

    - Review possible predisposing factors, such as: alcohol intake, viral illness (consider performing serology), concomitant medications including any recreational drug use, travel, blood transfusion, sexual behaviour

    - Physical examination for jaundice and other signs of liver disease

    - Perform additional liver function tests, perhaps including ALT, AST, bilirubin, alkaline phosphatase, GGT, viral serology, prothrombin time

    - Diagnostic imaging, such as ultrasound, CT, or MRI

    - Arrange to review the subject and repeat liver function tests after a suitable interval depending on the clinical picture (perhaps 4-10 days), or earlier if symptoms of liver disease appear or worsen

- The Study Team Physician is available to give advice (see Emergency Contact details).

- Statin-related ALT elevation is considered to be clinically significant if ALT is increased to >3xULN on 2 consecutive occasions. If this occurs without an obvious reversible precipitating factor, or if on clinical grounds, statin-induced liver disease is diagnosed or suspected, it is recommended that statin therapy should be discontinued. In these circumstances, an appropriate adverse event should be recorded, and the Study Team Physician must be informed.

- Study treatment must not be restarted without discussion with the Study Team Physician

Clinical Study Protocol Appendix D	
Drug Substance	Rosuvastatin
Study Code	D356FC00003
Appendix Edition Number	1.0
Appendix Date	

Appendix D
Guidance on Management of Muscle Symptoms and Increased Creatine Kinase (CK)

GUIDANCE ON MANAGEMENT OF MUSCLE SYMPTOMS AND INCREASED CREATINE KINASE (CK)

- Throughout the study, subjects should be instructed to promptly report unexplained muscle pain or weakness, particularly if associated with malaise or fever. If this occurs, creatine kinase (CK) should be measured as soon as possible.

- Also, if CK is found to be elevated >5xULN on routine testing, the subject should be questioned about muscle symptoms.

- A study site physician should be alerted to the occurrence of unexplained muscle symptoms and any CK values >5xULN, and must take immediate action if CK >10xULN.

- A suitably-experienced physician should be involved in deciding appropriate management for the subject, taking account of any local guidelines.

- The following questioning and follow-up investigations should be considered:

    - Clarify the nature, duration and intensity of any muscle symptoms
    - Review possible predisposing factors, such as: unaccustomed exercise (including decorating, gardening etc), heavy alcohol intake, viral illness (consider performing serology), concomitant medications and consider diagnosis of other conditions which can cause myopathy
    - Physical examination for muscle tenderness, weakness and rash
    - Measure CK again within a few days
    - Measure serum creatinine
    - Urinalysis (including myoglobin and sediment)
    - Arrange to review the subject again in 4 to 10 days, or earlier if symptoms of myopathy appear or worsen, or if the urine becomes very dark

- The Study Team Physician is available to give advice (see Emergency Contact details).

- Myopathy is defined as muscle aches or weakness in association with CK increased to >10xULN. If myopathy occurs without an obvious reversible precipitating factor, or if on clinical grounds, statin-induced myopathy is diagnosed or suspected, statin therapy should be discontinued. Myopathy should always be recorded as an adverse event, and the Study Team Physician must be informed.

- Study treatment should not be restarted without discussion with the Study Team Physician.

Clinical Study Protocol Appendix E	
Drug Substance	Rosuvastatin
Study Code	D356FC00003
Appendix Edition Number	1.0
Appendix Date	

Appendix E
Management of Increased Serum Creatinine

MANAGEMENT OF INCREASED SERUM CREATININE

Increases in serum creatinine over time might be due to ageing, progression of atherosclerotic disease, dehydration, renal toxic medications, infection etc.

- Serum creatinine level is to be measured at Visits 1 to 7.
- If the creatinine level increases >30% from the baseline value, the Investigator should evaluate the subject for any potential cause (e.g. dehydration, renal toxic medications, infection etc.).
- The patient may be brought back for an unscheduled visit for a repeat blood sample.
- If the creatinine remains elevated >30% from baseline, and above the limit of normal, study medication may be discontinued (in which case an Adverse Event must be reported).

If at any time the creatinine rise is marked, the Investigator may elect to repeat a serum creatinine laboratory assessment earlier than the next scheduled visit.

Clinical Study Protocol Appendix F

Drug Substance	Rosuvastatin
Study Code	D356FC00003
Appendix Edition Number	1.0
Appendix Date	

Appendix F
Management of Increased Urine Protein on Dipstick

GUIDANCE ON THE MANAGEMENT OF INCREASED URINE PROTEIN FOLLOWING DIPSTICK TEST

- A urinalysis will be performed at Visits 3 to 7.
- If the urine dipstick protein is increased from the baseline value, the Investigator should evaluate the patient for any potential cause.
- At Visits 4 to 7, for all patients with a urine dipstick protein of ++ or greater, where this represents a ≥ 1 grade shift (eg, from + to ++ or trace to ++), the central laboratory will automatically perform quantitative assessment of total protein, albumin and creatine.

If the urine protein/creatinine ratio is >0.5 mg protein per mg creatinine (US) or >56 mg protein per μmol creatinine (Rest of World), the Investigator may stop study medication following consultation with the relevant AstraZeneca personnel, eg, the Clinical Study Team Physician.

AstraZeneca

Clinical Study Protocol Appendix G	
Drug Substance	Rosuvastatin
Study Code	D356FC00003
Appendix Edition Number	1.0
Appendix Date	

Appendix G
Established Atherosclerotic Disease

ESTABLISHED ATHEROSCLEROTIC DISEASE

1. Patients with a history of transient ischemic attacks (TIA) or ischemic stroke, carotid artery disease as evidenced by a history of carotid endarterectomy, angioplasty, or other cerebral revascularisation. Patients with advanced (at least 60%) atherosclerosis in the common or internal carotid artery documented (by angiography or ultrasound) will also be eligible.

2. Patients with coronary artery disease, defined by a history of myocardial infarction or hospitalisation for treatment of unstable angina, angina pectoris corroborated by objective evidence of myocardial ischemia, coronary revascularisation or angiographic evidence of stenosis >50% in one or more major epicardial coronary artery.

3. Patients with peripheral arterial disease defined by a history of aortic aneurysm repair, aorto-iliac, femoral or other arterial surgery or angioplasty performed to relieve lower limb ischemia, lower limb amputation performed due to complications of atherosclerotic arterial disease, or intermittent claudication with an ankle-brachial pressure index (ABI) <0.9.

AstraZeneca

Clinical Study Protocol Appendix H	
Drug Substance	Rosuvastatin
Study Code	D356FC00003
Appendix Edition Number	1.0
Appendix Date	

Appendix H
Classification of Congestive Heart Failure

CLASSIFICATION OF CONGESTIVE HEART FAILURE

New York Heart Association classification of Congestive Heart Failure

Functional Class (I-IV):	
Class I	Patients with cardiac disease but without resulting limitations of ordinary physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, dyspnoea or anginal pain.
Class II	Patients with cardiac disease resulting in slight or moderate limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnoea or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitations, dyspnoea or anginal pain. Less than ordinary physical activity is defined as climbing one flight of stairs or walking two hundred yards. IIIa: No dyspnoea at rest IIIb: Recent dyspnoea at rest
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort, symptoms or cardiac insufficiency, or of the anginal syndrome.

AstraZeneca

Clinical Study Protocol Appendix I	
Drug Substance	Rosuvastatin
Study Code	D356FC00003
Appendix Edition Number	1.0
Appendix Date	

Appendix I
Therapeutic Lifestyle Change (TLC) Diet

NIH NATIONAL CHOLESTEROL EDUCATION PROGRAM

Therapeutic Lifestyle Change Diet

Recommended intake (NCEP/ATP III)

• Saturated fat *	Less than 7% of total calories
• Polyunsaturated fatty acids	Up to 10% of total calories
• Monounsaturated fatty acids	Up to 20% of total calories
• Total fat	25-35% of total calories
• Carbohydrate **	50-60% of total calories
• Fiber	20-30 g/day
• Protein	Approximately 15% of total calories
• Cholesterol	Less than 200 mg/day
• Total calories (energy) ***	Balance energy intake and expenditure to maintain desirable body weight/prevent weight gain

* Trans fatty acids are another LDL-raising fat that should be kept at a low intake.

** Carbohydrate should be derived predominantly from food rich in complex carbohydrates including grains, especially whole grains, fruits, and vegetables.

*** Daily energy expenditure should include at least moderate physical activity (contributing approximately 200 Kcal per day).

Clinical Study Protocol Appendix J

Drug Substance	Rosuvastatin
Study Code	D356FC00003
Appendix Edition Number	1.0
Appendix Date	

Appendix J
Framingham Risk Index

FRAMINGHAM RISK INDEX

Complete the FRI calculation **only** for subjects with two or more CHD risk factors.

(FRI) Calculation

(Taken from NIH Publication No. 01-3305 May 2001)

1. **Find points for each risk factor (Tables 1-5)**
2. **Calculate point total as the sum of points for each risk factor**
3. **Estimate 1-year risk from point total (Table 6)**

Table 1 Age

Estimate of 10-year risk for MEN		Estimate of 10-year risk for WOMEN	
AGE	**AGE POINTS**	**AGE**	**AGE POINTS**
20-34	-9	20-34	-7
35-39	-4	35-39	-3
40-44	0	40-44	0
45-49	3	45-49	3
50-54	6	50-54	6
55-59	8	55-59	8
60-64	10	60-64	10
65-69	11	65-69	12
70-74	12	70-74	14
75-79	13	75-79	16

Table 2 Total Cholesterol

MEN	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79	WOMEN	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160 mg/dL (4.10 mmol/L)	0	0	0	0	0	**<160 mg/dL (4.10 mmol/L)**	0	0	0	0	0
160-199 mg/dL (4.10-5.15 mmol/L)	4	3	2	1	0	**160-199 mg/dL (4.10-5.15 mmol/L)**	4	3	2	1	1
200-239 mg/dL (5.16-6.19 mmol/L)	7	5	3	1	0	**200-239 mg/dL (5.16-6.19 mmol/L)**	8	6	4	2	1
240-279 mg/dL (6.2-7.22 mmol/L)	9	6	4	2	1	**240-279 mg/dL (6.2-7.22 mmol/L)**	11	8	5	3	2
>280 mg/dL (7.23 mmol/L)	11	8	5	3	1	**>280 mg/dL (7.23 mmol/L)**	13	10	7	4	2

Table 3 Smoking Status

MEN	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79	WOMEN	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Non-smoker	0	0	0	0	0	**Non-smoker**	0	0	0	0	0
Smoker	8	5	3	1	1	**Smoker**	9	7	4	2	1

Table 4 HDL-Cholesterol

MEN HDL (mg/dL)	Points	WOMEN HDL (mg/dL)	Points
≥ 60 mg/dL (1.55 mmol/L)	-1	**≥ 60 mg/dL (1.55 mmol/L)**	-1
50-59 mg/dL (1.29-1.54 mmol/L)	0	**50-59 mg/dL (1.29-1.54 mmol/L)**	0
40-49 mg/dL (1.03-1.28 mmol/L)	1	**40-49 mg/dL (1.03-1.28 mmol/L)**	1
<40 mg/dL (1.03 mmol/L)	2	**<40 mg/dL (1.03 mmol/L)**	2

Table 5 Systolic Blood Pressure (BP)

MEN			WOMEN		
Systolic BP (mmHg)	**If Untreated**	**If Treated**	**Systolic BP (mmHg)**	**If Untreated**	**If Treated**
<120	0	0	**<120**	0	0
120-129	0	1	**120-129**	1	3
130-139	1	2	**130-139**	2	4
140-159	1	2	**140-159**	3	5
≥ 160	2	3	**≥ 160**	4	6

Table 6 Point Total

MEN Point Total	10-year Risk %	WOMEN Point Total	10-year Risk %
<0	<1	<9	<1
0	1	9	1
1	1	10	1
2	1	11	1
3	1	12	1
4	1	13	2
5	2	14	2
6	2	15	3
7	3	16	4
8	4	17	5
9	5	18	6
10	6	19	8
11	8	20	11
12	10	21	14
13	12	22	17
14	16	23	22
15	20	24	27
16	25	≥ 25	≥ 30
≥ 17	≥ 30		

Clinical Study Protocol Appendix K	
Drug Substance	Rosuvastatin
Study Code	D356FC00003
Appendix Edition Number	1.0
Appendix Date	

Appendix K
Optional Genetic Research

GENETICS RESEARCH SYNOPSIS

A 12-week Open-label, Randomised, Parallel-group, Multicentre, Phase IIIb Study to Compare the Efficacy and Safety of Rosuvastatin (CRESTOR™) 10 mg and 20 mg in Combination with Ezetimibe 10 mg and Simvastatin 40 mg and 80 mg in Combination with Ezetimibe 10 mg (fixed dose combination) in Patients with Hypercholesterolaemia and Coronary Heart Disease (CHD) or a CHD Risk Equivalent, Atherosclerosis or a 10-year CHD Risk of >20%

The genetic research activities described in this appendix (including the collection and storage of genetic samples), are optional for study sites as well as for individual patients. These research activities will hereafter be referred to as "this genetic research." The clinical study protocol (CSP) to which this document is appended will be referred to as "the main study." The term "genetic sample" means a blood sample collected for genetic research and/or DNA prepared from it.

This genetic research will be performed only after the appropriate Ethics Committee has approved it. Informed consent will be obtained using a form separate from that used for the main study. All sections of the protocol for the main study also apply to this genetic research.

Study centre(s) and number of patients who may be enrolled in this genetic research

Approximately 800 randomised patients from centres in the US, Latin America and Europe will be eligible to participate in the genetics research. Genetic sampling will only take place in countries/sites where it will not cause a delay in approval and start of the study.

Objectives

To obtain, with appropriate informed consent, DNA samples for future exploratory research on the effects of genetic polymorphisms on:

- Response to rosuvastatin and ezetimibe combination therapy
- Susceptibility to and prognosis of coronary heart disease (CHD) and lipid disorders

'Response' in this context encompasses efficacy, safety and tolerability. 'Efficacy' refers to the impact of statin treatment on lipid levels and laboratory parameters for which data are being collected in the main study.

Study design

For exploratory genetic research, one of two approaches will generally be employed to study genetic polymorphisms of interest:

Comparison of marker (allele, genotypic or haplotype) frequencies in cases and controls;

and/or

Comparison of clinical outcomes or other endpoints relevant to drug response (eg, low-density lipoprotein cholesterol (LDL-C) lowering) in genetically defined groups.

DNA samples will be stored for 20 years after the main study has completed.

Genetic samples and genotypic data will be coded as described in Section 4.2.2: Storage and coding of DNA samples.

Target population

This comprises of patients who provide separate, optional consent for this genetic research at Visit 1 and are subsequently randomised to treatment with study drug in the main study.

Co-variables

These cannot be specified in advance because they will depend on the particular phenotype (ie, disease susceptibility or drug response parameter) under investigation. However, in all cases they will be derived exclusively from information collected in the parent protocol. Thus, no additional clinical information will be collected for this genetic research.

Statistical methods

The number of patients who will agree to participate in this genetic research is unknown. It is therefore not possible to establish whether sufficient data will be generated. A statistical analysis plan will be prepared where appropriate.

TABLE OF CONTENTS PAGE

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
ADME	Absorption, Distribution, Metabolism and Excretion
°C	Degrees Celsius
eCRF	electronic Case Report Form
CGG	Clinical Genotyping Group
CHD	Coronary Heart Disease
CSA	Clinical Study Agreement
CSP	Clinical Study Protocol
CSR	Clinical Study Report
EDTA	Ethylenediamine Tetra-acetic Acid
LDL-C	Low-Density Lipoprotein Cholesterol
LIMS	Laboratory Information Management System
PK	Pharmacokinetics
RoW	Rest of World
UK	United Kingdom
US	United States (of America)

1. BACKGROUND

AstraZeneca plan to include investigations into genetic variations and their effect on drug response as part of the drug development program for all projects where it is considered to be appropriate. By using this information, the aim is to better understand the impact of genetic variation and how it can be utilised to bring better drugs to the market.

To achieve this goal a systematic collection of DNA for genetic analysis (derived from blood samples taken from consenting study patients) will be implemented across a broad range of relevant clinical studies. The ability to acquire appropriate consent to collect blood samples to establish an archive and allow future meta-analysis of data derived from a number of studies for rosuvastatin is of the utmost importance. This genetic research forms part of this strategy.

Genetic variability in lipid levels in the general population has been estimated to account for 40% to 60% of the total variability. Multiple studies have described significant interactions between common DNA sequence variations in candidate genes for lipid and drug metabolism that modulate lipid levels and therapeutic response to lipid-lowering therapy (Ordovas 2004). This has also recently been shown for the molecular target of ezetimibe ie, NPC1L1. Genetic variants in the NPC1L1 gene, have been associated with reduced sterol absorption (campesterol/lathosterol ratio), plasma LDL-C levels and with variation in response to ezetimibe treatment (Cohen et al 2006, Simon et al 2005).

1.1 Rationale for genetic research

AstraZeneca intends to perform genetic research in the rosuvastatin clinical development programme to explore how genetic variations may affect the clinical parameters associated with rosuvastatin.

The purpose of this genetic research is the explorative analysis of common genetic variants in NPC1L1, other cholesterol homeostasis related genes, and absorption, distribution, metabolism and excretion (ADME) related genes, to archive DNA samples for potential explorative analysis on how genetic variations may affect clinical parameters associated with lipid lowering therapies. By using this information, the aim is to better understand the impact of genetic variation and how it can be utilised to bring better drugs that meet the clinical needs to the patients.

An archive of appropriately consented samples from these trials is essential for realising the potential of genetic research to improve the health of persons with lipid disorders, metabolic disorders, cardiovascular diseases and other conditions for which statin treatment may prove beneficial.

2. GENETIC RESEARCH OBJECTIVES

To obtain, with appropriate informed consent, DNA samples for future exploratory research on the effects of genetic polymorphisms on:

- Response to rosuvastatin and ezetimibe combination therapy
- Susceptibility to and prognosis of coronary heart disease and lipid disorders

'Response' in this context encompasses efficacy, safety and tolerability. 'Efficacy' refers to the impact of statin treatment on lipid levels as well as clinical outcomes.

Genes that may be investigated include:

- Genes coding for proteins relevant to drug distribution, such as drug transport proteins, which may mediate the influx or efflux of statins or lipids in, eg, hepatocytes, renal tubular cells, intestinal epithelium, muscle or other cells. Variations in genes encoding such transporters could plausibly influence statin pharmacokinetics (PK) or response
- Genes coding for cholesterol uptake, ie, NPC1L1, ABCG5/8 and/or related genes in the cholesterol uptake pathway
- Genes coding for drug metabolising enzymes. Variations in these genes may contribute to PK variability
- Genes coding for the enzyme inhibited by statins, HMG-CoA reductase and/or related genes in the cholesterol biosynthesis pathway
- Genes with potential relevance to the progression and prognosis of diseases under investigation in rosuvastatin and ezetimibe combination therapy clinical trials

In addition to the above named genes which we believe may influence therapeutic response to rosuvastatin and combination therapy with ezetimibe, it is likely that additional information on other genes important for this drug and for the outcome of lipid disorders, cardiovascular disease and other conditions for which the statin therapy may prove beneficial for which the drug is being developed will become available in the future. It is, therefore important to retain the possibility of investigating additional genes in the context of rosuvastatin and ezetimibe combination therapy in the clinical study.

3. GENETIC RESEARCH PLAN AND PROCEDURES

3.1 Genetic research plan

This appendix to the Clinical Study Protocol (CSP) has been subjected to peer review according to AstraZeneca standard procedures.

The patient will be asked to participate in this genetic research at Visit 1. If the patient agrees to participate, a single blood sample will be taken for genetic research at Visit 3 or at any visit until the patient leaves the study.

3.2 Selection of genetic research population

3.2.1 Study selection record

All patients who take part in the main study will be asked to participate in this genetic research (but only if it has been approved by the relevant Independent Ethics Committee or Institutional Review Board). Participation is voluntary and if a patient declines to participate there will be no penalty or loss of benefit. The patient will not be excluded from any aspect of the main study.

3.2.2 Inclusion criteria

For inclusion in this genetic research, patients must fulfil all of the inclusion criteria described in the main body of the study protocol **and**:

- Provide informed consent for the genetic sampling and analyses.

If a patient declines to participate in the genetic research, there will be no penalty or loss of benefit to the patient. The patient will not be excluded from other aspects of the study described in this CSP, so long as they consent.

3.2.3 Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or the following:

- Previous bone marrow transplant

3.2.4 Discontinuation of patients from this genetic research

3.2.4.1 Criteria for discontinuation

Specific reasons for discontinuing a patient from this genetic research are:

- Withdrawal of consent for genetic research. Patients may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment.

3.2.4.2 Procedures for discontinuation

Patients who discontinue from the main study should always be asked specifically whether they are withdrawing or continuing their consent for this genetic research. It must be established whether the patient:

- Agrees to the genetic sample and any DNA extracted from the sample being kept for genetic research in the future

- Withdraws consent for the sample to be kept for genetic research in the future and wishes the sample to be destroyed. Destruction of the sample (or the DNA extracted from the sample) will only be possible so long as the particular sample is traceable. In the event that genetic research has already been performed, AstraZeneca will retain the results and associated data for regulatory reasons but these will not be used in any subsequent analyses.

The Principal Investigator is responsible for providing written notification to AstraZeneca of any patient who has withdrawn consent for the use of the sample taken for genetic research. AstraZeneca will provide written confirmation to the Investigator of the actions taken with the sample, which must be filed in the Investigator study file.

4. GENETIC MEASUREMENTS AND CO-VARIABLES

4.1 Summary of genetics objectives and analysis

The purpose of this genetic research is to generate data for use in future retrospective analyses. Future analyses will explore genetic factors, which may influence the disposition, efficacy, safety and tolerability to rosuvastatin and combination therapy with ezetimibe and/or susceptibility to or prognosis of CHD under investigation in this study. The results of this genetic research will not form part of the clinical study report (CSR) for this study. The results may be pooled with genetic data from other studies on rosuvastatin and combination therapy with ezetimibe to generate hypotheses to be tested in future studies.

4.2 Collection of samples for genetic research

Patients will provide a blood sample as per the inclusion criteria and visit schedule.

A single venous blood sample (9 or 10 mL) will be collected into a polypropylene tube containing ethylenediamine tetra-acetic acid (EDTA) and gently inverted a minimum of 5 times to mix thoroughly. Tubes will be labelled with the protocol study number, centre number, enrolment code and/or randomisation number and date of sample collection. No personal identifiers (patient name, initials or DOB) will be placed on the tube or accompanying documentation. A record of the date of the patient consent to the genetic research and the date of the blood sample collection will be recorded in the appropriate section of the eCRF.

Genotype is a stable parameter, therefore if for any reason the blood sample is not drawn at Visit 3, it may be taken at any visit until the last study visit. The genetic blood sample should ideally be drawn through the same cannula used to draw blood samples required for the main study.

4.2.1 Sample processing and shipping

Samples will be frozen (-20°C or below) and transported to the relevant DNA extraction laboratory within one month of collection and must remain frozen at all times.

Where possible samples should be shipped in batches and shipment should be coordinated with the receiving site to ensure that samples arrive within working hours. A requisition sheet, detailing the protocol study number, centre number, enrolment code and/or randomisation code and date of sample collection, should accompany the shipment.

4.2.2 Storage and coding of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality.

For all samples irrespective of the type of coding used the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number will used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any AstraZeneca employee working with the DNA.

The samples and data for genetic analysis in this study will be de-identified. This will require each blood sample being double coded and labelled with a second unique identifier. The sample and data will not be labelled with a personal identifier. The study number and patient number will be linked to this second unique identifier. The Investigator will not be able to link the blood sample to the patient. The link between the clinical study/patient number and the unique second number is maintained, but unknown to the Investigator. A link between the blood sample and the DNA extracted from the sample will be maintained in a confidential link file.

The link file will be stored in a secure environment outside of the Clinical Genotyping Group (CGG) Laboratory Information Management System (LIMS) database at AstraZeneca, UK. The link file will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent.

All DNA samples will be stored under secure conditions with restricted access at AstraZeneca. The blood, DNA samples or data derived from the samples may be made available to groups or organisations working with AstraZeneca on this study or as part of the development drug project. However, the samples and any results will remain the property of AstraZeneca at all times. AstraZeneca will not give blood, DNA samples or data derived from the samples to any other parties, except as required by law.

4.3 Genotyping

The generation of genotypic data will generally involve analysis of known polymorphic sites using one of a variety of well-established methods. Specifically, an initial step consisting of amplification of the target region containing the polymorphism of interest by means of the polymerise chain reaction will be followed by an allele detection/discrimination procedure. Genotyping may in some cases be accomplished by DNA sequencing of regions of interest within or near candidate regions. Cells from blood samples collected under this protocol will **not** be propagated or immortalised.

5. MANAGEMENT OF GENETIC RESEARCH DATA

In the case of genotypic data, only the date the patient gave consent to participation in the genetic research and the date the blood sample was taken from the patient will be recorded in the eCRF and database.

The genotypic data generated from the study will be stored in the AstraZeneca LIMS database or other appropriate system. This database is a secure database, which is separate from the database used for the main study. Some or all of the dataset from the main study may be duplicated within the AstraZeneca LIMS database for exploratory genetic analysis.

5.1 Reporting of genotypic results

Results from any genetic research performed will be reported separately from the CSR. AstraZeneca will not provide individual genotype results to patients, their family members, any insurance company, an employer, clinical study Investigator, general physician or any other third party, unless required to do so by law. The patient's DNA will not be used for any purpose other than those described in the study protocol.

Individual patients will not be identified in any report or publication resulting from this work. The data and results of this study may be reviewed with collaborators and published, but neither the patient's name nor any other personal identifiers will appear in any publication or report.

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The number of patients who will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether a statistically relevant number of patients will consent to provide sufficient data to be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate.

7. STUDY MANAGEMENT

7.1 Monitoring

Before first patient entry into the study, a representative of AstraZeneca will visit the investigational study site. In addition to the requirements described in the main study, this genetic research will be discussed.

During the study, a representative of AstraZeneca will have regular contacts with the investigational site. One of the purposes of these visits will be to perform source verification of the genetic consent of participating patients and to ensure that the investigational team are adhering to the specific requirements of this genetic research.

7.2 Training of staff

Before the first patient is entered into the study the investigational staff will have an opportunity to discuss the procedures associated with the collection of blood samples, extraction of DNA and genetic research with a representative of AstraZeneca. The ethical considerations specific to genotyping and the importance of the informed consent process will be made clear. The requirements for the collections of the patients' sample will also be made clear.

7.3 Changes to the protocol

Any changes to the genetic research will comply with the principles described in Section 7.4 of the main body of the protocol.

7.4 Study agreements

The Principal Investigator at each centre must comply with all the terms, conditions, and obligations of the Clinical Study Agreement (CSA) for this study. In the event of any inconsistency between this CSP and the CSA, the CSP shall prevail. Specific reference to requirements relating to this genetic research will be included in the study agreement(s).

8. ETHICS

8.1 Ethics review

In addition to documenting Ethics Committee approval of the main study, approval must be obtained for this genetic research and the associated genetic informed consent from the relevant Ethics Committee. It must be clearly stated in the approval that this genetic research is approved. The Investigator must submit written approval to AstraZeneca before any subject participates in this genetic research.

8.2 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics.

For studies including genetic analysis special precautions are taken as described in section 4.2.2 of this Appendix.

8.3 Informed consent

The genetic component of this study is optional and the patient may participate in other components of the study without participating in the genetic component. To participate in the genetic component of the study the patient must sign and date both the consent form for the main study (non-genetic components of the study) and the genetic component of the study. Copies of both signed and dated consent forms must be given to the patient and the original filed at the study centre. The Principal Investigator(s) is responsible for ensuring that consent is given freely and that the patient understands that they may freely discontinue from the genetic aspect of the study at any time.

8.4 Patient data protection

All data protection and confidentiality principles, described in the main study protocol, are applicable to this genetic research.

Due to the exploratory nature of this genetic research, there will be no routine communication of results to patients. AstraZeneca will not provide individual genotype results to patients, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient, however, it must be recognised that there are exceptional circumstances where individuals may see both genetic data and a patient's personal identifier, for example in the case of a medical emergency, when AstraZeneca Physicians and investigators might know the patients' identity and might have access to the genetic data, or during regulatory audit where designated authorities must be permitted access to the relevant files.

9. REFERENCES

Cohen et al 2006
Cohen JC, Pertsemlidis A, Fahmi S, Esmail S, Vega GL, Grundy SM, et al. Multiple rare variants in NPC1L1 associated with reduced sterol absorption and plasma low-density lipoprotein levels. PNAS 2006;103:1810-1815.

Ordovas 2004
Ordovas JM. Pharmacogenetics of lipid diseases. Hum Genomics 2004;1(2):111-25.

Simon et al 2005
Simon JS, Karnoub MC, Devlin DJ, Arreaza MG, Qiu P, Monks SA, et al. Sequence variation in NPC1L1 and association with improved LDL-cholesterol lowering in response to ezetimibe treatment. Genomics 2005;86(6):648-56.