AstraZeneca

Amended Clinical Study Protocol

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A Randomised, Double-Blind, 52-week, Parallel-Group, Multicentre, Phase IIb Study to Evaluate the Effects of Rosuvastatin 10 mg, Rosuvastatin 40 mg and Atorvastatin 80 mg on Urinary Protein Excretion in Hypercholesterolaemic Non-Diabetic Patients with Moderate Proteinuria

PLANET II: Prospective evaLuation of ProteinuriA and reNal function in non-diabETic patients with progressive renal disease

Sponsor:

AstraZeneca AB, 151 85 Södertälje, Sweden.

AstraZeneca Research and Development Site representative

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
1			
2			
3			

Administrative change No.	Date of Administrative Change	Local Administrative change No.	Date of local Administrative Change
2			
3			

PROTOCOL SYNOPSIS

A Randomised, Double-Blind, 52-week, Parallel-Group, Multicentre, Phase IIb Study to Evaluate the Effects of Rosuvastatin 10 mg, Rosuvastatin 40 mg and Atorvastatin 80 mg on Urinary Protein Excretion in Hypercholesterolaemic Non-Diabetic Patients with Moderate Proteinuria

PLANET II: Prospective evaLuation of ProteinuriA and reNal function in non-diabETic patients with progressive renal disease

International Co-ordinating Investigator

Study centres and number of patients planned

The study will be conducted as originally intended for approximately 345 randomised patients; however, difficulties with recruitment have led to a reduction in the total number of patients expected to be randomised from 345 to 225. These patients will be recruited from approximately 160 centres worldwide from the following countries: United States, Bulgaria , Romania, Germany, Hungary, Italy, Canada, Denmark, Brazil and South Africa. 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 when enough patients are screened to provide the globally projected number randomised.

Study period	**Phase of development**
Estimated date of first patient enrolled	IIb
Estimated date of last patient completed (defined as date of the last visit of the last patient)	

Objectives

Primary Objective

The primary objective of this study is to evaluate the effects of rosuvastatin and atorvastatin on urinary protein excretion by evaluation of the change in urinary protein/creatinine ratio

from baseline to Week 52 in non-diabetic patients with moderate proteinuria and hypercholesterolaemia.

Secondary Objectives

The secondary efficacy objectives of the study are as follows:

1. to evaluate the effects of rosuvastatin and atorvastatin on urinary protein excretion by evaluation of the change in urinary protein/creatinine ratio from baseline to Week 26.

2. to evaluate the effects of rosuvastatin and atorvastatin on urinary albumin excretion by evaluation of the change in urinary albumin/creatinine ratio from baseline to Weeks 26 and 52.

3. to evaluate the effects of rosuvastatin and atorvastatin on: low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), nonHDL-C, apolipoprotein A1 (ApoA-1), apolipoprotein B (ApoB), TC/HDL-C, LDL-C/HDL-C, nonHDL-C/HDL-C and ApoB/ApoA-1) to explore the relationship between renal effects and lipid changes at Weeks 26 and 52

4. to evaluate the effects of rosuvastatin and atorvastatin on renal function by evaluation of the change in estimated glomerular filtration rate (GFR) predicted from the Modification of Diet in Renal Disease (MDRD) [Levey et al 1999]equation from baseline to Weeks 26 and 52.

The secondary safety objective of this study is:

1. to evaluate the effect of rosuvastatin and atorvastatin on the incidence and severity of adverse events and laboratory data.

Please also refer to Appendix G for the optional genetics objectives and all other genetics related study information.

Study design

This is a randomised, double-blind, parallel-group, multinational, multicentre, Phase IIb study evaluating the effects of rosuvastatin 10 mg, rosuvastatin 40 mg and atorvastatin 80 mg over 52 weeks on urinary protein excretion in hypercholesterolaemic, non-diabetic patients with moderate proteinuria.

Patients will enter a 8-week lead-in period, after which eligible patients will be randomised to receive treatment with either rosuvastatin or atorvastatin, once daily for 52 weeks. After Week 14 (Visit 7), supplemental non-statin, lipid-lowering therapy will be permitted at investigator discretion. However, certain restricted medications that affect both lipids and proteinuria must have been initiated prior to Visit 1 and may not be adjusted during the study (See 3.3.4, Restrictions).

An independent Safety Committee will be employed to review safety data at regular intervals throughout the study.

Target patient population

Male and female, non-diabetic patients aged ≥18 with moderate proteinuria (baseline urinary protein/creatinine ratio ≥500 mg/g and ≤5000 mg/g), hypercholesterolaemia (fasting LDL-C ≥90 mg/dL (2.33 mmol/L) and receiving current treatment with ACE (Angiotensin converting enzyme) inhibitors and/or ARBs (Angiotensin receptor blockers) for ≥3 months prior to Visit 1.

Investigational product, dosage and mode of administration

Initial 4 week treatment period

Rosuvastatin 1 x 10 mg once daily in oral encapsulated form

Rosuvastatin 1 x 20 mg once daily in oral encapsulated form (capsule contains 2 x 10 mg rosuvastatin)

Atorvastatin 1 x 40 mg once daily in oral encapsulated tablet form

Remaining treatment period

Rosuvastatin 2 x 5 mg once daily in oral encapsulated form

Rosuvastatin 2 x 20 mg once daily in oral encapsulated form (each capsule contains 2 x 10 mg rosuvastatin)

Atorvastatin 2 x 40 mg once daily in oral encapsulated tablet form

Duration of treatment

Patients will initially enter an 8-week lead-in period during which they will undergo optimisation of existing anti-hypertensive treatments and withdrawal of statin treatment if applicable. Patients will also receive dietary advice, the principles of which are summarised in Appendix F. For the first 4 weeks of the lead-in period, patients may receive a bile acid sequestrant (e.g. cholestyramine) at the discretion of the investigator. For the second 4 weeks of the lead-in period, no lipid lowering therapy will be permitted, except for fibric acid derivatives or nicotinic acid initiated prior to study entry. No other lipid lowering therapy will be permitted to allow for an accurate baseline lipid profile.

At the end of the 8-week lead-in period, eligible patients will be randomised with a 1:1:1 randomisation ratio to receive blinded treatment with either rosuvastatin 10 mg, rosuvastatin 40 mg or atorvastatin 80 mg. For the first 4 weeks of the active treatment period, patients randomised to rosuvastatin 40 mg or atorvastatin 80 mg will receive a half-dose of study drug for 4-weeks to assess tolerability. If there are no safety concerns warranting the withdrawal of study medication after 4 weeks, then the treatment dose will be doubled to the full-randomised dose for 48 weeks. If this half-dose is not well tolerated giving rise to safety concerns

(see section 3.1), patients will be discontinued. Patients randomised to receive rosuvastatin 10 mg will receive this dose for 52 weeks.

During the first 4 weeks of the randomised treatment period, patients will each take 1 encapsulated tablet per day consisting of either rosuvastatin 10 mg, rosuvastatin 20 mg or atorvastatin 40 mg. During the remaining 48 weeks of the trial, patients will each take 2 encapsulated tablets per day. Each day, medication will consist of 2 x rosuvastatin 5 mg encapsulated tablets, 2 x rosuvastatin 20 mg encapsulated tablets or 2 x atorvastatin 40 mg encapsulated tablets.

Outcome variables

- **Efficacy**
  - **Primary outcome variable:**
    - Change in urinary protein/creatinine ratio from baseline to 52 weeks.
  - **Secondary outcome variables:**
    - Change in urinary protein/creatinine ratio from baseline to 26 weeks
    - Change in urinary albumin/creatinine ratio from baseline to 26 and 52 weeks
    - Percent change from baseline in lipids and lipoproteins (LDL-C, TC, HDL-C, TG, nonHDL-C, ApoA-1, ApoB, TC/HDL-C, LDL-C/HDL-C, nonHDL-C/HDL-C and ApoB/ApoA-1) at Weeks 26 and 52 and relationship between renal effects and lipid changes after 26 and 52 weeks
    - Change in estimated GFR from baseline to 26 and 52 weeks
- **Patient reported outcomes (PROs)**
  - There are no patient reported outcomes for this study
- **Health economics**
  - There are no health economic evaluations in this study
- **Pharmacokinetic**
  - There are no pharmacokinetic outcomes for this study
- **Pharmacodynamic**
  - as listed under efficacy

– **Safety**

- Safety evaluation, as determined by the incidence and severity of adverse events and abnormal laboratory values

– **Genetics**

- Please refer to Appendix G

Statistical methods

The primary analysis for each outcome variable will be performed using last observation carried forward (LOCF) in the intention-to-treat (ITT) population. Sensitivity analyses will be performed on the observed data in the ITT and per-protocol (PP) populations. For tests of superiority, the ITT population will be considered the primary analysis population. For tests of no clinically significant deterioration from baseline the ITT and PP populations will be considered equally important.

The value for the urinary protein/creatinine ratio at each evaluation time point will be based on the geometric mean of the results of the 3 first morning voids (FMVs). The outcome variable is the change from baseline in the log transformed urinary protein/creatinine ratio.

The analyses of change in urinary protein/creatinine ratio, from baseline to Week 52 (primary outcome variable) and Week 26 (secondary outcome variable) will be performed using an analysis of variance (ANOVA) model including factors for centre (or pooled centre if required), baseline GFR, baseline urinary protein/creatinine ratio, and baseline systolic blood pressure.

Hypothesis testing will be performed to assess whether the reduction from baseline in each treatment group is significantly different from zero (i.e., that a particular treatment has had a positive effect, compared to baseline) or if no clinically significant deterioration from baseline can be concluded based on a prespecified increase from baseline. No adjustment will be applied for the two rosuvastatin groups since the hypothesis testing in each of the treatment groups is independent.

The results will be presented as an adjusted mean ratio (post:pre treatment), with associated 95% confidence intervals and p-value. If the 95% confidence interval for the post: pre treatment ratio lies entirely below 1.1, then no clinically significant deterioration from baseline will be concluded. If the 95% confidence interval also lies entirely below 1.0 and a statistically significant p-value ($p<0.05$) is found, then a positive effect from baseline will be concluded.

The secondary outcome variable for change in urinary albumin/creatinine ratio will be calculated in the same way as for the outcome variable for change in urinary protein/creatinine ratio. The analysis will be performed in the same way as the analysis of the change in urinary protein/creatinine ratio.

Percentage change from baseline in lipids and lipoproteins (secondary outcome variables) will be summarised for each treatment using descriptive statistics. Additionally changes in lipids and lipoproteins will be compared between rosuvastatin 40 mg and atorvastatin 80 mg groups. The relationship between lipids and renal effects will be explored.

The secondary outcome variable for estimated GFR (calculated using the modified MDRD equation), will be based on a single measurement at each evaluation time point. The analysis of change in GFR will be performed in the same way as the analysis of the change in log transformed urinary protein/creatinine ratio but using the absolute change from baseline as the response.

As an exploratory analysis (for descriptive purposes only since the study is not powered for treatment comparison) by adding treatment as a factor in the model, 95% confidence intervals will be presented for the estimate of the difference in treatment effects between the three treatment groups. This analysis will be performed on the primary outcome variable (urinary protein/creatinine ratio) and the secondary outcome variables relating to urinary albumin/creatinine ratio and estimated GFR.

Adverse events and other safety data will be summarised using descriptive statistics.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ACE	Angiotensin converting enzyme
ACVD	Atherosclerotic cardiovascular disease
AE	Adverse event (see definition in Section 4.7.1.1)
ALT	Alanine aminotransferase (=SGPT)
ANOVA	Analysis of variance
ApoA-1	Apolipoprotein A-1
ApoB	Apolipoprotein B
ARB	Angiotensin receptor blocker
ATP III	Adult Treatment Panel III
AST	Aspartate aminotransferase (=SGOT)
Beta-HCG	Beta-human chorionic gonadotrophin
CABG	Coronary artery bypass graft
C	Celsius
CDCP	Centre for Disease Control and Prevention
CK	Creatine kinase
CKD	Chronic kidney disease
CV	Coefficient of variation
dL	Decilitre
eCRF	Electronic case report form
e-code	Enrolment code
FMV	First morning void
GCP	Good clinical practice
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
HbA1c	Glycated haemoglobin
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
HDPE	High-density polyethylene

Abbreviation or special term	Explanation
HIV	Human immunodeficiency virus
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
HRT	Hormone replacement therapy
hsCRP	High sensitivity C-reactive protein
ICH	International Conference on Harmonisation
IB	Investigators brochure
IEC	Independent ethics committee
IgG	Immunoglobulin G
INR	International normalised ratio
IRB	Institutional review board
ITT	Intention-to-treat
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.
IVRS	Interactive Voice Response System
K/DOQI	Kidney Disease Outcomes Quality Initiative
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LOCF	Last observation carried forward
MCV	Mean cell volume
MCH	Mean cell haemoglobin
MCHC	Mean cell haemoglobin concentration
MDRD	Modification of diet in renal disease
MedDRA	Medical dictionary for regulatory activities
mg	Milligram
mg/dL	Milligram per decilitre
MI	Myocardial infarction
mL	Millilitre
NCEP	National Cholesterol Education Program
NHLBI	National Heart, Lung and Blood Institute
Non-HDL-C	Non-high-density lipoprotein cholesterol
NKF	National Kidney Foundation

Abbreviation or special term	Explanation
NYHA	New York Heart Association
OCT	Oral contraceptive therapy
OAE	Other Significant Adverse Event (i.e., 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).
Outcome variable	A variable (usually a derived variable) specifically defined to be used in the analysis of a study objective.
Pap	Papanicolaou cervical smear
PD	Pharmacodynamic
PK	Pharmacokinetic
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.
SAP	Statistical analysis plan
SAS	Statistical Analysis System®
SAE	Serious adverse event (see definition in Section 4.7.1.1).
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase (=AST)
SGPT	Serum glutamic pyrivic transaminase (=ALT)
ST	Study team
TC	Total cholesterol
TG	Triglycerides
TIA	Transient Ischaemic Attack
TLC Diet	Therapeutic Lifestyle Changes Diet
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
SDV	Source data verification
VLDL	Very-low-density lipoprotein
VLDL-C	Very-low-density lipoprotein cholesterol
WBC	White blood cell
WBDC	Web based data capture

1. INTRODUCTION

1.1 Background

Statins, by virtue of their LDL-C lowering and perhaps other pleiotropic effects [Bocan 2002] have been shown convincingly to reduce cardiovascular morbidity and mortality in multiple large outcomes trials in various populations [Vijan and Hayward 2004, Colhoun et al 2004]. Furthermore, the degree of cardiovascular protection is directly related to the extent of LDL-C reduction [Cannon et al 2004], helping drive the current recommendation of increasingly aggressive treatment goals, particularly in patients with coronary heart disease risk equivalents [Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), final report, 2002, Grundy et al 2004]. Beyond their proven benefit in reducing cardiovascular morbidity and mortality, there is growing evidence from studies in both animal models and in humans that treatment with statins may also influence the natural history of chronic kidney disease (CKD). In patients with chronic kidney disease (CKD), statins have been reported to reduce the degree of proteinuria (microalbuminuria and macroalbuminuria) [Bianchi et al 2003, Fried et al 2001, Lee et al 2002, Tonolo et al 2000] and arrest the progression of GFR decline or improve GFR in patients with decreased baseline renal function [Athyros et al 2004, Vidt et al 2004]. These therapeutic strategies aimed at slowing or preventing the progression to end-stage renal disease have become increasingly critical as the incidence of CKD has increased. The observed beneficial effects on the kidney could be an indirect result of lower LDL-C levels, but may also derive from other effects attributed to statins, such as reduced vascular inflammation or improvement in endothelial function [McFarlane et al, 2002].

3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are the most widely used prescription medication for the treatment of hyperlipidaemia. By inhibiting the rate-controlling step in cholesterol biosynthesis, these agents effectively lower plasma concentrations of atherogenic particles containing cholesterol, such as low-density lipoproteins (LDL) and very low-density lipoproteins (VLDL). Partial inhibition of hepatic cholesterol synthesis causes up-regulation of hepatic membrane LDL receptors, which are responsible for the clearance of LDL-cholesterol (LDL-C) from the circulation. In addition, reduced hepatic synthesis of cholesterol is thought to result in a modest reduction in the secretion of VLDL particles by the liver and an increase in receptor-mediated VLDL-C catabolism. The reduction in concentration of these apolipoproteins B (ApoB) containing lipoproteins is generally identified clinically through reduction of LDL-C and VLDL-cholesterol (VLDL-C) concentrations. There is also convincing evidence that statins increase levels of the anti-atherogenic high-density lipoproteins (HDL-C) [Stein et al 2000, LaRosa et al 1999], which could confer additional benefit to the reduction of atherogenic lipoproteins.

Rosuvastatin (Crestor®; AstraZeneca) and atorvastatin (Pfizer) are highly effective statins in modifying the atherogenic lipid profile. Please refer to the IB for further information regarding rosuvastatin.

1.2 Rationale for this study

The National Kidney Foundation (NKF) Task Force on cardiovascular disease, 2002 has concluded that the incidence of atherosclerotic cardiovascular disease is higher in patients with CKD compared to the general population. The Task Force concluded that patients with CKD should be considered to be in the highest risk category, i.e., a coronary heart disease risk equivalent, for risk factor management. Therefore, the NKF Kidney Disease Outcomes Quality Initiative (K/DOQI) Work Group, 2002 concluded that for patients with CKD, dyslipidaemia management should be undertaken in conjunction with all other available measures to reduce the overall risk of atherosclerotic cardiovascular disease consistent with NCEP guidelines. These guidelines include lowering of LDL-C levels to targets recommended for other coronary heart disease risk equivalents.

Independent of other factors, proteinuria is a potent predictor of progression to end-stage renal disease. Thus, studies focusing on prespecified renal endpoints such as proteinuria reduction and preservation or improvement of GFR are needed to determine whether statins are not only safe but also effective as renal protection agents, above and beyond drugs such as angiotensin converting enzyme inhibitors (ACE) and angiotensin receptor blockers (ARBs) with more established renal protective properties.

The rationale for this study is based on the recommendation that CKD is a coronary heart disease risk equivalent and the possibility that rosuvastatin added to conventional background therapy may reduce proteinuria and thereby signal a renal protective property that would further support its use in proteinuric CKD patients.

The establishment of such a renal protective property would provide further evidence that rosuvastatin may prevent the progression of CKD, as well as reduce the risk of cardiovascular events that occur at a higher rate in CKD patients.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this study is to evaluate the effects of rosuvastatin and atorvastatin on urinary protein excretion by evaluation of the change in urinary protein/creatinine ratio from baseline to Week 52 in non-diabetic patients with moderate proteinuria and hypercholesterolaemia.

2.2 Secondary objectives

The secondary efficacy objectives of the study are:

1. to evaluate the effects of rosuvastatin and atorvastatin on urinary protein excretion by evaluation of the change in urinary protein/creatinine ratio from baseline to Week 26.

2. to evaluate the effects of rosuvastatin and atorvastatin on urinary albumin excretion by evaluation of the change in urinary albumin/creatinine ratio from baseline to Weeks 26 and 52.

3. to evaluate the effects of rosuvastatin and atorvastatin on: low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), nonHDL-C, apolipoprotein A1 (ApoA-1), apolipoprotein B (ApoB), TC/HDL-C, LDL-C/HDL-C, nonHDL-C/HDL-C and ApoB/ApoA-1) to explore the relationship between renal effects and lipid changes at Weeks 26 and 52.

4. to evaluate the effects of rosuvastatin and atorvastatin on renal function by evaluation of the change in estimated glomerular filtration rate (GFR) predicted from the Modification of Diet in Renal Disease (MDRD) equation from baseline to Weeks 26 and 52.

The secondary safety objective of this study is:

1. to evaluate the effect of rosuvastatin and atorvastatin on the incidence and severity of adverse events and laboratory data

Please refer to Appendix G for the optional genetics objectives and all other genetics related information.

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design and flow chart

This Clinical Study Protocol has been subjected to a peer review according to AstraZeneca standard procedures.

This is a 52 week, randomised, double-blind, multinational, multicentre study with 3 parallel treatment groups: rosuvastatin 10 mg, rosuvastatin 40 mg and atorvastatin 80 mg. The primary outcome variable of the study is the change in urinary protein/creatinine ratio from baseline to 52 weeks. The study will be conducted as originally intended for approximately 345 randomised patients; however, difficulties with recruitment have led to a reduction in the total number of patients expected to be randomised from 345 to 225. These patients will be recruited from approximately 160 centres worldwide from the following countries: United States, Bulgaria, Romania, Germany, Hungary, Italy, Canada, Denmark, Brazil and South Africa. It is anticipated that in order to achieve this number of randomised patients, approximately 1150 patients will need to enter the lead-in period of the study. Centres will be required to randomise approximately 5 patients each. Centres may be discontinued from the study if recruitment rates are poor and new centres may be added if necessary to achieve recruitment goals. Recruitment will be competitive across countries and centres (thus centres

and country numbers are approximate). There is no maximum number of patients that centres can recruit, and centres will stop enrolment once enough patients are screened to provide the globally projected number randomised.

An independent Safety Committee will be employed to review safety data at regular intervals throughout the study (see section 6.7.1).

There are 10 clinic visits planned. Visits 1, 2 and 3 occur during the lead-in period. Visit 4 is the randomisation visit, and Visits 5, 6, 7, 8, 9 and 10 occur during the randomised treatment period.

Male and female, non-diabetic patients aged ≥18 years with moderate proteinuria and hypercholesterolaemia will be invited to attend the clinic. Patients will then enter an 8-week lead-in period during which they will undergo optimisation of existing anti-hypertensive treatment, withdrawal of statin treatment (if applicable) and will be given appropriate dietary advice. For the first 4 weeks of the lead-in period, patients may receive a bile acid sequestrant (e.g. cholestyramine) at the discretion of the investigator. For the second 4 weeks of the lead-in period, no lipid lowering therapy will be permitted, except for fibric acid derivatives or nicotinic acid initiated prior to study entry. No other lipid lowering therapy will be permitted to allow for an accurate baseline lipid profile.

During the lead-in period, patients should undergo initiation and/or titration of their overall anti-hypertensive medication regimen aiming for a blood pressure target of <130/80 mmHg. Patients must have received treatment with a stable and optimised dose of an ACE inhibitor and/or an ARB for ≥3 months prior to Visit 1 based on regional guidelines and investigator discretion. ACE inhibitor and/or ARB dose may not be adjusted after Visit 1. Patients must have a fasting LDL-C concentration at Visit 1 of:

- ≥90 mg/dL (2.33 mmol/L) if patient has not taken statin therapy within 2 weeks of Visit 1
- ≥60 mg/dL (1.55 mmol/L) if patient has taken statin therapy within 2 weeks of Visit 1

Patients who have taken rosuvastatin < 6 months prior to Visit 1 are not permitted to enter this study.

Patients should be given dietary advice for LDL-C reduction (see Appendix F).

To qualify for the study at Visit 1, one or more of the following proteinuria criteria must be met:

1. Urinary dipstick for protein ≥ 1+ (clinic or central laboratory), or
2. At least one of the following documented ≤3 months prior to Visit 1:

- Urinary protein to creatinine ratio ≥500 mg/gm to ≤5000 mg/gm
- 24-hour urinary protein excretion of ≥500 mg to ≤5000 mg
- Urinary albumin to creatinine ratio ≥350 mg/gm to ≤3500 mg/gm
- 24-hour urinary albumin excretion ≥350 mg to ≤3500 mg

After 4 weeks, eligible patients will return to the clinic for Visit 2 where blood pressure will be checked and if necessary, antihypertensive treatment adjusted accordingly (excluding ACE inhibitors/ARBs). Bile acid sequestrant must be stopped at this visit, but may be restarted after Visit 7 at investigator discretion.

After a further 3 weeks, eligible patients will return to the clinic for Visit 3. At Visit 3, to be eligible to continue, patients must have fasting LDL-C of ≥90 mg/dL (2.33mmol/L). Patients will collect a FMV urine specimen on 3 consecutive days (the 2 days prior to the visit, and then on the morning of the visit). To be eligible for randomisation at Visit 4, the geometric mean urinary protein/creatinine ratio from these three samples must be ≥500 mg/g and ≤5000 mg/g.

At Visit 4, all patients meeting the inclusion and exclusion criteria will be eligible for randomisation. Once eligibility has been confirmed, the Interactive Voice Response System (IVRS) will be used to randomise the patient. Patients will be randomised with a 1:1:1 randomisation ratio to receive treatment with either rosuvastatin 10 mg, rosuvastatin 40 mg or atorvastatin 80 mg.

During the first 4 weeks, patients randomised to receive rosuvastatin 40 mg or atorvastatin 80 mg will receive a half-dose of study drug to assess tolerability. Non-toleration of study drug could include elevations of ALT, CK (see appendices D and E), any symptoms of myalgia or at the investigator's discretion. If this half-dose is not well tolerated, patients will be discontinued. If there are no safety issues warranting withdrawal of study medication after 4-weeks, treatment dose will doubled to the full-randomised dose for 48 weeks. Patients randomised to receive rosuvastatin 10 mg will receive this dose for 52 weeks.

During the first 4 weeks of the randomised treatment period, patients will each take 1 encapsulated tablet per day consisting of either rosuvastatin 10 mg, rosuvastatin 20 mg or atorvastatin 40 mg. During the remaining 48 weeks of the trial, patients will each take 2 encapsulated tablets per day. Each day, medication will consist of 2 x rosuvastatin 5 mg encapsulated tablets, 2 x rosuvastatin 20 mg encapsulated tablets or 2 x atorvastatin 40 mg encapsulated tablets. During the randomised treatment period, supplemental non-statin, lipid-lowering therapy will be permitted after Visit 7 (Week 14) at investigator discretion. However, certain restricted medications that affect both lipids and proteinuria must have been initiated prior to Visit 1 and may not be adjusted during the study (See 3.3.4, Restrictions).

For Visits 2 and 3, the allowed visit window will be ±3 days. For Visit 4, the allowed visit window will be –1 to +3 days. For Visits 5, 6, 7, 8, 9 and 10 the allowed visit window will be

±7 days. It is important to 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 (i.e. Visit 1 for visits prior to randomisation, and Visit 4 following randomisation). However, if a patient attends the clinic for a visit where 3 FMV samples are required, but these have not been performed, these should be performed as soon as possible, and before the next visit is performed. As far as possible, the 3 FMV samples should be taken on consecutive days, but where a patient has forgotten to perform a sample, collections from 3 out of 4 consecutive days will be acceptable. If a patient attends the clinic for any of their visits where lipids will be measured without having fasted for at least 8 hours then they must be asked to return as soon as possible, within the visit window for a fasted blood sample.

Patients will additionally have the option to participate in optional genetics research. All genetics objectives, information and procedures relating to this optional research are detailed in Appendix G.

Informed consent will be taken before any study related procedures are performed.

Visit 1 (Week –8)

- Medical history and demography will be obtained
- Inclusion/exclusion eligibility into lead-in will be determined
- Dietary counselling
- Prior and concomitant medications recorded
- Review and titrate (if necessary) patient's anti-hypertensive medication, excluding ACE inhibitors and/or ARBs, to an individually optimised dose for a blood pressure target of <130/80 mmHg based on regional guidelines and investigator discretion
- Discontinue current lipid-lowering therapy if applicable (if initiated prior to study entry, fibric acid derivatives or nicotinic acid may be continued; optional bile acid sequestrants may be given for 4 weeks, at the discretion of the investigator).
- Full physical examination (including height, weight and waist circumference)
- Vital signs
- Fasting blood samples will be taken for lipid analysis, clinical chemistry, and calculation of GFR, TSH, HbA1c and haematology. An assay of beta-HCG will also be performed for female patients of childbearing potential
- Urine sample will be collected for urinalysis to send to the central lab. The investigator will perform a dipstick test for proteinuria on this sample.

- Review laboratory results when available. Patients who do not meet the inclusion criteria (as described in section 3.3.2) are screen failures and should be contacted and asked not to return for Visit 2, except as described below.

    - Patients who failed to qualify for the study prior to Amendment 1 based on inclusion/exclusion criteria and were not randomised may re-enter the study on one occasion under the Amended protocol (after local amended protocol approval). Any patients who screen fail for any reason under the Amended protocol will **not** be allowed to re-enter the study.

Visit 2 (Week –4)

- Lead-in eligibility will be confirmed from the Visit 1 sample results. If the results do not meet the eligibility criteria as described in section 3.3.2, no further study procedures should be performed on the patient, except as described below.

    - Patients who failed to qualify for the study prior to Amendment 1 based on inclusion/exclusion criteria and were not randomised may re-enter the study on one occasion under the Amended protocol (after local amended protocol approval). Any patients who screen fail for any reason under the Amended protocol will **not** be allowed to re-enter the study.

- Discontinue bile acid sequestrant if applicable

- Dietary counselling

- Vital signs

- Review and titrate (if necessary) patient's anti-hypertensive medication, excluding ACE inhibitors and/or ARBs, to an individually optimised dose for a blood pressure target of <130/80 mmHg based on regional guidelines and investigator discretion

- Concomitant medications recorded

- Adverse events will be assessed

- Remind patient to fast before next visit to allow collection of fasting lipid samples

- Patients should be given 3 urine specimen containers to enable collection of the 3 FMV urine collections for Visit 3. Patients should be instructed to collect samples on the 2 days immediately prior to Visit 3, and then on the morning of Visit 3.

Visit 3 (Week –1)

- Lead-in eligibility will be confirmed. If the results do not meet the eligibility criteria as described in section 3.3.2, no further study procedures should be performed on the patient, except as described below.

    - Patients who failed to qualify for the study prior to Amendment 1 based on inclusion/exclusion criteria and were not randomised may re-enter the study on one occasion under the Amended protocol (after local amended protocol approval). Any patients who screen fail for any reason under the Amended protocol will **not** be allowed to re-enter the study.

- Dietary counselling

- Vital signs

- Review and titrate (if necessary) patient's anti-hypertensive medication, excluding ACE inhibitors and/or ARBs, to an individually optimised dose for a blood pressure target of <130/80 mmHg based on regional guidelines and investigator discretion

- Concomitant medications recorded

- Fasting blood samples will be taken for lipid analysis, high sensitivity CRP (hsCRP), abbreviated clinical chemistry, haematology and calculation of GFR. An assay of beta-HCG will also be performed for female patients of childbearing potential if it is suspected that they have become pregnant

- An additional blood sample will be taken. Plasma from this sample will be stored and may be used at a later date for additional analyses of lipids and markers of cardiovascular risk.

- Urine chemistry. Patients should collect a FMV urine for 3 days. Urine should be collected on the 2 days prior to the visit and then on the morning of the visit. If a patient attends the clinic without bringing their 3 FMV samples, these should be performed as soon as possible, and before the next visit is performed. As far as possible, the 3 FMV samples should be taken on consecutive days, but where a patient has forgotten to perform a sample, collections from 3 out of 4 consecutive days will be acceptable. Following collection and analysis, patients who do not have a geometric mean urinary protein/creatinine ratio of ≥500 mg/g and ≤5000 mg/g are screen failures and should be contacted and asked not to return for Visit 4. One of the urine samples will also be used for urinalysis.

- Adverse events will be assessed

- Remind patient to fast before next visit to allow collection of fasting lipid samples

Visit 4 (Week 0)

- Dietary counselling
- Concomitant medications recorded
- Vital signs
- Inclusion/exclusion eligibility will be assessed. Eligible patients should be randomised using IVRS
- Fasting blood samples will be taken for lipid analysis (including apolipoprotein analysis) and hsCRP. An assay of beta-HCG will also be performed for female patients of childbearing potential if it is suspected that they have become pregnant
- Adverse events will be assessed
- Randomised study drug will be dispensed. Instruct patient to return unused medication at next visit.
- An optional blood sample for genetic research may be taken (see Appendix G)

Visit 5 (Week 4)

- Dietary counselling
- Concomitant medications recorded
- Vital signs
- Blood sample will be taken for abbreviated clinical chemistry and calculation of GFR. An assay of beta-HCG will also be performed for female patients of childbearing potential if it is suspected that they have become pregnant
- Adverse events will be assessed
- Study drug compliance check, drug accountability and tolerability assessment following the first 4 weeks of study drug administration. If there are no safety concerns over tolerability, randomised study drug should be dispensed. If tolerability issues lead to early withdrawal complete the Final Visit/ Early Discontinuation Visit 10
- Patients should be informed that their study treatment will increase from one capsule per day to two capsules per day from this visit until the end of the study
- An optional blood sample for genetic research may be taken (see Appendix G)

Visit 6 (Week 8)

- Dietary counselling
- Concomitant medications recorded
- Vital Signs
- Blood sample will be taken for abbreviated clinical chemistry and calculation of GFR. An assay of beta-HCG will also be performed for female patients of childbearing potential if it is suspected that they have become pregnant
- Adverse events will be assessed
- Study drug compliance and accountability check
- Randomised study drug will be dispensed
- Remind patient to fast before next visit to allow collection of fasting lipid samples
- Patients should be given urine specimen containers for the 3 day FMV urine collections required at Visit 7, and should be instructed to collect samples on the 2 days prior to the next visit and then on the morning of the visit
- An optional blood sample for genetic research may be taken (see Appendix G)

Visit 7 (Week 14)

- Dietary counselling
- Concomitant medications recorded
- Vital Signs
- Urine chemistry. Patients should collect FMV urine for 3 days. Urine should be collected on the 2 days prior to the visit and then on the morning of the visit. If a patient attends the clinic without bringing their 3 FMV samples, these should be performed as soon as possible, and before the next visit is performed. As far as possible, the 3 FMV samples should be taken on consecutive days, but where a patient has forgotten to perform a sample, collections from 3 out of 4 consecutive days will be acceptable
- Fasting blood samples will be taken for lipid analysis, abbreviated clinical chemistry, and calculation of GFR. An assay of beta-HCG will also be performed for female patients of childbearing potential if it is suspected that they have become pregnant
- Adverse events will be assessed

- Study drug compliance and accountability check
- Randomised study drug will be dispensed
- Remind patient to fast before next visit to allow collection of fasting lipid samples
- Patients should be given urine specimen containers for the 3 day FMV urine collections required at Visit 8, and should be instructed to collect samples on the 2 days prior to the next visit and then on the morning of the visit
- Supplemental non-statin, lipid-lowering therapy may be initiated at investigator discretion. However, certain restricted medications that affect both lipids and proteinuria must have been initiated prior to Visit 1 and may not be adjusted during the study (See 3.3.4, Restrictions).
- An optional blood sample for genetic research may be taken (see Appendix G)

Visit 8 (Week 26)

- Dietary counselling
- Concomitant medications recorded
- Vital Signs
- Fasting blood samples will be taken for lipid analysis (including apolipoprotein analysis), abbreviated chemistry, haematology, hsCRP and calculation of GFR. An assay of beta-HCG will also be performed for female patients of childbearing potential if it is suspected that they have become pregnant
- An additional blood sample will be taken. Plasma from this sample will be stored and may be used at a later date for additional analyses of lipids and markers of cardiovascular risk.
- Urine chemistry and urinalysis. Patients should collect FMV urine for 3 days. Urine should be collected on the 2 days prior to the visit and then on the morning of the visit. If a patient attends the clinic without bringing their 3 FMV samples, these should be performed as soon as possible, and before the next visit is performed. As far as possible, the 3 FMV samples should be taken on consecutive days, but where a patient has forgotten to perform a sample, collections from 3 out of 4 consecutive days will be acceptable. One of these samples will also be used for urinalysis.
- Adverse events will be assessed
- Study drug compliance and accountability check

- Randomised study drug will be dispensed
- Patients should be given urine specimen containers for the 3 day FMV urine collections required at Visit 9, and should be instructed to collect samples on the 2 days prior to the next visit and then on the morning of the visit
- Remind patient to fast before next visit to allow collection of fasting lipid samples
- An optional blood sample for genetic research may be taken (see Appendix G)

Visit 9 (Week 39)

- Dietary counselling
- Concomitant medications recorded
- Vital signs
- Fasting blood samples will be taken for lipid analysis, abbreviated clinical chemistry and calculation of GFR. An assay of beta-HCG will also be performed for female patients of childbearing potential if it is suspected that they have become pregnant
- An additional blood sample will be taken. Plasma from this sample will be stored and may be used at a later date for additional analyses of lipids and markers of cardiovascular risk.
- Urine chemistry. Patients should collect FMV urine for 3 days. Urine should be collected on the 2 days prior to the visit and then on the morning of the visit. If a patient attends the clinic without bringing their 3 FMV samples, these should be performed as soon as possible, and before the next visit is performed. As far as possible, the 3 FMV samples should be taken on consecutive days, but where a patient has forgotten to perform a sample, collections from 3 out of 4 consecutive days will be acceptable.
- Adverse events will be assessed
- Study Drug compliance and accountability check
- Randomised study drug will be dispensed
- Patients should be given urine specimen containers for the 3 day FMV urine collections required at Visit 10, and should be instructed to collect samples on the 2 days prior to the next visit and then on the morning of the visit
- Remind patient to fast before next visit to allow collection of fasting lipid samples

- An optional blood sample for genetic research may be taken (see Appendix G)

Final Visit / Early Discontinuation – Visit 10 (Week 52). To be completed by all randomised patients

- Dietary counselling
- Concomitant medications recorded
- Full physical examination (including weight)
- Vital signs
- Fasting blood samples will be taken for lipid analysis (including apolipoprotein analysis), hsCRP, clinical chemistry, HbA1c, calculation of GFR and haematology. An assay of beta-HCG will also be performed for female patients of childbearing potential if it is suspected that they have become pregnant
- An additional blood sample will be taken. Plasma from this sample will be stored and may be used at a later date for additional analyses of lipids and markers of cardiovascular risk.
- Urine chemistry and urinalysis. Patients should collect FMV urine for 3 days. Urine should be collected on the 2 days prior to the visit and then on the morning of the visit. If a patient attends the clinic without bringing their 3 FMV samples, these should be performed as soon as possible, and before the next visit is performed. As far as possible, the 3 FMV samples should be taken on consecutive days, but where a patient has forgotten to perform a sample, collections from 3 out of 4 consecutive days will be acceptable. One of these samples will also be used for urinalysis. Early discontinuation subjects will only have 3 FMV samples collected if available
- Adverse events will be assessed
- Study drug compliance and accountability check
- An optional blood sample for genetic research may be taken (see Appendix G)

Unscheduled Visits

Patients can return for evaluation/assessments at any time if their condition warrants medical attention.

Figure 1 Study flow chart

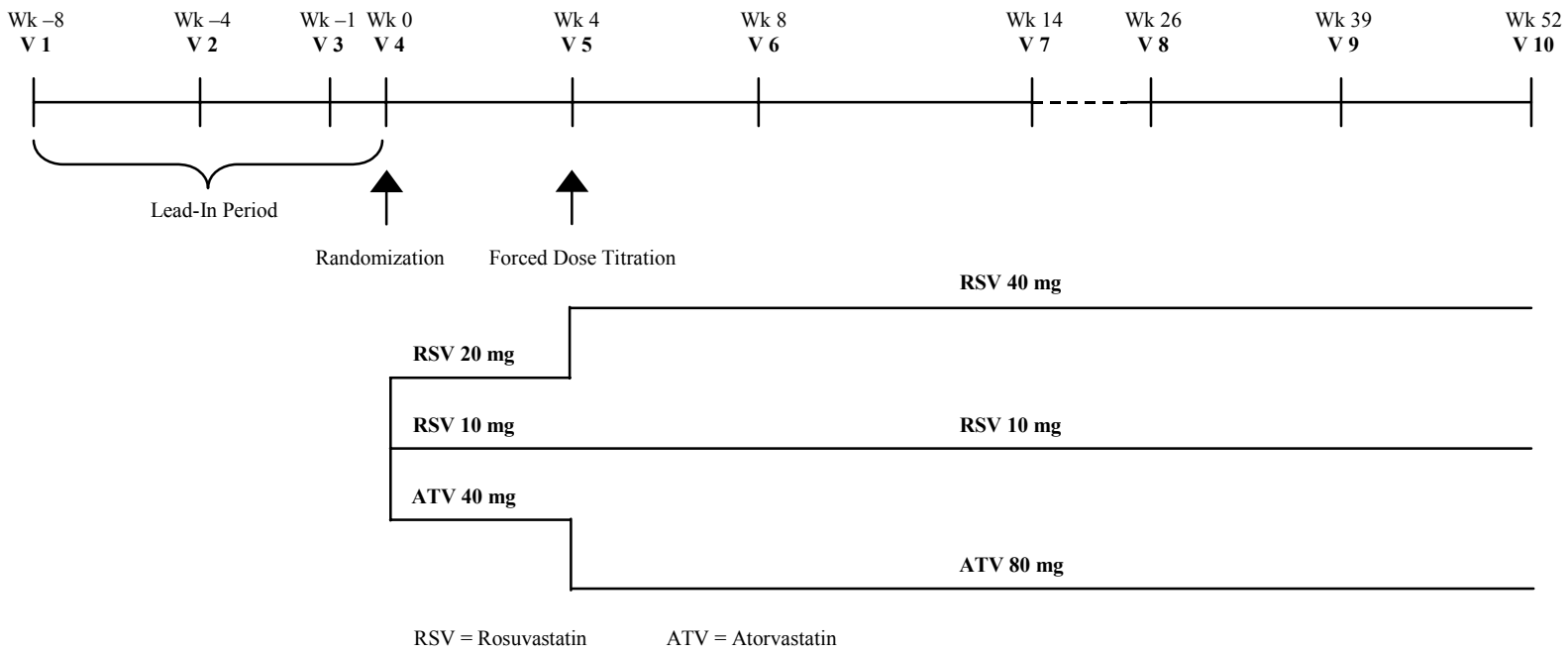

Table 1 Study Plan

Week	**-8**	**-4**	**-1**	**0**	**4**	**8**	**14**	**26**	**39**	**52**
Visit [o, p]	**1**	**2**	**3**	**4** [q]	**5** [t]	**6**	**7** [u]	**8**	**9**	**10** [n]
Informed consent [r]	✓									
Dietary counselling	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Medical history/demography	✓									
Concomitant medication	✓ [a]	✓	✓	✓	✓	✓	✓	✓	✓	✓
Physical examination [b]	✓									✓
Vital signs	✓ [c]	✓[c]	✓ [c]	✓	✓	✓	✓	✓	✓	✓
Eligibility criteria	✓	✓	✓	✓						
Fasting lipid profile [d]	✓		✓ [m]	✓			✓	✓ [m]	✓ [m]	✓ [m]
Apolipoproteins [e]				✓				✓		✓
TSH	✓									
Urinalysis [f]	✓		✓					✓		✓
Urine chemistry [g]			✓				✓	✓	✓	✓
GFR [h]	✓		✓		✓	✓	✓	✓	✓	✓
Clinical chemistry [i]	✓									✓
Abbreviated clinical chemistry [j]			✓		✓	✓	✓	✓	✓	
hsCRP			✓	✓				✓		✓
Haematology [k]	✓		✓					✓		✓
Beta-HCG [l]	✓									
Adverse events [s]		✓	✓	✓	✓	✓	✓	✓	✓	✓
Study drug dispensing				✓	✓	✓	✓	✓	✓	
Study drug compliance and accountability					✓	✓	✓	✓	✓	✓

[a] Prior medications to be collected at Visit 1
[b] Weight will be measured at Visits 1 and 10. Height and waist circumference will additionally be measured at Visit 1
[c] Review and titrate if necessary patient's anti-hypertensive medication, excluding ACE inhibitors and/or ARB's, to an individually optimised dose to a blood pressure target of <130/80 mmHg based on regional guidelines and investigator discretion
[d] Lipid profile: LDL-C, TC, HDL-C, TG, nonHDL-C, TC/HDL-C, LDL-C/HDL-C and non-HDL-C/HDL-C
[e] Apolipoprotein analysis to include ApoA-1, ApoB, ApoB/ApoA-1
[f] Urinalysis will consist of: visual description (colour and appearance), a dipstick test (specific gravity, pH, protein (qualitative), haematuria, glucose, ketones, bilirubin and blood), microscopy (red blood cells, white blood

cells, bacteria, casts and crystals). Samples will also be frozen to permit future analysis, including gel electrophoresis, if required. At Visit 1, the investigator should collect a urine sample for urinalysis to send to the central laboratory. The investigator will perform a dipstick test for proteinuria on this sample.

[g] Three consecutive FMV urine collections will be performed. Tests will include urine protein, albumin, creatinine, IgG and retinol binding protein.

[h] GFR will be calculated from the modified MDRD equation using serum creatinine concentration measured at each evaluation time point.

[i] Clinical chemistry will consist of: albumin, total bilirubin, blood urea nitrogen, creatine kinase, serum creatinine, calculated creatinine clearance, ALT, AST, fasting glucose, alkaline phosphatase, phosphorus, potassium, sodium, calcium, total protein, gamma-glutamyl transferase (GGT) and HbA1c

[j] Abbreviated clinical chemistry will consist of: ALT, AST, creatine kinase and serum creatinine

[k] Haematology will consist of platelet count, haemoglobin, haematocrit, RBC count, RBC indices (MCV, MCH, MCHC), WBC count and WBC differential (neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils)

[l] An assay of beta-human chorionic gonadotrophin (Beta-HCG) will only be performed at Visit 1 for women of childbearing potential. After Visit 1, an assay of Beta-HCG should only be performed when it is suspected that a woman may have become pregnant during the study

[m] An additional blood sample will be taken at Visits 3, 8, 9 and 10. Plasma from these samples will be stored and may be used at a later date for additional analyses of lipids and markers of cardiovascular risk.

[n] This visit will also be performed for all patients that prematurely discontinued, post randomisation

[o] Patients should be called 3 days prior to each study visit to remind them of their visit date and visit requirements, and in addition it is recommended to call mid-way between each of the study visits (6-10) regarding their study participation. Patients should be reminded to fast prior to Visits 1, 3, 4, 7, 8, 9 and 10 and to collect 3 FMV urines prior to Visits 3, 7, 8, 9 and 10

[p] An optional blood sample for genetic research may be taken at visits 4-10 (see appendix G for optional genetic protocol sampling)

[q] IVRS must be used to randomise the patients

[r] Informed consent will be taken at or before Visit 1, before any study related procedures are performed

[s] SAEs should be followed up for 30 days after the last dosing of study treatment

[t] Tolerability assessment following the first 4 weeks of study drug administration

[u] Non-statin, lipid-lowering therapy may be initiated at investigator discretion, except restricted medications that affect proteinuria which must have been initiated prior to Visit 1 (See 3.3.4, Restrictions).

3.2 Rationale and risk/benefit assessment

3.2.1 Rationale for study design, doses and control groups

The increasingly aggressive recommended treatment goals for high risk patients of LDL-C <2.59 mmol/L (<100 mg/dL) [Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) guidelines, final report 2004, Grundy et al 2004] have created a de facto indication for high efficacy statin therapy. For this reason, the current study utilises two of the more potent statins: rosuvastatin and atorvastatin.

Compelling evidence exists for a mortality benefit of statin therapy for patients with coronary heart disease risk equivalents. Therefore, a 52-week study to determine the effect of rosuvastatin on proteinuria in dyslipidaemic patients cannot ethically include a placebo arm. This randomised study includes 3 active treatment groups. To determine whether statin dose affects the proteinuria response, 2 doses of rosuvastatin are used (10 mg and 40 mg). In

addition, the high dose of atorvastatin (80 mg) provides a comparison group for the assessment of the safety profile of high dose statin therapy in patients with established CKD.

Proteinuria has been shown to be a potent predictor of progression of renal dysfunction and therefore an important clinical target for assessing the potential renal protective effects of rosuvastatin. Consistent with recent recommendations from the K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease Work Group,2003, urinary protein to creatinine ratio on a FMV is used as opposed to the traditional timed urine collections, to reduce the variability associated with 24-hour urine collections. 3 FMVs will be used to further reduce the variability at each time point.

The 8-week lead in period serves two purposes, both of which are important components of the study design. Firstly, the lead-in period allows time for the washout of possible residual effects of pre-existing statin use, which is important to establish a reliable baseline to determine the change from baseline during double-blind treatment. Secondly, the 8-week lead-in allows for optimisation of blood pressure control to minimize the confounding effects of blood pressure on urinary protein excretion.

The one-year duration of this study should allow sufficient rosuvastatin exposure for a positive effect on urinary protein excretion, if present, to be detected. This one-year duration has precedent from previous studies [Bianchi et al 2003) showing beneficial effects of statins on protein excretion.

3.2.2 Risk/benefit and ethical assessment

The identified patient population for this study has clear indication for statin therapy based on the LDL-C inclusion criteria and the coronary heart disease risk equivalent. To determine the effect of statin therapy at different doses on proteinuria, patients are randomised to low or high doses of rosuvastatin or a high dose of atorvastatin. Therefore, in the absence of a response-based design, some patients may be exposed to higher doses of statin than would conventionally be used to achieve LDL-C targets.

No upper limit of LDL-C exists that would exclude patients from the trial. Since one-third of patients will be randomised to a lower dose of rosuvastatin without the opportunity to up-titrate, non-statin, lipid-lowering therapy is permitted during the randomised period of the study to allow supplemental lipid lowering in addition to their blinded study medication at investigator discretion (e.g., bile acid sequestrants). However, lipid-lowering medications that also have the potential to affect proteinuria (e.g., fenofibrate) must have been initiated prior to Visit 1 (See 3.3.4, Restrictions).

Although the risk of adverse effects of statins are slightly higher at higher doses, there is potential for a greater reduction in proteinuria and lipids at higher doses, with the attendant benefit on decreased progression of renal disease. Please refer to the IB for further information about rosuvastatin.

An independent Safety Committee will be employed to monitor unblinded data at regular intervals throughout the study, and will advise on any necessary modification or requirements to stop the study following these reviews if any safety concerns arise.

3.3 Selection of study population

3.3.1 Study selection record

Patients may be recruited from primary or secondary care. Advertisements may be used by centres if appropriate. Investigators must keep a record of patients who were considered for enrolment but were never enrolled e.g., patient screening log. This information is necessary to establish that the patient population was selected without bias.

3.3.2 Inclusion criteria

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

1. Provision of written informed consent

2. Male or female aged ≥18 years

3. Fasting LDL-C levels collected at Visit 1:

    - ≥90 mg/dL (2.33 mmol/L) if patient has not taken statin therapy within 2 weeks of Visit 1

    - ≥60 mg/dL (1.55 mmol/L) if patient has taken statin therapy within 2 weeks of Visit 1

4. Proteinuria as evidenced by one or more of the following criteria at Visit 1:

    a. Urinary dipstick for protein ≥ 1+ (clinic and/or central laboratory), or

    b. One or more of the following documented ≤3 months prior to Visit 1:

        - Urinary protein to creatinine ratio ≥500 mg/gm to ≤5000 mg/gm

        - 24-hour urinary protein excretion ≥500 mg to ≤5000 mg

        - Urinary albumin to creatinine ratio ≥350 mg/gm to ≤3500 mg/gm

        - 24-hour urinary albumin excretion ≥350 mg to ≤3500 mg

5. Stable and individually optimized treatment with ACE inhibitor and/or an ARB for ≥3 months prior to Visit 1

For continuation in the lead-in period of the study after Visit 1 and for inclusion into the randomised treatment period of the study, patients must fulfil the following criteria:

6. Fasting LDL-C levels ≥ 90 mg/dL (2.33 mmol/L) collected at Visit 3

7. Urinary protein/creatinine ratio ≥500 mg/g and ≤5000 mg/g based on the geometric mean of 3 consecutive FMV urine collections at Visit 3

8. Best achievable blood pressure control per investigator judgement, not to exceed 150 mmHg systolic and/or 95 mmHg diastolic at Visit 4

3.3.3 Exclusion criteria

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

1. History of statin intolerance, statin-induced myopathy, or serious hypersensitivity reaction to other HMG-CoA reductase inhibitor (statin) *(for safety reasons)*

2. Previous rosuvastatin use < 6 months prior to Visit 1 *(because of the potency of rosuvastatin, this may confound the effects seen in this study)*

3. Bile acid sequestrant therapy after Visit 2 *(to prevent confounding the study results because of the potential carry over effects of bile acid sequestrant on cholesterol levels)*

    - Bile acid sequestrant therapy will be allowed after Visit 7 (Week 14) at investigator discretion

4. 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 (a serum b-Human chorionic gonadotropin [beta-HCG] analysis) *(for safety reasons)*

5. Patients having one or more of the following events within 12 weeks of V1: a myocardial infarction, unstable angina, myocardial revascularization (percutaneous transluminal coronary angioplasty, coronary artery bypass graft surgery or another revascularization procedure) or a transient ischemic attack (TIA) or stroke *(these patients should be treated outside of a clinical study)*

6. Moderate to severe congestive cardiac failure (New York Heart Association [NYHA] Class III or IV) *(these patients should be treated outside of a clinical study)*

7. Patients awaiting a planned myocardial revascularization prior to starting the study, i.e. planned prior to Visit 1 *(these patients should be treated outside of a clinical study)*

8. History of malignancy (unless a documented disease-free period exceeding 5 years is present) with the exception of basal cell or squamous cell carcinoma of the skin. Women with a history of cervical dysplasia would be permitted to enter the study

provided they have 3 consecutive clear Papanicolaou (Pap) smears *(to reduce the chances of the patient being discontinued from the study due to ill-health; such patients are not suited to this type of study)*

9. Uncontrolled hypothyroidism defined as a thyroid stimulating hormone (TSH) >1.5 times ULN at Visit 1 *(this is due to the relationship between myopathy and patients with hypothyroidism undergoing statin therapy)*

10. Type I or II diabetes *(due to study examining the non-diabetic patient population)*

11. History of homozygous familial hypercholesterolaemia or known Type III hyperlipoproteinemia (familial dysbetalipoproteinemia) *(due to lipid levels exhibited by this group of patients they are considered unsuitable for this study as they often require combination lipid-lowering therapy)*

12. History of alcohol or drug abuse, or both in the last 5 years *(alcohol is known to increase TG levels and increase the risk of myopathy; such patients are also known to be unreliable in terms of attending regular scheduled visits and taking study medication)*

13. Current active liver disease as defined by elevations of >2 x ULN in ALT at Visits 1 or 3 or severe hepatic impairment *(because of the potential for statins to cause disturbances in liver function, as directed on the labels of currently approved statins).*

14. Unexplained creatine kinase (CK) > 2 x ULN at Visits 1 and 3 *(because of the potential for statins to cause myopathy and to avoid confounding the safety profile*)

15. Participation in another investigational drug study <4 weeks before Visit 1 or in accordance with local ethics if a longer period is stipulated. Patients who withdrew from the treatment phase of this or a previous rosuvastatin study cannot re-enter this study *(to avoid potential misinterpretation of overlapping adverse events).*

16. 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.

17. Patients whose hormone replacement therapy (HRT) or oral contraceptive therapy (OCT) was initiated or changed within the 3 months prior to Visit 1 (*HRT and OCT can interfere with lipid levels and confound the study results).*

18. Use of oral or intravenous immunosuppressive medications ≤3 months prior to Visit 1

19. Severe renal impairment, as judged by estimated GFR (MDRD equation) <40 ml/min/1.73m^2 at Visit 3 *(patients with severe renal impairment should not be treated with high doses of statins because of an increase in plasma concentrations)*

20. Any known clinical condition that, in the opinion of the investigator, would require an adjustment of the ACE inhibitor and/or ARBs after Visit 1 *(to prevent confounding the study results, as ACE inhibitors and ARBs are known to affect urinary protein)*.

21. Statin therapy after Visit 1. Patients may be either statin naïve or have undergone statin withdrawal at Visit 1 *(to prevent confounding the study results because of potential carry over effects of statins on renal function and cholesterol levels).*

22. Underlying renal disease attributed to autosomal dominant polycystic kidney disease, primary idiopathic intersitial nephritis, HIV (human immunodeficiency virus) nephropathy or ischemic renal disease due to bilateral renal artery stenosis or unilateral renal artery stenosis in a single kidney *(it is unlikely that these patients would benefit from treatment with statins in this study, these patients are likely to have a different response to treatment).*

23. Asian ethnicity *(because of the altered pharmacokinetics. A rise in plasma concentration with high dosage of rosuvastatin in Asian patients with CKD is not appropriate).*

24. Involvement in the planning and conduct of the study (applies to both AstraZeneca staff or staff at the study site).

3.3.4 Restrictions

Patients must comply with the following restrictions during the study:

1. Patients who are blood donors should not donate blood during the study and for 3 months following their last dose of study treatment *(to avoid donation of study drug to other individuals).*

2. Patients will fast (water is permitted) for 8 hours prior to each visit where lipids are to be measured. Patients should also refrain from consuming alcohol and cigarette smoking on the morning of each of these clinic visits *(to obtain accurate and consistent results of lipid measurements).*

3. Patients should be advised to maintain their normal physical activities or exercise *(to avoid the effects of changes in physical activity on laboratory measurements, which may risk observation of spurious rises in CK).*

4. Patients will be expected to follow the NCEP Therapeutic lifestyle Changes (TLC) diet for the duration of the study *(because dietary intake is known to affect blood*

cholesterol concentration and thus a standard diet is required in studies of lipid-modifying agents).

5. Patients should not receive treatment during the study with any of the disallowed medications outlined in Section 3.7 *(for safety reasons and/or to avoid confounding the study results).*

6. Doses of ACE inhibitors and/or ARBs should not be adjusted after Visit 1, without first consulting the study team physician.

7. NSAIDs may be used intermittently during randomised phase but not within 10 days of Visits 3, 7, 8, 9, 10 (proteinuria assessment visits)

8. Medications with the potential to affect proteinuria (see list below) are allowed to be used concomitantly but must already be initiated at Visit 1 and may not be adjusted during the duration of the study. These medications include:

    - Fenofibrate
    - Aldosterone antagonists (e.g., spironolactone)
    - Renin-inhibitors
    - Glitazones
    - Metformin
    - Niacin/nicotinic acid (includes vitamins/supplements with >50 mg niacin/nicotinic acid)
    - Erythropoietin

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:

- Study treatment not tolerated at Visit 5 and raising safety concerns. Non-toleration of study drug could include elevations of ALT, CK (see appendices D and E), any symptoms of myalgia or at the investigator's discretion.
- Voluntary discontinuation by the patient who is at any time free to discontinue their participation in the study, without prejudice to further treatment
- Safety reasons as judged by the investigator and/or AstraZeneca

- Occurrence of an adverse event, which in the opinion of the investigator warrants the patient's discontinuation. Patients who are discontinued from the study for non-serious or serious adverse events should be followed until the adverse event has been resolved or stabilised and no further change is expected

- If at any time, the patient experiences unexplained muscle pain, tenderness or weakness which is accompanied by CK>10 x ULN, study medication should be discontinued. See management of increased creatine kinase (CK) (Appendix E)

- If ALT (SGPT) is demonstrated to be 3 x ULN on two consecutive occasions >48 hours apart, without obvious reversible precipitating factors, withdrawal of study medication is recommended (see Appendix D)

- If estimated GFR decreases to ≤ 20 ml/min/1.73m^2, patients should be withdrawn.

- Severe non-compliance to protocol as judged by the investigator and/or AstraZeneca (any deviation from the protocol should be reported to the study team who will decide whether the patient should be discontinued from the study)

- Incorrect enrolment (screen failure) i.e., the patient was not randomised as does not meet the required inclusion/exclusion criteria

- Patient lost to follow-up

- Pregnancy

- Deterioration in the patient's condition which in the opinion of the investigator warrants study medication withdrawal.

- Medical need for treatment with a protease inhibitor. Patients must discontinue study medication prior to beginning treatment with a protease inhibitor.

3.3.5.2 Procedures for discontinuation

Patients who discontinue should always be asked about the reason(s) for their discontinuation and the presence of any adverse events. If possible, they should be seen and assessed by an investigator(s). Adverse Events (AEs) should be followed-up. Serious Adverse Events (SAEs) should be followed-up until resolution or until the patient is lost to follow-up. All investigational products should be returned to the clinic by the patient.

3.4 Treatments

3.4.1 Identity of investigational product and comparators

The investigational product will be supplied by AstraZeneca. The study medication will consist of encapsulated tablets of rosuvastatin (Crestor®, AstraZeneca) 5 mg, 10mg and 20 mg and encapsulated tablets of atorvastatin (Pfizer) 40 mg as shown in Table 2.

Table 2 Dose and formulation number

Treatment	Presentation	Strength	Formulation Number
Rosuvastatin	5 mg encapsulated tablet	5 mg	F13379
Rosuvastatin	10 mg encapsulated tablet	10 mg	F12927
Rosuvastatin	20 mg encapsulated tablet (containing 2 x 10 mg)	20 mg	F12935
Atorvastatin	40 mg encapsulated tablet	40 mg	F12560

The rosuvastatin and atorvastatin tablets will be encapsulated by on behalf of AstraZeneca. Encapsulated comparator products in Phase III lipid trials have demonstrated efficacy consistent with published results and results reported in comparator prescribing information. The direct measure of therapeutic equivalency, via LDL-C reduction is the ultimate measure of the impact of this blinding technique. In addition, in vitro comparative profile dissolution testing performed for commercial products containing atorvastatin (encapsulated versus non-encapsulated tablets), yielded data that closely matched the extent of dissolution at 60 minutes. Thus, dissolution testing showed that encapsulation has no effect

The in vitro bioequivalence of encapsulated Crestor tablets to Crestor tablets has been evaluated by comparative dissolution studies in three media. The comparative dissolution results demonstrate the in vitro bioequivalence of encapsulated Crestor tablets to Crestor tablets.

Rosuvastatin and atorvastatin will be packaged by AstraZeneca in high-density polyethylene (HDPE) bottles containing 50 capsules and 2 x 1g desiccant.

3.4.2 Doses and treatment regimen

AstraZeneca will provide centres with blinded supplies of study medication. Medication will be dispensed on a visit-by-visit basis. At each dispensing visit, patients will be given a bottle(s). Each bottle will contain sufficient tablets and overage to accommodate the visit schedules (see Table 3).

At Visit 4 (Week 0) following confirmation of eligibility, patients will be randomised to one of three treatment groups; rosuvastatin 10 mg, rosuvastatin 40 mg or atorvastatin 80 mg. For those patients randomised to receive rosuvastatin 40 mg or atorvastatin 80 mg, a half-dose of medication will be dispensed for the first 4 weeks. Therefore for these first 4 weeks, depending on which treatment group patients are randomised to, each bottle will contain treatment (plus overage) of either rosuvastatin 10 mg, rosuvastatin 20 mg or atorvastatin 40 mg encapsulated tablets. Patients should take one encapsulated tablet per day.

For the remaining 48 weeks and following tolerability assessments at Visit 5, patients will be dispensed further bottles containing either rosuvastatin 5 mg encapsulated tablets, rosuvastatin 20 mg encapsulated tablets or atorvastatin 40 mg encapsulated tablets. Patients should take a total of 2 encapsulated tablets per day. Each bottle will contain sufficient encapsulated tablets and overage to accommodate the visit schedule (see Table 3).

All study medication will be taken orally, with water if required, once daily at any time of day or night.

As all investigational product is encapsulated there will be no difference in appearance between any of the treatments in the study.

Table 3 Visit schedule

Dispensing Visit	Number of weeks until next dispensing visit	Number of bottles	Number of capsules
4	4	1	50 (28 days treatment, 1 tablet per day + 22 days overage)
5	4	2	100 (28 days treatment, 2 tablets per day + 22 days overage)
6	6	2	100 (42 days treatment, 2 tablets per day + 8 days overage)
7	12	4	200 (84 days treatment, 2 tablets per day + 16 days overage)
8,9	13	4	200 (91 days treatment, 2 tablets per day +9 days overage)

3.4.3 Labelling

All investigational product will be packaged and labelled by AstraZeneca according to local regulatory requirements and in accordance with Good Manufacturing Practice stating that the drug is for clinical use only and should be kept out of the reach of children.

3.4.4 Storage

All investigational products must be kept in a secure place under appropriate storage conditions. A description of the appropriate storage and shipment conditions are specified on

the investigational product label and investigator brochure. All study drugs will be stored in their original containers (as supplied by AstraZeneca) in a lockable storage facility until dispensed to the patients.

3.4.5 Accountability

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

- Accurate records are maintained, accounting for the receipt of the investigational product and for the disposition of the product
- The medication identification number dispensed corresponds to the number allocated by IVRS, prior to treatment dispensation
- Deliveries of such products from AstraZeneca are correctly received by a responsible person (e.g., a pharmacist).
- Study treatments are handled and stored safely and properly and in agreement with the storage instructions printed on the label.
- Study treatments are only dispensed to study patients in accordance with the protocol and are prescribed by the investigator or a person authorised to do so by the principal investigator
- Under no circumstances will the investigator allow the investigational products to be used for other purposes than directed by the protocol.
- It is essential that all medication is accounted for by the investigator or institution, and that any discrepancies are explained and documented. 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 the drug accountability recorded on the eCRFs.
- The patient must return all unused investigational products to the investigator. The number of encapsulated tablets returned must be checked against the number dispensed to determine patient compliance. Returned and unused product is accounted for and returned to the AstraZeneca Distribution Site (or designee) for destruction, or destroyed locally upon agreement with, and approval from AstraZeneca. All returned product should be documented.

3.5 Method of assigning patients to treatment groups

The actual treatment assigned to individual patients will be determined according to a non-centre specific randomisation scheme which will be produced by AstraZeneca using an

AstraZeneca computer software tool, GRand (Global Randomisation System) prior to the inclusion of the first patient.

Once a patient has signed the written informed consent form, they will be allocated an enrolment code (e-code) which is a unique identifying number that must be used as the identification number throughout the study. If a patient discontinues from the study, the e-code will not be re-used.

Patients who failed to qualify for the study prior to Amendment 1 based on inclusion/exclusion criteria and were not randomised may re-enter the study on one occasion under the Amended protocol (after local amended protocol approval). Any patients who screen fail for any reason under the Amended protocol will **not** be allowed to re-enter the study. Patients who re-enter the study will be considered new patients and will be assigned a new e-code.

The study doctor will establish patient eligibility before treatment randomisation. At Visit 4 (Week 0) patients who satisfy the entry criteria will be randomly assigned to receive either rosuvastatin 10 mg, rosuvastatin 40 mg or atorvastatin 80 mg with a 1:1:1 randomisation ratio. IVRS must be used to randomise the patient. It is important that patients are not randomised ahead of their randomisation visit (Visit 4).

At each dispensing visit it is important to check that the medication identification number matches the number allocated by IVRS, prior to treatment dispensation. If a treatment is incorrectly dispensed (i.e., medication identification number does not match the number allocated by IVRS), the error should be rectified and AstraZeneca 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

The study employs a double-blind design. There will be no difference in appearance between the medications for each treatment group as the tablets are all encapsulated. In each phase, medication for each treatment group will be supplied in identical bottles and will be labelled appropriately so as to maintain the study blind.

All study personnel (except the Safety Committee, see section 6.7.1) will be unaware of the randomised treatment until all decisions on the evaluability of the data from all patients have been made and documented.

Except for LDL-C, lipid results will be blinded during the randomised treatment period to prevent unintentional unblinding of study treatments. After Visit 7 (Week 14), LDL-C results will be provided to investigators to allow the addition of supplemental, non-statin, lipid-lowering therapy at their discretion.

3.6.2 Methods for unblinding the study

The treatment code must not be broken except in medical emergencies when the appropriate management of the patient necessitates knowledge of the treatment randomisation. The investigator(s) must document and report to AstraZeneca any breaking of the treatment code. AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities.

If a treatment code is required to be broken, the randomised treatment for each randomised patient, will be available to the investigator(s) or pharmacists using IVRS. Routines for this will be described in the IVRS manual that will be provided to each investigational centre.

Treatment codes will not be broken by AstraZeneca or the Steering Committee for the planned analyses of data until all decisions regarding the patients in each patient population have been made and documented.

The independent Safety Committee will not be blinded, and will be provided with the random scheme prior to the first subject being randomised.

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

Patients must not have been treated with rosuvastatin < 6 months prior to Visit 1.

Patients must be receiving ACE inhibitors or ARBs as an inclusion requirement for the study, and dose must be optimised prior to Visit 1. These drugs should not be modified after the subject enters the study. If it is felt that ACE/ARBs require adjustment, this should first be discussed with the AstraZeneca physician. Other anti-hypertensive medications may be modified as required to maintain a patient's blood pressure throughout the study.

All disallowed medications should be stopped on entry to the study and are disallowed during the lead-in period and whilst the patient is receiving study medication. With the exception of lipid-modifying agents (which will affect the study objectives and baseline lipid characteristics), the listed medications are disallowed on the basis of safety concerns relating to one or both of the study treatments. In particular there is a risk of myopathy with antibiotics, antifungals, immunosuppressants, and protease inhibitors (due to possible increases in plasma levels).

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

Patients taking fibric acid derivatives or nicotinic acid are permitted to continue this therapy at a constant dose if started prior to Visit 1. However, there may be an increased risk of skeletal muscle side effects when these medications are co-administered with statins, such as

atorvastatin or rosuvastatin. Patients treated with fibric acid derivatives or nicotinic acid should be monitored for skeletal muscle side effects.

If antacids are required, they should be taken 2 hours after dosing with study medication.

Table 4 Disallowed concomitant medication

Class of drug	Generic name
Antibiotics	Erythromycin base, clarithromycin
	Erythromycin ethyl succinate, acetyl sulfisoxazole
Antifungal (chronic systemic use)	Fluconazole
	Ketoconazole
	Itraconazole
Lipid regulation	Gemfibrozil
	Atorvastatin (except for study medication)
	Lovastatin
	Pravastatin
	Rosuvastatin (except for study medication)
	Simvastatin
	Fluvastatin
	Cyclosporin
Immunosuppresants	Lymphocyte immune globulin
	Rho(d) immune globulin
	Azathioprine sodium
	Muromonab-CD3
	Prograf (FK-506)
	Cellcept (mycophenolate mofetil)
	Oral or intravenous corticosteroids
Protease Inhibitors (Used to Treat HIV Infection)	All protease inhibitors including Amprenavir, Atazanavir sulphate, Darunavir, Fosamprenavir calcium, Indinavir, Lopinavir, Nelfinavir mesylate, Ritonavir, Saquinavir mesylate, Tipranavir

3.7.1.1 Vitamin K antagonist usage (e.g., Warfarin, Coumarins)

Clinical studies have shown a potentiation of the anticoagulant effect during concomitant administration of rosuvastatin 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**

- when a patient has the **dose of their study medication adjusted**

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

3.7.1.2 Digoxin

Concomitant use of atorvastatin with digoxin requires appropriate monitoring. As study medication is double-blind, please monitor all patients by assessment of steady-state plasma digoxin concentrations.

3.8 Treatment compliance

Patients will be asked to return all unused medication and empty bottles. The number of encapsulated tablets issued minus the number of encapsulated tablets returned will be used to calculate the number of encapsulated tablets taken. From this information compliance will be calculated:

Compliance = (encapsulated tablets taken during the period ÷ encapsulated tablets which should have been taken during the period) x 100

Compliance will be checked at all visits after Visit 4. Any patient taking less than 80% or more than 120% of the prescribed study medication will continue in the study but will be counselled on the importance of taking their medication as directed.

4. MEASUREMENTS OF STUDY VARIABLES AND DEFINITIONS OF OUTCOME VARIABLES

4.1 Primary variable

The primary outcome variable is the change in urinary protein/creatinine ratio from baseline to Week 52.

This outcome variable is used as the basis for the sample size calculations (section 6.5).

4.2 Screening and demographic measurements

The following screening and demographic data will be collected in the eCRF:

- Date of birth, sex and race
- Significant medical and surgical history
- Prior and concomitant medication
- Height, weight, waist circumference, vital signs and physical examination

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 efficacy variables for the study are described in the table below:

Table 5 Efficacy outcome variable(s)

Objective	Variable(s)
Primary	Change in urinary protein/creatinine ratio from baseline to 52 weeks
Secondary	
1st	Change in urinary protein/creatinine ratio from baseline to 26 weeks
2nd	Change in urinary albumin/creatinine ratio from baseline to 26 and 52 weeks

Table 5 Efficacy outcome variable(s)

Objective	Variable(s)
Primary	Change in urinary protein/creatinine ratio from baseline to 52 weeks
3rd	Percent change from baseline in lipids and lipoproteins (LDL-C, TC, HDL-C, nonHDL-C, TG, ApoA-1, ApoB, TC/HDL-C, LDL-C/HDL-C, nonHDL-C/HDL-C and ApoB/ApoA-1) at Week 26 and 52 and relationship between renal effects and lipid changes after 26 and 52 weeks
4th	Change in estimated GFR from baseline to 26 and 52 weeks

4.6.1 Urinary protein/creatinine ratio

4.6.1.1 Methods of assessment

Patients will be supplied with urine specimen collection containers. Patients will collect FMV urine samples on 3 consecutive mornings at each assessment time point. These should be collected on Day -2 relative to the visit, Day -1 relative to the visit, and then on the morning of the clinic visit. If a patient attends the clinic for a visit where 3 FMV samples are required, but these have not been performed, these should be performed as soon as possible, and before the next visit is performed. As far as possible, the 3 FMV samples should be taken on consecutive days, but where a patient has forgotten to perform a sample, collections from 3 out of 4 consecutive days will be acceptable. Patients should store samples in the refrigerator prior to taking to the study centre. Samples will then be shipped by the investigator to the central laboratory.

4.6.1.2 Derivation or calculation of outcome variable

The three FMV urine samples will be analysed separately for protein and creatinine. The urinary protein to creatinine ratio is calculated as urine protein concentration (mg/dL) divided by urine creatinine concentration (g/dL), expressed as mg/g. For the analysis, the geometric mean of the ratios calculated from each of the 3 FMV will be considered the value at each evaluation time point. The outcome variable is the change from baseline in the log transformed urinary protein/creatinine ratio.

All samples will be labelled with the patient initials, e-code and date of collection. Analyses of all laboratory samples and calculation of protein/creatinine ratio will be performed by a central laboratory. Further details of the central laboratory can be found in the central laboratory manual.

4.6.2 Urinary albumin/creatinine ratio

4.6.2.1 Methods of assessment

Patients will be supplied with urine specimen collection containers (same containers as for urinary protein/creatinine samples, section 4.6.1.1). Patients will collect FMV urine samples on 3 consecutive mornings at each assessment time point. These should be collected on Day -2 relative to the visit, Day -1 relative to the visit, and then on the morning of the clinic

visit. If a patient attends the clinic for a visit where 3 FMV samples are required but some or all of these collections have not been performed, these should be performed as soon as possible, and before the next visit is performed. As far as possible, the 3 FMV samples should be taken on consecutive days, but where a patient has forgotten to perform a sample, collections from 3 out of 4 consecutive days will be acceptable. Patients should store samples in the refrigerator prior to taking to the study centre. Samples will then be shipped by the investigator to the central laboratory.

4.6.2.2 Derivation or calculation of outcome variable

The three FMV urine samples will be analysed separately for albumin and creatinine. The urinary albumin to creatinine ratio is calculated as urine albumin concentration (mg/dL) divided by urine creatinine concentration (g/dL), expressed as mg/g. For the analysis, the geometric mean of the ratios calculated from each of the 3 FMV will be considered the value at each evaluation time point. The outcome variable is the change from baseline in the log transformed urinary albumin/creatinine ratio.

All samples will be labelled with the patient initials, e-code and date of collection. Analyses of all laboratory samples and calculation of albumin/creatinine ratio will be performed by a central laboratory. Further details of the central laboratory can be found in the central laboratory manual.

4.6.3 Lipid assessments

Lipids and lipoproteins will be assessed from laboratory data.

4.6.3.1 Methods of assessment

Patients must fast for at least 8 hours and have been sitting for at least 5 minutes before blood samples are taken for lipid analysis. If a patient attends for one of these study visits without having fasted (from 8 hours before) then they must be asked to return within the visit windows for their fasting blood sample.

Fasting concentrations of LDL-C, HDL-C, TG, TC and nonHDL-C will be determined at Visits 1, 3, 4, 7, 8, 9 and 10. The following ratios will also be calculated at these visits: TC/HDL-C, LDL-C/HDL-C and nonHDL-C/HDL-C.

Fasting concentrations of apolipoproteins ApoB and ApoA-1 will be determined at Visits 4, 8 and 10. The ApoB/ApoA-1 ratio will also be calculated at these visits.

HsCRP will be analysed at Visits 3, 4, 8 and 10.

Additional fasting blood samples will be collected at Visits 3, 8, 9 and 10. Plasma from these samples will be stored at the central laboratory and may be used at a later date for additional lipid analysis (for example lipid and lipoprotein subfractions) and/or markers of cardiovascular risk. These samples will not be used for genetic analysis. For any genetic research to be performed, the patient must give separate informed consent (see Appendix G).

All samples will be labelled with the patient initials, e-code and date of collection. Analyses of all laboratory samples will be performed by a central laboratory. The central laboratory will be responsible for all lipid analysis and is certified for standardisation of lipid analysis as specified in the Standardisation Program for 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.

4.6.3.2 Derivation or calculation of outcome variable

Concentrations of fasting LDL-C will be determined at all relevant visits 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 Friedewald equation is as follows:

For SI units (mmol/l):

$$\text{LDL-C} = \text{Total cholesterol} - \{\text{HDL-C} + {}^{\text{TRIGLYCERIDES}}/_{2.2}\}$$

For non-SI units (mg/dL):

$$\text{LDL-C} = \text{Total cholesterol} - \{\text{HDL-C} + {}^{\text{TRIGLYCERIDES}}/_{5}\}$$

4.6.4 Glomerular filtration rate

4.6.4.1 Methods of assessment

GFR will be estimated using the modified MDRD equation, using serum creatinine concentration collected at Visits 1, 3, 5, 6, 7, 8, 9 and 10.

4.6.4.2 Derivation or calculation of outcome variable

The modified MDRD equation (Levey et al 1999) is as follows:

$$\text{MDRD GFR} = 186 \times (\text{serum creatinine in mg/dL})^{-1.154} \times (\text{age in years})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if black})$$

The outcome variable is the change in GFR (post-treatment value divided by pre-treatment value).

All samples will be labelled with the patient initials, e-code and date of collection. Analyses of all laboratory samples and calculation of GFR will be performed by a central laboratory. Further details of the central laboratory can be found in the central laboratory manual.

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

Adverse event

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

Serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), and at any dose of the investigational product, comparator or placebo, that fulfils one 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 one of the outcomes listed above.

The causality of SAEs (i.e., 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 to the Clinical Study Protocol.

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 (OAE)

OAEs will be identified by the Clinical Study Team Physician during the evaluation of safety data for the Clinical Study Report. Significant adverse events 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, a narrative may be written and included in the Clinical Study Report.

4.7.1.2 Recording of adverse events

Adverse events will be identified at all visits except Visit 1 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, if any action was taken, the outcome and to assess the intensity of the reported adverse event 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 (see Appendix B).

If a diagnosis of the patient's condition has been made, then the diagnosis should be recorded as the adverse event (e.g., 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 which persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke which results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

AstraZeneca will classify events using Medical Dictionary for Regulatory Activities (MedDRA).

For screen failure patients, SAEs should be recorded from the time the patient consents to participate in the study up until the decision is made to discontinue the patient. Non-serious reports are not required for these patients.

For randomised patients, all adverse events and serious adverse events should be recorded from the time a patient consents to participate in the study up until discontinuation of study treatments.

Patients should be instructed to report hospitalisations and any other medically serious events that occur within 30 days after last dosing of study treatment. The investigator should record these and any other serious events he is aware of in the 30-day period following discontinuation of study treatment, on the eCRF and should report them to AstraZeneca in the usual manner.

After the initial AE/SAE report, the investigator is required to proactively follow the patient's condition. During the study all AE/SAEs should be followed-up until resolution, or until the condition stabilises and no further change is expected. AstraZeneca reserves the right to ask for further information on any adverse event which may be considered of interest.

Any SAEs ongoing at the final visit or reported within 30 days of study treatment discontinuation, should be followed-up until resolution or until stabilised and no further change is expected.

Clinically significant abnormal laboratory values, vital signs or physical examination will not be recorded as adverse events unless:

- SAE criteria is fulfilled
- the patient discontinues the study due to the abnormality
- the investigator considers that the abnormality should be reported as an AE

However, if an abnormal laboratory value/vital sign is associated with clinical signs and symptoms, the sign/symptom should be reported as an AE and the associated laboratory result/vital sign should be considered additional information.

If there is a worsening of renal disease as defined by a decrease in eGFR, the guidance in Appendix H should be followed. Decreases in eGFR should only be reported as AEs if they fulfil the criteria listed in the bullets above.

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 investigational product may have interfered with the effectiveness of a contraceptive medication.

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.

4.7.1.3 Reporting of serious adverse events

Investigators and other site personnel must inform appropriate AstraZeneca representatives of any SAE that occurs in the course of the study within 1 day (i.e., immediately but no 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.

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

If follow-up indicates a change in the SAE from serious to fatal or life-threatening, this information needs to be available in the WBDC system within 1 calendar day.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca within 1 day as described above. For a non-serious AE that becomes serious but which is not fatal or life-threatening a report should be received within 5 days.

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

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. The investigator is responsible for informing the Ethics Committee/IRB and/or the Regulatory Authority of the SAE as per local requirements. In countries implementing the EU Clinical Trials Directive, this will be taken care of by AstraZeneca (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, 6, 7, 8, 9 and 10.

– At Visits 3, 5, 6, 7, 8 and 9 the following abbreviated clinical chemistry tests will be performed: ALT (SGPT), AST (SGOT), creatine kinase and serum creatinine.

– At Visits 1 and 10 the following clinical chemistry tests will be performed: albumin, total bilirubin, blood urea nitrogen, creatine kinase, serum creatinine, calculated creatinine clearance, ALT (SGPT), AST (SGOT), fasting glucose, alkaline phosphatase, phosphorus, potassium, calcium, sodium, total protein, gamma-glutamyl transferase (GGT) and HbA1c. GFR will be calculated from the serum creatinine concentrations at Visits 1, 3, 5, 6, 7, 8, 9 and 10. Thyroid-stimulating hormone (TSH) will be measured at Visit 1 only.

Haematology testing will be performed at Visits 1, 3, 8 and 10 which will consist of: platelet count, haemoglobin, haematocrit, RBC count, RBC indices (MCV, MCH, MCHC), WBC count and WBC differential (neutrophils, bands, lymphocytes, monocytes, eosinophils and basophils).

Three 10 mL FMV urine samples will be collected for central laboratory analysis at Visits 3, 7, 8, 9 and 10. Urine chemistry analysis will consist of urine protein, albumin and creatinine, urine retinol binding protein and urine IgG. Urinalysis will also be performed on one of these FMV samples at Visit 3, 8 and 10. At Visit 1 a separate urine sample will be collected for urinalysis as FMV urines are not collected. At all visits, urinalysis will include visual description (colour and appearance), a dipstick test (specific gravity, pH, protein (qualitative), haematuria, glucose, ketones, bilirubin and blood), microscopy (red blood cells, white blood cells, bacteria, casts and crystals). Urine samples will be frozen to permit future analysis, including gel electrophoresis, if required.

An assay of serum beta-HCG concentration will be performed for women of childbearing potential at Visit 1. If the test is positive for pregnancy, the patient should not enter the study. An assay of serum beta-HCG concentration will be performed at subsequent visits if it is suspected that the patient may have become pregnant. If the test is positive for pregnancy the patient will be discontinued from the study.

In the event of elevated liver function tests, see Appendix D 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 E for guidance with regards to management of increased creatine kinase.

See Appendix H for guidance with regards to decreased eGFR. In the event that estimated GFR decreases to ≤ 20 ml/min/1.73m^2, the patient should be withdrawn from the study.

The volume of blood to be collected is detailed in section 4.8.

4.7.2.2 Derivation or calculation of outcome variables

All analysis will be performed by the central laboratory. A urine dipstick will be performed by the investigator in the clinic at Visit 1.

Please refer to section 4.7.1.2 for details on how AEs based on laboratory assessments should be reported and recorded.

4.7.3 Vital signs and physical examination

4.7.3.1 Methods of assessment

Vital signs will be measured at all visits. This will include blood pressure and resting heart rate.

A full physical examination including weight will be performed by the investigator at Visits 1 and 10. Height and waist circumference will additionally be measured at Visit 1.

4.7.3.2 Derivation or calculation of outcome variables

The patient should be requested to sit for 5 minutes before resting heart rate and blood pressure are measured. Blood pressure will be measured 3 times at each visit, and the mean of these three readings will be recorded in the eCRF.

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 6 Volume of blood to be drawn from each patient

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Pharmacodynamic (lipid assays)		10	7	70
Pharmacodynamic (lipid assays) - samples for storage		10	4	40
Safety	Clinical chemistry	7.5	8	60
	Haematology	3	4	12
Total				182 mL

The total volume of blood associated with the scheduled protocol visits should not exceed 182 mL. Additional samples may additionally be required if unscheduled visits are performed or repeats are necessary because of issues with storage/transportation etc.

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. The patient population in this study are not expected to be of a high infective risk, although there is a possibility that some high infective risk patients may be included. 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 appropriate documentation should accompany the samples.

4.8.1 Analysis of biological samples

4.8.1.1 Clinical chemistry 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. 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.

4.8.1.2 Pharmacokinetic samples (Not applicable)

5. DATA MANAGEMENT

Electronic CRFs (eCRFs) will be provided for the recording of data. 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 instructions manual. The instructions manual will also provide the study site with data entry instructions. If any data are not available, omissions will be indicated on the record forms. 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.

Laboratory data will be electronically transferred to AstraZeneca. 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

Coding will be performed according to the Medical Dictionary for Regulatory Activities (MedDRA) and the World Health Organisation Drug Dictionary (WHODD).

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

6.1 Statistical evaluation – general aspects

Statistical analysis will be performed by statistical personnel at AstraZeneca in accordance with a comprehensive Statistical Analysis Plan (SAP) which will be prepared before unblinding of the data. Tables and listings will be produced using the computer package Statistical Analysis System (SAS®).

Data may be combined with data from the PLANET I study in diabetic patients with progressive renal disease (study code D3569C00007).

6.2 Description of outcome variables in relation to objectives and hypotheses

Each outcome variable relates to the corresponding objective as described in Section 4.6.

Primary efficacy outcome variable

- change in urinary protein/creatinine ratio from baseline to 52 weeks

Secondary efficacy outcome variables

- change in urinary protein/creatinine ratio from baseline to 26 weeks
- change in urinary albumin/creatinine ratio from baseline to 26 and 52 weeks
- percent change from baseline in lipids and lipoproteins (LDL-C, TC, HDL-C, nonHDL-C, TG, ApoA-1, ApoB, TC/HDL-C, LDL-C/HDL-C, nonHDL-C/HDL-C and ApoB/ApoA-1) after 26 and 52 weeks and relationship between renal effects and lipid changes after 26 and 52 weeks
- change in estimated GFR from baseline to 26 and 52 weeks

Secondary safety outcome variables

- Safety evaluation as determined by the incidence and severity of adverse events and abnormal laboratory values

6.3 Description of analysis sets

Efficacy

Efficacy data will be evaluated based on the intention-to-treat (ITT) and per-protocol (PP) populations.

The ITT population will consist of randomised patients who have a baseline reading and at least one post-baseline reading for at least one efficacy variable, and who have taken at least one dose of study medication. The PP population will consist of all patients in the ITT population who did not have a major protocol violation or deviations that would be likely to affect the efficacy outcomes (for example, adjustment of ACE inhibitors or ARBs).

Patients will be evaluated using randomised treatment/dose (i.e., rosuvastatin 10 mg, rosuvastatin 40 mg, or atorvastatin 80 mg) for the ITT efficacy analyses, and actual treatment/dose received for the PP efficacy analyses.

For the test of superiority (versus baseline), the ITT population is the primary analysis population. Analyses of the ITT population will be performed using the last observation carried forward (LOCF) method and also using observed data. The LOCF analysis is the primary analysis. LOCF is defined as the last non-missing post-baseline value for a variable carried forward. If no non-missing value exists after baseline, the value will be treated as missing in the analysis. LOCF is a conservative approach since urinary protein/creatinine ratio, urinary albumin/creatinine ratio, estimated GFR, and lipid levels would be expected to either improve over time or remain constant in the presence of treatment. The analyses will be repeated for the PP population as a robustness check using only observed data. Any differences in interpretation of the results from the ITT population will be explored. For tests of no clinically significant deterioration from baseline the ITT and PP populations will be considered equally important.

Safety

The randomised safety population will consist of all patients who were randomised and took at least 1 dose of study medication. Safety data will be evaluated using actual treatment/dose received. In addition safety data from the lead-in period will be evaluated for all patients who enter the lead-in period.

The safety, ITT, and PP populations (including violations and deviations) will be determined prior to treatment unblinding.

6.3.1 Patient characteristics and discontinuation

The number of patients in each population will be presented. The number of patients discontinued and reasons for discontinuation during the lead-in period and during the randomised treatment period will be presented. Demographic data and other baseline characteristics will be presented for all randomised patients by randomised treatment/dose.

6.4 Method of statistical analysis

6.4.1 Efficacy

6.4.1.1 Urinary protein/creatinine ratio

The urinary protein/creatinine ratio will be calculated as urine protein concentration (mg/dL) divided by urine creatinine concentration (g/dL), expressed as mg/g. The geometric mean of the ratios calculated from each of the 3 FMV will be considered the value at each evaluation time point. The baseline for urinary protein/creatinine will be based on the available readings corresponding to Visit 3. The outcome variable is the change from baseline in the log transformed urine protein/creatinine ratio.

Hypothesis testing will be undertaken to assess whether the decrease from baseline is significantly different from zero (i.e. that a particular treatment has had a positive effect, compared to baseline) for rosuvastatin 10 mg and rosuvastatin 40 mg. The same testing will be performed for the atorvastatin 80 mg group. No adjustment will be applied for the two rosuvastatin groups since the hypothesis testing in each of the treatment groups is independent. Evidence of no clinically significant deterioration from baseline will also be assessed in each treatment group using confidence intervals.

The effect on change in urinary protein/creatinine ratio from baseline will be estimated from an analysis of variance (ANOVA) model of the log transformed urinary protein/creatinine data. A separate model will be fitted for each treatment arm. Factors that will be considered in the model include centre (or pooled centre if required), baseline GFR, baseline protein/creatinine ratio, and baseline systolic blood pressure. Adjusted means will be weighted by centre.

The results will be presented as an adjusted mean ratio (post:pre treatment), with associated 95% confidence intervals and p-value. If the 95% confidence interval also lies entirely below 1.0 and a statistically significant p-value ($p<0.05$) is found, then a positive effect compared to baseline will be concluded. If the 95% confidence interval for the post:pre treatment ratio lies entirely below 1.1, then no clinically significant deterioration from baseline will be concluded.

Depending on the distribution of patients across centres, it may be sensible to pool some smaller centres together by country or region. The will be discussed and agreed by biostatistical personnel and the clinical team at AstraZeneca before treatment unblinding.

Residual analyses will be performed on all ANOVA models fitted, and if the model assumptions are found not to be realistic, alternative transformations or analyses will be performed.

For tests of superiority (versus baseline), the primary analysis will be performed using last observation carried forward (LOCF) after 52 weeks in the ITT population. As a robustness check, a sensitivity analysis will be performed on the observed data in the ITT population and the PP population. Analysis of change from baseline to 26 weeks will be similarly performed

as a secondary efficacy outcome variable. For tests of no clinically significant deterioration from baseline the ITT and PP populations will be considered equally important.

As a secondary exploratory analysis, 95% confidence interval will be presented for the estimate of the difference in treatment effects between the three treatment groups (ie between rosuvastatin 10 mg and atorvastatin 80 mg, between rosuvastatin 40 mg and atorvastatin 80 mg, and between rosuvastatin 10 mg and rosuvastatin 40 mg). This will be estimated from an ANOVA model as above but with an additional factor for treatment. It is recognised that this analysis is for data description only since the study is not powered to show a difference between treatment groups.

6.4.1.2 Urinary albumin/creatinine ratio

The urinary albumin/creatinine ratio will be calculated as urine albumin concentration (mg/dL) divided by urine creatinine concentration (g/dL), expressed as mg/g. The geometric mean of the ratios calculated from each of the 3 FMV will be considered the value at each evaluation time point. The baseline for urinary albumin/creatinine will be based on the available readings corresponding to Visit 3. The outcome variable is the change from baseline in the log transformed urinary albumin/creatinine ratio.

Hypothesis testing will be performed for change from baseline to 26 weeks and 52 weeks as described for urinary protein/creatinine ratio.

6.4.1.3 Lipids and lipoproteins

Percentage change from baseline in lipids and lipoprotein at Weeks 26 and 52 for each treatment group will be assessed using descriptive statistics. The baseline for lipid values and lipid ratios will be the mean value of the available readings from Visits 3 and 4. The baseline for lipoproteins and lipoprotein ratios will be the reading from Visit 4.

ANOVA will be performed on the lipid and lipoprotein data at Weeks 26 and 52, comparing rosuvastatin 40 mg with atorvastatin 80 mg. Factors will be included in the model for treatment and centre (or pooled centre if required). Adjusted means will be weighted by centre. The results from these comparisons will be presented as adjusted means and the difference between adjusted means, with associated 95% confidence intervals and p-values. Rosuvastatin 10 mg will not be formally compared with atorvastatin 80 mg.

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

Residual analyses will be performed on all ANOVA models fitted, and if the model assumptions are found not to be realistic, alternative transformations or analyses will be performed.

The relationship between changes in lipids and renal effects will be explored. Details will be provided in the SAP.

6.4.1.4 Glomerular filtration rate (GFR)

GFR will be estimated using the modified MDRD equation [Levey et al, 1999]:

MDRD GFR = 186 x (serum creatinine in mg/dL)$^{-1.154}$ x (age in years)$^{-0.203}$ x (0.742 if female) x (1.210 if black)

The outcome variable is the change in estimated GFR. The baseline for estimated GFR will be based on the available reading from Visit 3.

Hypothesis testing (for superiority only) will be performed on change from baseline to 26 weeks and 52 weeks based on the untransformed values. Otherwise the hypothesis testing will be performed as described for urinary protein/creatinine ratio.

6.4.1.5 Other assessments

Descriptive statistics of changes in urine IgG and urine retinol binding protein will be presented. No formal testing will be performed.

6.4.2 Safety

Adverse events will be classified according to two definitions:

- reported during the lead-in period
- treatment emergent during the randomised treatment period (any event that starts during the randomised period or is ongoing from the lead-in period and subsequently worsens [increases in intensity] during the randomised period). An adverse event that starts on one dose/treatment and increases in intensity on a subsequent dose/treatment will be considered treatment emergent on both doses/treatments. Any adverse events starting/worsening up to 30 days after the last dose of study medication will be classified as treatment emergent.

Any reported adverse event that starts/worsens more than 30 days after last dose of study medication will not be classified as treatment emergent.

The incidence of adverse events will be categorised by system organ class and preferred term according to MedDRA and will be tabulated by treatment/dose. Tests of statistical significance will not be performed.

Haematology, clinical chemistry, vital signs, physical exam, other urinalysis data, and other safety data will be summarised using descriptive statistics.

6.5 Determination of sample size

The primary outcome variable for this study which the sample size calculation has been based on is the change in urinary protein/creatinine ratio from baseline to Week 52.

Hypothesis testing will be undertaken to assess whether this change from baseline in urinary protein/creatinine is significantly different from zero (i.e., testing for a positive effect compared to baseline) for each of the rosuvastatin 10 mg and rosuvastatin 40 mg treatment groups. Evidence of no clinically significant deterioration from baseline will also be assessed using pre-specified limits. Similar hypothesis testing will also be performed for the atorvastatin 80 mg group.

No adjustment will be applied for the two rosuvastatin groups since the hypothesis testing in each of the treatment groups is independent. Therefore a 2-sided significance level of 5% will be applied for testing for a positive effect versus baseline and a 95% confidence interval will be assessed for testing for no clinically significant deterioration from baseline of the primary outcome variable in each of the treatment groups. The required power is 90%.

Protein excretion information from the literature has been used as an estimate for urinary protein/creatinine ratio [Bianchi et al 2003, Lee et al 2002]. Protein excretion is log normally distributed, therefore treatment ratios are appropriate to represent effects in each treatment group. It is assumed that the rosuvastatin 10 mg effect will be similar to that in the literature and rosuvastatin 40 mg will be assumed to have a similar effect to rosuvastatin 10 mg. Three replicates of both the baseline and post-treatment measurement will be taken in an attempt to reduce the variability of the primary outcome variable.

Data taken from the literature suggest that a coefficient of variation (CV) of 75% would be a conservative estimate of the variability. Assuming a treatment ratio (pre treatment:post treatment of urinary protein/creatinine) of 0.80 and a CV of 75% approximately 97 evaluable patients per group would be required to show an effect versus baseline.In this study, ‘no clinically significant deterioration (from baseline)’ is defined as an increase in the protein/creatinine ratio from baseline to 52 weeks of less than 10%. The literature does not indicate any recognised clinical level of ‘no clinically significant deterioration from baseline’. Changes seen in non-statin treated patients have shown an increase of 15% over 12 months [Bianchi et al 2003] and also a 10% decrease over 6 months [Lee et al 2002] in protein excretion. It is considered that an annual increase from baseline of less than 10% would not be clinically significant and, based on the literature, this level of change could be considered normal in a non-statin treated population. Therefore a value of 1.1 for the post:pre treatment ratio may be considered reasonable for a limit to assess for no clinically significant deterioration from baseline.

With 97 evaluable patients per group, a treatment ratio of 0.80, and a CV of 75% it is expected that the study will have >99% power to show that the 95% confidence interval is below 1.1. If the treatment ratio is 0.90 then there will still be about 83% power.

To allow for approximately 15% dropout (non-evaluable patients) approximately 115 randomised patients per treatment group will be required (total of 345 randomized patients in the study). Assuming a screen failure rate of approximately 70%, around 1150 patients are required to enter the study.

6.6 Interim analyses (Not applicable)

6.7 Committees

6.7.1 Safety Committee

An independent Safety Committee will be established prior to the first patient enrolled to monitor the safety aspects of this study in accordance with the Safety Committee Charter. This Safety Committee will be provided with safety data at regular intervals throughout the study and will begin to review data starting approximately 6 months after the first patient is enrolled. They will receive the randomisation scheme prior to the first patient enrolled to allow them to review this data unblinded. AstraZeneca and the Steering Committee will not be permitted to access the unblinded data. The Safety Committee will be responsible for making recommendations to AstraZeneca and the Steering Committee regarding safety concerns, modifications or stopping the study.

6.7.2 Steering Committee

A Steering Committee will be established with representatives from multiple countries. The Steering Committee will have responsibility for ensuring that the study is carried out to high scientific and ethical standards in accordance with the Steering Committee Charter. The members will meet periodically to review the study conduct and progress and resolve any other study related issues and will liase with the Safety Committee and AstraZeneca regarding the study for reasons of ethics, safety or efficacy. All Steering Committee members will remain blinded to the study data during the study.

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 protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement 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 protocol, that data are being accurately recorded in the eCRFs, and that investigational product 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 (e.g., 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 Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the centre to perform audits or inspections, including source data verification. The purpose of an AstraZeneca audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (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 Co-ordinating Investigator and AstraZeneca.

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

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

AstraZeneca will distribute amendments and new versions of the protocol to each principal investigator(s), who in turn is responsible for the distribution of these documents to his or her IRB or IEC, 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 Clinical Study Agreement for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the Clinical Study Protocol 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 Clinical Study Protocol and other agreements between AstraZeneca and the Principal Investigator/Study Site.
- approval of the study by the IRB/IEC.
- 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 28 months

Estimated date of last patient completed (defined as date of the last visit of the last subject) is

8. ETHICS

8.1 Ethics review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favourable opinion in writing by an IRB or IEC 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 IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the study. The protocol must be re-approved by the IRB or IEC annually, as local regulations require.

AstraZeneca will provide IECs and the principal investigators with safety updates/reports according to local requirements.

The principal investigator is also responsible for providing the IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca will provide this information to the principal investigator.

Progress reports and notifications of serious and unexpected adverse drug reactions will be provided to the IRB or IEC 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 Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, 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, including the following:

- Asking the patient to attend the clinic fasted at the first visit.

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.

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 patient initials, e-code and study code.

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

9. PROCEDURES IN CASE OF EMERGENCY, OVERDOSE OR PREGNANCY

9.1 AstraZeneca emergency contact procedure

In the case of a medical emergency, contact the Global or European study team physician on the numbers shown below.

Role in the study	Name	Address & telephone number
ST Leader responsible for the protocol at central R&D site		
ST Physician responsible for the protocol globally at central R&D site and US sites		
ST Physician responsible for the protocol at European sites		

Role in the study	Name	Address & telephone number
24-hour emergency cover at central R&D site	The caller should ask to be put in touch with the person on call from the Crestor clinical team.	
Central laboratory contact details are available in the Central Laboratory Manual.		

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.**

The treatment code may not be broken unless in an emergency situation when the appropriate management of the patient necessitates knowledge of the treatment allocation. In such an emergency, the investigator will, if time and circumstances permit, contact the local study monitor prior to breaking the treatment code. If the code is broken, the date, time and reason should be recorded and the investigator should sign the record.

9.3 Procedures in case of overdose

Doses of study treatment in excess of that specified in the study protocol are considered to be an overdose. There is no specific antidote to rosuvastatin. Experience of overdose with other statins is limited. The patient should be treated symptomatically and supportive measures instituted as required.

Use of study medication in doses in excess of that specified in the protocol should not be recorded in the eCRFs as an AE of 'Overdose' unless there are associated symptoms or signs.

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 AZ "Clinical Study Overdose Report Form."

An overdose with associated SAEs should be recorded as the SAE diagnosis/symptoms on the relevant AE forms in the eCRFs.

An overdose without associated symptoms should not be recorded as an AE in the eCRFs. The overdose should be reported on the separate AZ "Clinical Study Overdose Report Form".

9.4 Procedures in case of pregnancy

Women who are pregnant, planning a pregnancy or not using reliable mechanical or chemical contraception are not permitted to enter this study.

If a patient becomes pregnant during the study they will be discontinued from the study.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication.

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 to AstraZeneca on the pregnancy outcomes report form. The first part of the form is used to collect information before the outcome of the pregnancy is known. The form should be completed as soon as possible after it has been identified that the patient received study drug during pregnancy and should be reported to the appropriate AstraZeneca Drug Safety Department within 45 days. The second part of the form records the outcome of the pregnancy and should be sent to the appropriate AstraZeneca Drug Safety Department within AE or SAE timeframes, or within 45 days if the outcome of pregnancy is a normal birth.

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AstraZeneca

Clinical Study Protocol: Appendix B

Drug Substance	Rosuvastatin
Study Code	D3569C00011
Appendix Edition Number	1.0
Appendix Date	

Appendix B
Additional Safety Information

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

Life-threatening

'Life-threatening' means that the subject 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 subject'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 subject 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 subject 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 subject 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.

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Clinical Study Protocol Appendix C	
Drug Substance	Rosuvastatin
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Appendix C
Insurance and Indemnity

INSURANCE AND INDEMNITY

AstraZeneca's liability is covered by a liability insurance policy, please contact your AstraZeneca representative for further information.

With respect to any liability directly or indirectly caused by the investigational products in connection with this Clinical Study, AstraZeneca assumes liability by law on behalf of the investigator(s) and his assistants for possible injury to the subject provided the investigator(s) and his assistants have followed the instructions of AstraZeneca in accordance with this protocol and any amendments thereto, that the investigational products administered to the subject in this Clinical Study have been supplied by AstraZeneca and that the investigator and his assistants have in general performed this clinical study in accordance with scientific practice and currently acceptable techniques and know-how.

AstraZeneca can forward a letter of indemnity if needed by the investigator(s)/institution.

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Clinical Study Protocol Appendix D

Drug Substance	Rosuvastatin
Study Code	D3569C00011
Appendix Edition Number	1.0
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Appendix D
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 at least 48 hours apart. 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.

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Clinical Study Protocol Appendix E	
Drug Substance	Rosuvastatin
Study Code	D3569C00011
Appendix Edition Number	1.0
Appendix Date	

Appendix E

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.

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Clinical Study Protocol Appendix F	
Drug Substance	Rosuvastatin
Study Code	D3569C00011
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Appendix F

National Institute of Health (NIH) National Cholesterol Education Programme (NCEP) TLC Diet

NIH National Cholesterol Education Programme
TLC 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
• Fibre	20-30 g/day
• Protein	Approx 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 predominately from food rich in complex carbohydrates including grains, especially whole grain, fruits and vegetables.

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

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Clinical Study Protocol Appendix G

Drug Substance	Rosuvastatin
Study Code	D3569C00011
Appendix Edition Number	2.0
Appendix Date	

Appendix G
Optional Genetic Research

GENETIC RESEARCH SYNOPSIS

A Randomised, Double-Blind, 52-week, Parallel-Group, Multicentre, Phase IIb Study to Evaluate the Effects of Rosuvastatin 10 mg, Rosuvastatin 40 mg and Atorvastatin 80 mg on Urinary Protein Excretion in Hypercholesterolaemic Non-Diabetic Patients with Moderate Proteinuria

PLANET II: Prospective evaLuation of ProteinuriA and reNal function in non-diabETic patients with progressive renal disease

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 trial protocol 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 or Institutional Review Board 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 planned for genetic sampling

Approximately 160 centres worldwide will recruit patients to reach the goal of 345 randomized patients. However, difficulties with recruitment have led to a reduction of the number of patients expected to be randomized from 345 to 225. These patients will be eligible to participate in the 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 atorvastatin
- susceptibility to and prognosis of cardiovascular disease, renal disease, metabolic 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, genotype, or haplotype) frequencies in cases and controls;

and/or

Comparison of clinical outcomes or other endpoints relevant to drug response (e.g., LDL-cholesterol 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 have been randomised to treatment with study drug in the main study and who provide separate, optional consent for this genetic research.

Co-variables

These cannot be specified in advance because they will depend on the particular phenotype (i.e., 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 consent to take part in this genetic research cannot be predetermined. An appropriate statistical analysis plan will be prepared prior to the generation and analysis of genotypic data.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS RELEVANT TO GENETIC RESEARCH

Abbreviation or special term	Explanation
DNA	Deoxyribonucleic acid
EDTA	Ethylenediamine tetra-acetic acid
Genetic sample	A blood sample collected for genetic research and any DNA that has been prepared from it
LIMS	Laboratory Information Management System

1. RATIONALE FOR OPTIONAL GENETIC RESEARCH

AstraZeneca are conducting numerous investigations into the effects of genetic variation on drug response and on susceptibility to disease. The ultimate goal is to bring safer and more effective drugs to market. Research on genetic susceptibility to disease may lead to the identification of novel molecular targets for therapeutic intervention. Research on the genetics of drug response may lead to improvements in the design and interpretation of clinical trials and, in some situations to genetically guided treatment strategies.

In particular, AstraZeneca are collecting genetic samples in selected clinical trials involving rosuvastatin. An archive of appropriately consented samples from these trials is essential for realizing 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. OBJECTIVES OF GENETIC RESEARCH

The objective of this genetic research is to obtain DNA samples, with appropriate informed consent, for future exploratory research on the effects of genetic polymorphisms on:

- response to rosuvastatin and atorvastatin
- susceptibility to and prognosis of cardiovascular disease, renal disease, metabolic disorders, including diabetes 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 or laboratory parameters for which data are being collected in the main study.

Genes that may be investigated include the following:

- 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, e.g., hepatocytes, renal tubular cells, intestinal epithelium, muscle, or other cells. Variations in genes encoding such transporters could plausibly influence statin pharmacokinetics or response.
- Genes coding for drug metabolising enzymes. Variations in these genes may contribute to pharmacokinetic 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 clinical trials.

- Genes with potential relevance to susceptibility to adverse effects associated with statins or other lipid-lowering medications.

Undoubtedly, future research will suggest other genes or gene categories as candidates for influencing not only response to statin therapy but also susceptibility to and outcome of lipid disorders, cardiovascular disease, renal disease, metabolic disorders and other conditions for which statin therapy may prove beneficial. The optional consent form for this genetic research therefore requests permission to study how genes are involved in disease susceptibility and drug response, and does not list specific genes by name. It is important to note, however, that the genetic samples in this study will not be used for purposes other than those listed above.

3. GENETIC RESEARCH PLAN AND PROCEDURES

3.1 Genetic research plan

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

The patient will ordinarily be asked to participate in this genetic research as soon as possible after randomisation in to the main study. If the patient agrees to take part, a single blood sample will be taken. This will ordinarily occur at the next scheduled visit following consent in to the genetics Appendix, but may take place at another scheduled visit, or, if necessary, at a specially arranged visit.

3.2 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 in this genetic research is entirely voluntary. Thus, a patient who declines to participate in this genetic research will not be excluded from participation in the main study or experience other penalty or loss of benefit.

3.2.2 Inclusion criteria

Patients must fulfil all of the inclusion criteria described for the main study **and**:

- Provide separate, optional informed consent for this genetic research.

3.2.3 Exclusion criteria

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

- Previous bone marrow transplant

- Blood transfusion in the 120-day period preceding the date of genetic sample collection.

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 include:

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

3.2.4.2 Procedures for discontinuation

A patient who discontinues participation in the main study should be asked if he or she also wishes to continue participation in, or withdraw from, this genetic research. In other words, it must be clearly determined whether the patient:

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

- wishes to withdraw consent for genetic sample storage and possible future genetic research.

In the latter case the genetic sample will be destroyed. It is important to note that genetic sample destruction is possible only so long as it is traceable i.e. not anonymous. If any genetic data has already been generated, AstraZeneca will retain this data for regulatory purposes but will not use such data in any subsequent analyses. Where possible, reasons for withdrawing should be noted.

The principal investigator is responsible for providing written notification to AstraZeneca if a patient withdraws consent for genetic research. This notification should identify the patient by his or her enrolment code (e-code), and not by name or other personal identifier. AstraZeneca will provide written confirmation to the investigator that the corresponding genetic sample has been destroyed. The investigator should communicate this to the patient, and keep this document on file at the study site.

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 exploratory studies. Such studies will explore the effects of genetic variation on response to rosuvastatin and atorvastatin and/or susceptibility to or prognosis of cardiovascular disease, renal disease, lipid

and metabolic disorders, or other disorders for which statins may prove beneficial if relevant clinical data is being collected in the main study. The results of this genetic research will not form part of the clinical study report, but will be described in supplementary reports when available. Data from this genetic research may be pooled and analysed with data from other studies. The scope of any such meta-analyses will not exceed that set by the consent of the individual 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 five times to mix thoroughly. The tubes will be labelled with the main study number, the centre number, the e-code and date of sample collection. No personal identifiers (e.g., patient name, initials, date of birth, social security number etc.) will be placed on the tube or accompanying documentation. A record of the date of patient consent to genetic research and the date of the collection of the corresponding blood sample should be recorded in the appropriate section of the CRF.

Genotype is a stable parameter, therefore if for any reason the blood sample is not drawn at the first scheduled visit after consenting to the genetics appendix, it may be taken at another visit that has been scheduled for the main study, or at a specially arranged visit. To minimise unnecessary venipuncture, the blood sample should ordinarily be drawn through the same cannula used to obtain a blood sample required for the main study.

4.2.1 Sample processing and shipping

Blood samples for genetic research will be shipped at ambient temperature so that they arrive at the central laboratory within 48 hours of being drawn . If it is not possible to ship a sample on the same day that it is collected, it should be stored overnight at 4° C and shipped at ambient temperature the next day.

Where it is not possible for the samples to be received at the central laboratory within 48 hours of being drawn, then samples should be frozen (-20^{o}C *or below*) and shipped frozen to the central laboratory within one month of collection. Samples must remain frozen at all times.

If possible, blood samples shipment should be coordinated with the receiving site to ensure that samples arrive within working hours, on normal working days. A requisition sheet, detailing the protocol study number, centre number, e-code and date of sample collection, should accompany the shipment.

4.2.2 Storage and coding of DNA samples

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

The genetic samples from this study and data generated from them will be "coded", the procedure for which is as follows. Upon arrival in the DNA extraction laboratory, the blood sample provided for genetic research will be assigned a unique number, referred to as a DNA number, that replaces the original e-code on the sample tube. DNA will then be extracted from the blood sample. The DNA sample, and a small amount of residual blood (retained exclusively for purposes of quality control) will thereafter be identifiable only by the unique DNA number. The DNA number will used to track the genetic sample and corresponding genetic data at the AstraZeneca genetics laboratories or at a designated contract laboratory. No personal details identifying individual patients will be available to any AstraZeneca employee working with the DNA. AstraZeneca may store the genetic samples for a period of 20 years after the main study has finished, but are not obliged to do so. Samples will be destroyed on request as discussed in section 3.2.4.2

Only the investigator has information that connects a patient's personal identity with his or her e-code. However, a link between the patient's e-code and the corresponding DNA number will be maintained at AstraZeneca. This link, and any genetic data generated from research on the patient's DNA sample, will be stored in a secure, restricted-access environment within the Clinical Genotyping Group Laboratory Information Management System (LIMS) at AstraZeneca, Alderley Park, UK. This link may be used (1) to identify relevant DNA samples for analysis, (2) to facilitate correlation of genotypic results with clinical data, (3) to allow regulatory audit and (4) to trace samples for destruction in case of withdrawal of consent for genetic research. Access to the link file will require written authorisation from the Clinical Development Team Leader.

All genetic samples will be stored under secure conditions with restricted access at AstraZeneca or at a contracted laboratory. The genetic samples and data derived from them may be made available to groups or organisations working with AstraZeneca. However, these samples and data will remain the property of AstraZeneca at all times. AstraZeneca will not give genetic samples or data derived from them 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 polymerase 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 immortalized.

5. GENETIC DATA MANAGEMENT

Only the date of consent to participate in this genetic research, and the date the corresponding blood sample was collected will be recorded in the CRF and entered into the database used for the analyses of data for the objectives described in the main study. Specifically, genetic data will not be entered or merged into this database.

Instead, the genotypic data generated from the study will be stored in an entirely separate, secure database (generally, the AstraZeneca LIMS database). Some or all of the clinical study dataset may be duplicated within this genetic analysis database to enable exploratory genetic analysis.

5.1 Reporting of results of genetic research

The purpose of the genetic research is to generate data for use in future retrospective analyses. Future analyses will explore genetic factors that may influence the disposition, efficacy, safety and tolerability to rosuvastatin and/or susceptibility to or prognosis of cardiovascular disease, renal disease or lipid and metabolic disorders under investigation in the main study protocol. The results of the genetic research will not form part of the clinical study report for this study, but will be described in supplementary reports when available. The results may be pooled with genetic data from other studies on rosuvastatin to generate hypotheses to be tested in future studies. The scope of any such meta-analyses will not exceed that set by the consent of the individual studies.

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. Genetic samples will not be used for any purpose other than those described in this appendix.

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

Either of two approaches will generally be employed to study polymorphisms in genes of interest:

(1) Comparison of marker (allele, genotype, or haplotype) frequencies in cases and controls

and/or

(2) Comparison of clinical outcomes or other endpoints relevant to drug response (e.g., LDL-cholesterol lowering) in genetically defined groups.

In the future new technologies, such as whole genome analysis, may be feasible and may be employed on this sample set. In all cases, samples will only ever be used within the scope of the objectives set out in this appendix.

The number of patients who will agree to participate in the genetic component of this study 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. An appropriate statistical analysis plan will be prepared prior to genotyping of samples.

For studies of genetic susceptibility to disease, appropriately consented control samples will be derived from other sources.

7. STUDY MANAGEMENT

7.1 Monitoring

Before first patient entry into the study, a representative of AstraZeneca will visit the study site. In addition to the requirements described in the main body of the clinical study protocol the genetic component of the study will be discussed.

As described in the protocol for the main study, a representative of AstraZeneca will have regular contacts with the study site. One purpose 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 collection and handling of genetic samples will also be made clear.

7.3 Changes to the protocol

Any changes to this 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 is responsible for ensuring that the ethical considerations and processes for genetic sample collection and protection of patient confidentiality that are contained in this appendix, are understood and followed at the study site.

The principal investigator at each centre must also comply with all the terms, conditions, and obligations of the Clinical Study Agreement for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the Clinical Study Protocol (including this appendix) shall prevail. Specific reference to this genetic research will be included in the study agreement(s). This appendix may be approved independently of the main study protocol.

8. ETHICS

8.1 Ethics review

In addition to IRB/IEC approval of the main study, approval for this genetic research, including the corresponding consent form, must also be obtained. It should be clearly stated in the approval that the optional genetic research outlined in this Appendix is approved. The investigator must submit documentation of this approval to AstraZeneca before any patient participates in this genetic research.

8.2 Ethical conduct of genetic research

This genetic research 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.

Special precautions regarding the handling of genetic samples and data will be taken as described in section 4.2.2 of this Appendix.

8.3 Informed consent

Patients may participate in the main study without participating in this genetic research. To participate in this genetic research the patient must sign and date both the consent form for the main study and the consent form for this optional genetic research. 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 patients understand that they may freely discontinue participation in this genetic research at any time.

8.4 Patient data protection

All of the principles regarding data protection and confidentiality described in the main body of the clinical study protocol are applicable to this genetic research.

Reference to participation in this genetic research should not be recorded in the patient's medical records unless required to do so by local regulations. All notes should be kept within the clinical study records.

Due to the exploratory nature of the genetic research in this study, 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 patients personal identifier, for example in the case of a medical emergency, when an AstraZeneca Physicians might know a patient's identity and might also have access to his or her genetic data, or during regulatory audit where designated authorities must be permitted access to the relevant files.

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Clinical Study Protocol Appendix H

Drug Substance	Rosuvastatin calcium
Study Code	D3569C00011
Appendix Edition Number	2.0
Appendix Date	

Appendix H
Management of Decreased Renal Function

1. MANAGEMENT OF DECREASED RENAL FUNCTION

Decreases in GFR over a 52-week period might be due to a variety of factors, including progression of underlying disease, dehydration, nephrotoxic medications, infections, etc. Therefore, some patients in the study may experience renal dysfunction after treatment with study drug which may be unrelated to study drug. In an attempt to standardise the steps to be taken in study patients with an increase in creatinine post-randomisation, the following guidelines have been developed.

Three levels of response to decreased renal function are described:

A. If at any time after enrolment a patient's estimated GFR decreases by more than 30%, the investigator should consider evaluating the patient for potentially reversible causes of renal dysfunction including:

1. concurrent use of NSAIDS, antibiotics, or other medications known to affect measures of serum creatinine
2. volume depletion
3. urinary tract infection
4. obstructive uropathy
5. use of study medication

The patient may be brought back for an unscheduled visit for a repeat blood sample at the investigator's discretion.

B. If at any time after enrolment a patient's estimated GFR decreases to <30 ml/min/1.73m^2, the investigator should look for potentially reversible causes of renal dysfunction (see above). If the GFR at 2 consecutive study visits remains <30 ml/min/1.73m^2, the investigator should temporarily stop the study drug.

If after temporary discontinuation, the GFR increases to ≥30 ml/min/1.73m^2, study medication can be re-started.

If after temporary discontinuation, the GFR remains <30 ml/min/1.73m^2, the patient should be permanently discontinued from the medication and withdrawn from the study (in which case an Adverse Event must be reported).

C. Discontinuation Point – if a patient's GFR decreases to ≤20 ml/min/1.73m^2, the investigator should permanently discontinue study drug (and an adverse event must be reported).

Repeat serum creatinine measurements should be made at least weekly until the estimated GFR value returns to an acceptable value.