AstraZeneca

Clinical Study Protocol

Drug Substance	Rosuvastatin
Study Code	DM-CRESTOR-0002
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A double blind, double dummy, phase IV, randomized, multicenter, parallel group, placebo control trial to evaluate the effect of rosuvastatin on triglycerides levels in Mexican hypertriglyceridemic patients.

Sponsor:

AstraZeneca Mexico, Mexico City.

AstraZeneca
Site representative

Ana Polanco	**Date**
Project Physician	

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	28.03.07

Administrative change No.	Date of Administrative Change	Local Administrative change No.	Date of local Administrative Change
		NA	NA

PROTOCOL SYNOPSIS

A double blind, double dummy, phase IV, randomized, multicenter, parallel group, placebo control trial to evaluate the effect of rosuvastatin on triglycerides levels in Mexican hypertriglyceridemic patients.

National Co-ordinating Investigator

Dr. Juan Talavera

Study centres and number of patients planned

The study will be conducted in approximately 330 randomised patients. They will be recruited from approximately 10 to 12 centres around Mexico and it is planned that centres should randomise approximately 30 patients each. The approximate numbers of randomised patients will be recruited from Mexico City (150 patients), Monterrey (90 patients), Guadalajara (60 patients), Toluca (30 patients) and San Luis Potosi (30 patients). Centres may be discontinued from the study if recruitment rates are poor and new centres will be added if necessary to achieve recruitment goals. Recruitment will be competitive and centres will stop enrolment when enough patients are screened to provide the projected number of randomised patients.

Study period		**Phase of development**
Estimated date of first patient enrolled	May 2007	IV
Estimated date of last patient completed (defined as date of the last visit of the last patient)	February 2008	

Objectives

Primary Objective

The primary objective of this study is to evaluate the efficacy of rosuvastatin in reducing triglycerides (TG) levels in hypertriglyceridemic (HTG) Mexican patients from baseline to week 8.

Secondary Objectives

The secondary efficacy objectives of the study are as follows:

1. To evaluate the efficacy of RSV on:
    a. Reducing non-HDL-C levels.

2. To evaluate the efficacy of RSV in improving atherogenic lipid profile on:
    a. Reduction of low-density lipoprotein cholesterol (LDL-C)
    b. Reduction of total cholesterol (TC)
    c. Increase of high-density lipoprotein cholesterol (HDL-C)
    d. Changes in apolipoprotein A1 (ApoA-1), apolipoprotein B (ApoB) and
    e. Changes in TC/HDL-C, LDL-C/HDL-C, nonHDL-C/HDL-C and ApoB/ApoA-1 index, from baseline to week 8.

3. To determine the efficacy of RSV in reducing other CV risk markers: high-sensitive C-reactive protein (hsCRP) from baseline to week 8.

Study design

This is a randomised, double-blind, double dummy, parallel-group, placebo control, national, multicentre, phase IV study to evaluate the effects of rosuvastatin 10 mg, rosuvastatin 20 mg and placebo over 8 weeks on triglycerides levels in hypertriglydemic patients.

Patients will enter a 5-week lead-in period, after which eligible patients will be randomised to receive treatment with either rosuvastatin 10 or 20 mg/day or placebo once daily for 8 weeks.

Target patient population

Male and female patients aged ≥18 years with basal triglycerides levels between ≥200 and <800 mg/dl (regardless LDL-C levels), statin naïve. Patients will be considered statin naïve when they had, at least, 6 months or more without taking any statin therapy for before visit 1.

Investigational product, dosage and mode of administration

Investigational product: rosuvastatin 10 and 20 mg
Rosuvastatin 10 mg: One tablet of rosuvastatin 10 mg + one tablet of placebo matching rosuvastatin 20 mg, once daily in oral tablet form
Rosuvastatin 20 mg: One tablet of rosuvastatin 20 mg + one tablet of placebo matching rosuvastatin 10 mg, once daily in oral tablet form
Placebo: One tablet of placebo matching rosuvastatin 10 mg and one tablet of placebo matching rosuvastatin 20 mg, once daily in oral tablet form

Duration of treatment

Patients will initially enter a 5-week lead-in period during which they will undergo Therapeutic Life Stile Change (TLC) advisory according to NCEP ATPIII guidelines (See Appendix F). In this period no lipid lowering therapy will be allowed.

At the end of the 5-week lead-in period, during visit 2, a new TG analysis will be made and eligible patients (those with TG levels between ≥200 mg/dl and <800 mg/dl on visit 2), will be randomised (on visit 2.1) with a 1:1:1 randomisation ratio to receive blinded treatment with either rosuvastatin 10 mg, rosuvastatin 20 mg or placebo. During the 8 weeks of the randomised treatment period, patients will continue with the TLC.

End Points

– **Primary end point:**

1. Change (reduction) in triglycerides levels from baseline to end of treatment (week 8).

– **Secondary end points:**

- Change (reduction) in no-HDL-C from baseline to end of treatment,.
- Change in LDL-C; TC; ApoB; ApoA1; ApoB/ApoA1; TC/HDL-C; LDL-C/HDL-C, non-HDL-C/HDL-C index from baseline to the end of treatment.
- Change in hsCRP levels from baseline to the end of treatment.

– **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 stated in the protocol

– **Safety**

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

– **Genetics**

– There are no genetics outcomes for this study

Statistical methods

Lipids and lipoproteins are: Triglycerides, no-HDL-C, LDL-C, total cholesterol, HDL-C, ApoA1, and ApoB levels and ApoB/ApoA1, no-HDL-C/HDL-C and LDL-C/HDL-C indexes. Baseline for calculating percent change in a lipid or lipoprotein will be the values from the randomization visit (visit 2.1).

The following analyses will be performed for TG:

- Last observation carried forward (LOCF) on the ITT (Intention to treat) population for primary and secondary endpoints at week 8. This will be the primary analysis.
- Observed data on the per Protocol (PP) population for primary and secondary endpoints at week 8.

Initially a Friedman analysis will be performed, then, for comparing basal state against 8 week, inside each group, a Willcoxon test will be performed. For comparing each one of Rosuvastatin groups against placebo group at week 8 a U Man Whitney test will be done. Also, the percentage of reduction –week 8 minus basal- obtained in the placebo group will be contrasted against the percentage of reduction in each one of the Rosuvastatin groups using a U Man Whitney test. In all the cases a $p< 0.05$ will be considered significant.

Lipids (other than TGs), apolipoproteins and hsCRP comprising secondary endpoint (1, 2 and 3) will be analysed in a similar way.

Adverse events can occur in the dietary lead-in phase and/or the randomised phase of the study. The latter phase will include the period up to 30 days after the last dose of study medication. All adverse events will be classified according to the following:

- Reported during the dietary lead-in period
- Treatment emergent. This is further categorized as:
  - Ongoing from the dietary lead-in period and subsequently worsening during the randomised period, and
  - Starting during the randomized period.

All adverse events will be categorized by the body system and preferred term assigned to the event using National Medical Terminology Officially Accepted terms and listed for each subject. For subjects in the dietary lead-in safety population events occurring during the dietary lead-in phase will be summarised by frequency; in the randomized safety population treatment emergent events will be reported as frequencies in each treatment group. Frequencies of adverse events leading to withdrawal from the randomized period will also be tabulated and reported by treatment group. Adverse events leading to death, serious adverse events and drug related adverse events would be presented similarly.

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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
AE	Adverse event (see definition in Section 4.8.1.1)
ALT	Alanine aminotransferase (=SGPT)
ANOVA	Analysis of variance
ApoA-1	Apolipoprotein A-1
ApoB	Apolipoprotein B
ATP III	Adult Treatment Panel III
AST	Aspartate aminotransferase (=SGOT)
BMI	Body Mass Index
β-HCG	Beta-Human chorionic gonadotrophin
C	Celsius
CK	Creatine kinase
CRF	Case Report Form
CV	Cardio Vascular
dL	Decilitre
e-code	Enrolment code
FMV	First morning void
GCP	Good clinical practice
GGT	Gamma-glutamyl transferase
HbA1c	Glycated haemoglobin
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
hsCRP	High sensitivity C-reactive protein
HTG	Hypertriglyceridemia (TG between ≥200 and <800 mg/dL)
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IRB	Institutional review board
ITT	Intention-to-treat

Abbreviation or special term	Explanation
Co-ordinating investigator	A Co-ordinating Investigator is the investigator that coordinates the investigators and/or activities nationally.
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LOCF	Last observation carried forward
mg	Milligram
mg/dL	Milligram per decilitre
MI	Myocardial infarction
mL	Millilitre
NCEP	National Cholesterol Education Program
Non-HDL-C	Non-high-density lipoprotein cholesterol
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 4.8.1.1).
Outcome variable	A variable (usually a derived variable) specifically defined to be used in the analysis of a study objective.
PD	Pharmacodynamic
PI	Prescribing Information
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 4.8.1.1).
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase (=AST)
SGPT	Serum glutamic pyrivic transaminase (=ALT)
ST	Study team
Statin naïve	Patients will be considered statin naïve if they had, at least, 6 month or more without taking any statin treatment prior to visit 1.
TC	Total cholesterol
TG	Triglycerides

Abbreviation or special term	Explanation
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

1. INTRODUCTION

1.1 Background

Hypertriglyceridemia (HTG) has been lately recognized as an independent factor for cardiovascular disease (CVD), regardless LDL-C levels(1). HTG is a component of the so-called Metabolic Syndrome (MS) along with the reduction in high density lipoprotein cholesterol (HDL-C) levels(2,3). MS is a mayor risk factor for diabetes -that in turn is a mayor risk factor of CVD -and it is recognized also as a mayor risk factor for CVD itself (2,4). It also seems that the most common dislipidemia in diabetes are HTG, low serum levels of HDL-C and an increase in the serum fraction of small dense low density lipoprotein cholesterol (LDL-C) particles(5). Serum LDL-C elevation is some times present, but is not a criteria of the metabolic syndrome.

The mechanisms by witch TGs are involved in CVD are not well establish, nevertheless, it seems it has to do with the atherogenic process. There is now some evidence that points that HTG comes along with LDL-C small dense particles (sd-LDL-C) (6). Small dense LDL particles have been suggested to be highly atherogenic due the higher penetration into the arterial wall, their low binding affinity for the LDL receptor, their prolonged plasma half- life, and their lower resistance to oxidative stress compare to that of larger LDL(7). A recent report of the Québec cardiovascular study has confirmed that predominance sd-LDL is a strong and independent predictor factor for CVD during the first 7^{th} years of follow-up(8).

In Mexico, the prevalence of MS and Diabetes had been increasing in an alarming way. There are around 6.5 million people with diabetes and as a country Mexico will pass from the 9^{th} place in the world to the 7^{th} place in 2025 in diabetes prevalence(24). From 1940 mortality due to diabetes has raised from 5 to more than 50/100,000 habitants (aprox 6 death per hour)(9, 10). During 2005, diabetes was the first cause of general mortality(11). Diabetes has been associated with HTG and low HDL-C levels. In Mexico more than 65% of diabetic population had HTG and more than 60% had low HDL-C which was significantly more than the 31-50% and 33-39% that had the non diabetic population respectively(9).

Talking about prevalence of MS is quite more difficult. It will depend on the definition use to make the diagnosis. Nevertheless, Aguilar-Salinas *et al.* made an estimation of prevalence using WHO and NCEP ATP III criterion and found that in Mexico age-adjusted prevalence was 13.61% for WHO criteria and 26.6% for the ATPIII definition. Prevalence was 9.2 and 21.4%, respectively, in subjects without diabetes. Thirty five percent of affected cases were >40 years old(12).

In a different analysis, Barquera, *et al*. found that the most common dislipidemia in Mexican population are hipoalfalipoproteinemia (HDL-C <40mg/dl) and HTG (TG>150 mg/dl). The probability of the association of low HDL-C; HTG and hypercholesterolemia is 0.080 in general population, and it rises up to 0.16 when it is associated to obesity (13).

1.2 Rationale for this study

Currently the treatments for HTG are fibrates. Although the FIELD trial proved that fenofibrate could reduce total CV events (due to myocardial infarcts and revascularization), it fails to reduce the risk of the primary outcome of coronary events (14). Other trials have demonstrated that fenofibrates can reduce significantly TG levels (-37%), but they increase LDL-C levels. It seems fenofibrates can reduce the sd-LDL and increase the larger LDL, reducing atherogenic lipid profile (15). Actually, the NCEP ATPIII guidelines recommend to first lower LDL-C levels before TG levels, especially in patients with high risk (as diabetics) to levels below 100 mg/dl or even to levels below 70 mg/dl (2, 3).

Rosuvastatin has proven to reduce LDL-C –45 to -50% in many controlled trials (16-19) and TG from –21 to –37% (20, 21); while increasing HDL-C between 7 to 10% (18-19).

For this reason, assuming that CV risk is a sum of factors that includes high LDL-C (or not so high sd-LDL), HTG and low HDL-C; modifying the whole atherogenic lipid profile will reduce CV risk in our hypertriglyceridemic patients. The rational for this study is based on the assumption that rosuvastatin will provide the necessary reduction of triglycerides and at the same time, will reduce LDL-C reducing the risk of CVD.

2. STUDY OBJECTIVES

2.1 Primary objective

The primary objective of this study is to evaluate the efficacy of rosuvastatin in reducing triglycerides levels in hypertriglyceridemic Mexican patients from baseline to week 8.

2.2 Secondary objectives

The secondary efficacy objectives of the study are as follows:

1. To evaluate the efficacy of RSV from baseline to week 8 on:
   a. Non-HDL-C levels

2. To evaluate the efficacy of RSV from baseline to week 8 on
   a. Low-density lipoprotein cholesterol (LDL-C)
   b. Total cholesterol (TC)
   c. High-density lipoprotein cholesterol (HDL-C)
   d. Apolipoprotein A1 (ApoA-1), apolipoprotein B (ApoB) and
   e. TC/HDL-C, LDL-C/HDL-C, nonHDL-C/HDL-C and ApoB/ApoA-1 indexes.

3. To determine the efficacy of RSV in reducing high-sensitive C- reactive protein (hsCRP) from baseline to week 8.

The secondary safety objective of this study is:

- To evaluate the effect of RSV on the incidence and severity of adverse events and laboratory data

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design and flow chart

This is an 8 week, randomised, double blind, double dummy, national, multicentre study with 3 parallel treatment groups: rosuvastatin 10 mg, rosuvastatin 20 mg and placebo. The primary end point of the study is the change in triglycerides levels from baseline to week 8. Approximately 10 to 12 centres will be required in order to recruit 330 randomised patients, of whom 285 to 300 are expected to be fully evaluable (i.e., to allow for approximately 10 to 15% of randomised patients being non-evaluable). The approximate numbers of randomised patients will be recruited from Mexico City (150 patients), Monterrey (90 patients), Guadalajara (60 patients), Toluca (30 patients) and San Luis Potosi (30 patients). It is anticipated that in order to achieve this number of randomised patients, approximately 990 patients will need to enter the lead-in period of the study (screen failure rate 3:1). Centres will be required to randomise approximately 30 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 cities and centres (thus, centres 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 projected number randomised.

There are 4 clinic visits planned. Visit 1 and 2 occurs during the lead-in period. Visit 2.1 is the randomisation visit, and Visit 3 occurs during the randomised treatment period, is the final visit. For visit 1, the allowed window will be +3 days, for visit 2 the allowed visit window will be ± 3 days. For visit 2.1 the allowed visit window will be ± 2 day and for visit 3 the allowed visit window will be ± 3 days.

Male and female patients aged ≥18 with hypertriglyceridemia (HTG) and statin naïve (as defined by protocol) will be recruited. Patients will then enter a 4-week lead-in period during which they will undergo TLC dietary advice (see Appendix F) and no lipid lowering therapy will be allowed. All eligible patients will be randomised in a 1:1:1 ratio to receive ether rosuvastatin 10 or 20 mg/day or placebo once a day. Patients will be followed for 8 weeks. All patients will be offered the opportunity to continue with active commercially available therapy with rosuvastatin once the protocol is complete.

Visit 1. Dietary lead-in period (week –5)

1) Provision of written informed consent.

2) Medical History including complete physical examination, anthropometrics and vital signs, weight, height, body mass index (BMI) and abdominal circumference.

3) Eligible Criteria

   a) Male and female subjects aged ≥18 years

   b) Statin naïve patients (as defined by protocol)

c) Without previous lowering lipid treatment other than statins 6 months before visit 1.

d) Fasting TG concentrations at visit 1 of: ≥200 mg/dL and <800 mg/dL.

e) Fasting LDL-C ≥100mg/dL and ≤190 mg/dL at visit 1

(**Note:** the results of the above laboratory sample will not be available at visit 1 to make the eligibility decision. Therefore, if the subject's medical history meets the eligibility criteria the subject can enter into the dietary lead-in period of the study. However, when the laboratory results are available, if the results do not meet the above criteria, the subject should be contacted and discontinued from the study)

f) Subjects willing to follow all study procedures including the attendance at clinics for scheduled study visits, fasting prior to clinic visits (Visits 1, 2 and 3 blood draws) and compliance with study treatment regimen.

4) Therapeutic Life Stile Change (TLC) advisory (see Appendix F)

5) Record of concomitant medication

6) Laboratory samples (see table 1)

7) Patients who do not meet the entry criteria should be considered screen failure and a screen failure CRF should be completed.

Visit 2. (Week –1)

Visit window allowed is ± 3 days. To continue in the study, patients should fulfil the following criterion:

1. Fasting TG ≥200 mg/dL and < 800mg/dL at visit 1.

2. Fasting LDL-C ≥100mg/dL and ≤190 mg/dL at visit 1

3. TLC advisory

4. Complete physical examination including anthropometrics and vital signs

5. Laboratory samples (see table 1)

a) Fasting TG ≥200 mg/dL and < 800mg/dL at visit 2.

(**Note:** the results of the above laboratory sample will not be available at visit 2 to make the eligibility decision. Therefore, subjects will be randomised at visit 2.1, one week after visit 2, when the laboratory results are available. If the results do not meet the above criteria, the subject will be contacted and discontinued from the study)

5. Record of Adverse Events

6. Record of concomitant medication

Visit 2.1. Randomisation (Week 0)

Visit window allowed is ± 2 day. During this visit, laboratory results of the prior visit will be available and patients fulfilling the inclusion criterion will be randomised.

1. Fasting TG ≥200 mg/dL and < 800mg/dL from visit 2.

2. Fasting LDL-C ≥100mg/dL and ≤190 mg/dL at visit 2.

3. Record of adverse events

4. Study drug will be dispensed in this visit.

5. Record of concomitant medication

Visit 3. Final (Week 8)

Visit window allowed is ±3 days. Visit 3 will occurred after 8 weeks of following patients with treatment. This will be the final visit.

1. TLC advisory

2. Complete physical examination including anthropometrics and vital signs

3. Laboratory samples (see table 1)

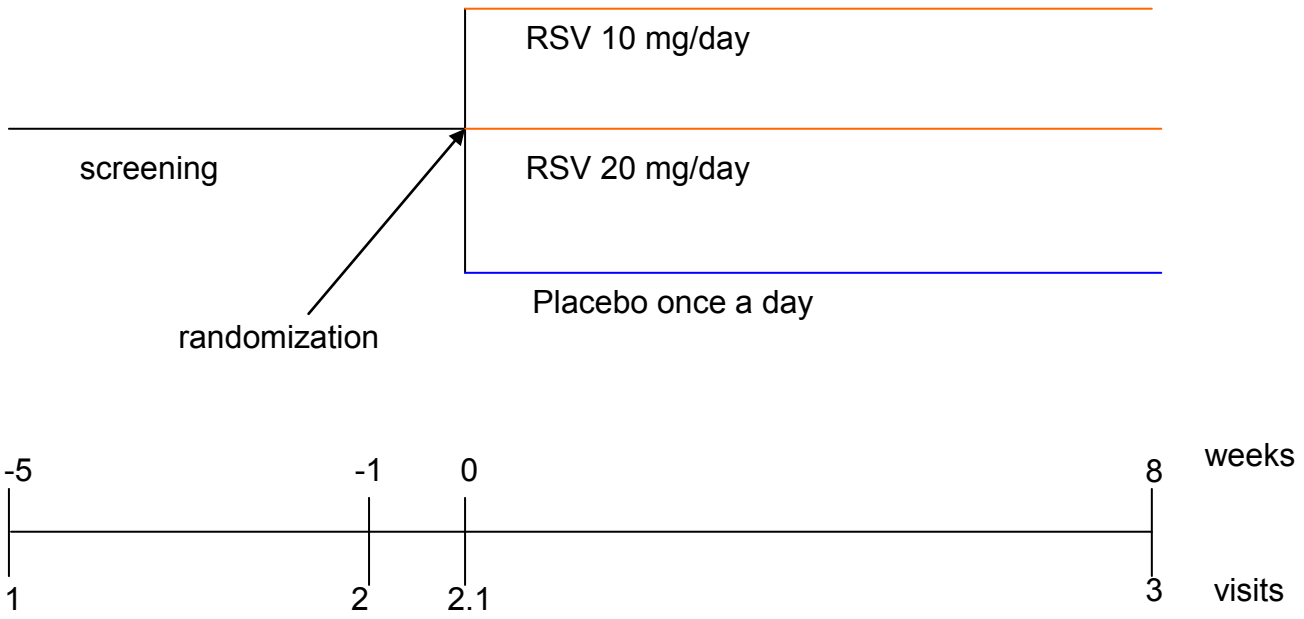
4. Record of adverse events

5. Record of concomitant medication

6. Study drug will be recovered in this visit. Tablets will be counted and noted for assessing compliance.

7. All patients will be offered the opportunity to continue with active commercially available therapy with rosuvastatin, according to the expert opinion of investigator, once the protocol is complete.

Figure 1 Study flow chart



RSV: rosuvastatin

Table 1 Study Plan

Week	**-5**	**-1**	**0**	**8**
Visit	**1**	**2**	**2.1[n]**	**3**
Visit window		**± 3 days**	**± 2 day**	**± 3 days**
Informed consent [a]	✓			
Dietary counselling	✓		✓	✓
24 hrs diet recall	✓		✓	✓
Medical history/demography	✓			
Concomitant medication	✓[b]	✓	✓	✓
Physical examination [c]	✓[d]	✓		✓
Vital signs	✓	✓		✓
Eligibility criteria [e]	✓	✓	✓	
Randomization			✓	
Fasting lipid profile [f]	✓	✓		✓
Apolipoproteins [g]		✓		✓
TSH	✓			
Glucose	✓	✓		✓
HbA_{1c}	✓			
Urinalysis [h]		✓		✓
Reduced hepatic profile [j]	✓			
Complete hepatic profile [k]		✓		✓
Urea	✓	✓		✓
Creatinine	✓	✓		✓
CK	✓	✓		✓
β-HCG [l]	✓			
hsCRP		✓		✓
Adverse events [m]		✓	✓	✓
Study drug dispensing			✓	
Study drug compliance and accountability				✓

[a] Informed consent will be taken at or before Visit 1, before any study related procedures are performed
[b] Prior medications to be collected at Visit 1

[c] Weight and waist circumference will be measured at Visits 1, 2 and 3. Height will additionally be measured at Visit 1

[d] Review and titrate if necessary patient's anti-hypertensive medication, to an individually optimised dose to a blood pressure target of <130/80 mmHg based JNCVII guidelines and investigator discretion.

[e] Patients should fulfil all inclusion criterion with no exclusion criterion to continue in the study during visit 1, 2 and 2.1.

[f] Lipid profile: TG, LDL-C, TC, HDL-C, nonHDL-C, TC/HDL-C, LDL-C/HDL-C and non-HDL-C/HDL-C

[g] Apolipoprotein analysis to include ApoA-1, ApoB, ApoB/ApoA-1 ratio

[h] 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.

[j] Reduced hepatic profile will consist of: ALT, AST and GGT

[k] Complete hepatic profile will consist of: total bilirubin, ALT, AST, alkaline phosphatase and gamma-glutamyl transferase (GGT)

[l] An assay of B-HCG will only be performed at visit 1 for women of childbearing potential.

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

[n] Patients will be randomised once the laboratory results from visit 2 are available. Study drug will be dispensed at visit 2.1.

3.2 Rationale and risk/benefit assessment

3.2.1 Rationale for study design and control group

The NCEP ATPIII recommendations for patients with HTG are first to lower the LDL-C levels and then the TG levels in order to reduce the CV risk(2). In HTG patients, a drug that can reduce both parameters will have an additional benefit.

Statins have been shown convincingly to reduce cardiovascular morbidity and mortality in multiple large outcomes trials in various populations, with substantial reductions in LDL-C and TG levels in non-diabetic and diabetic patients (22, 23). Statins reducing TG levels are known to be directly related to the LDL-C reduction potency meaning that more potent statins should be more effective in lowering TG. For this reason, the current study will use one of the most potent statins (RSV) and will test its efficacy in reducing TG levels in Mexican HTG patients.

This study is using a placebo arm as a control. Patients that are currently on statin therapy cannot enter the study because it would not be ethic to stop their statin therapy. As we are using a placebo arm, the study will only last for 8 weeks and all patients will be treated with TLC diet as appropriate. After completing the study period, all patients will be offer to continue with active commercially available therapy determine by the investigator experience.

The 5-week lead in period will serve as a washout period of possible residual effects of pre-existing lipid lowering therapy (other than statins) use, which is important to establish a reliable baseline to determine the change from baseline during double-blind treatment.

3.2.2 Risk/benefit and ethical assessment

The identify population for this study are candidate for TLC intervention according to ATPIII guidelines. There is no definition on whether monotherapy with statins will be useful in these patients or not, but there are some evidence on the effect of statins on atherogenic lipid

changes (TG reduction, non-HDL-C reduction, HDL-C increase) and its relation to CV risk reduction (21-23).

This is a placebo control trial and this is the reason why patients with LDL-C ≥190mg/dL will be excluded from the study because they are candidate to receive statin therapy, so it would not be appropriate to randomise them to the placebo group. All patients entering the trial will be under TLC diet as marked in ATPIII guidelines during all the study period. All patients will be followed during 8 weeks of treatment, and will be offer to continue with an active treatment after study period is concluded as decided by the investigator.

Although the risk of adverse effects with statin therapy exists, there is potential for a greater benefit by reducing TG and non-HDL-C, with the attendant benefit on decreased CV risk in HTG patients. Please refer to the PI for further information about rosuvastatin. All SAEs should be followed until the adverse event has been resolved or stabilised and no further change is expected.

3.3 Selection of study population

3.3.1 Study selection record

Patients may be recruited from primary or secondary care. Centres if appropriate may use advertisements. 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. Statin naïve patients (as defined by protocol)

4. No previous lipid lowering treatment other than statins 6 months before visit 1

5. Fasting TG concentrations at visit 1 of: ≥ 200 mg/dL and < 800 mg/dlL

6. Fasting LDL-C concentrations at visit 1 of: ≥100 mg/dL and ≤ 190 mg/dL

   (**Note:** the results of the above laboratory sample will not be available at visit 1 to make the eligibility decision. Therefore, if the subject's medical history meets the eligibility criteria the subject can enter into the dietary lead-in period of the study. However, when the laboratory results are available, if the results do not meet the above criteria, the subject should be contacted and discontinued from the study)

7. Fasting TG concentrations at visit 2 of: ≥ 200 mg/dL and < 800 mg/dlL

8. Fasting LDL-C concentrations at visit 2 of: ≥100 mg/dL and ≤ 190 mg/dL

9. Subjects willing to follow all study procedures including the attendance at clinics for scheduled study visits, fasting prior to clinic visits (Visits 1, 2 and 3 blood draws) and compliance with study treatment regimen.

3.3.3 Exclusion criteria

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

1. LDL-C levels ≥ 190 mg/dL

2. History of any other lipid lowering therapy 6 months before visit 1.

3. Subjects considered to be unstable after a myocardial infarction, unstable angina, myocardial revascularisation or a transient ischemic attack (TIA) or stroke

4. Subjects awaiting a planned myocardial revascularization prior to starting the study (ie, planned prior to visit 1)

5. Severe congestive cardiac failure (New York Heart Association [NYHA] Class IIIb or IV)

6. Uncontrolled diabetes diagnosis by HbA_{1c} ≥ 8%, or fasten oral glucose ≥150mg/dL.

7. 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.

8. Uncontrolled hypothyroidism defined as a thyroid stimulating hormone (TSH) >1.5 times the upper limit of normal (ULN) at Visit 1. (This is due to the relationship between myopathy and patients with hypothyroidism undergoing statin therapy)

9. History of homozygous familial hypercholesterolaemia. (Due to the lipid levels exhibited by this group of patients they are considered unsuitable for this study as they often require combination lipid-lowering therapy)

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

11. Current active liver disease [alanine aminotransferase (ALT) (SGPT) > 3 x ULN] or severe hepatic impairment

12. Unexplained rise of creatine kinase (CK) ≥3 x ULN at visit 1

13. Serum creatinine > 176 μmol/L (2.0 mg/dL) at visit 1

14. Pregnancy, breast-feeding, and women of childbearing potential who are not using a reliable contraception method.

15. Subjects previously screened for this study and/or subjects randomised to treatment who subsequently withdraw cannot re-enter this study.

16. Patients participating in any other clinical trial.

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

3.3.4 Restrictions

Patients must comply with the following restrictions during the study:

1. Patients will fast (water is permitted) for 12 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).*

2. 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).*

3. 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).*

4. 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).*

5. Concomitant medication is allowed to treat other problems than HTG such as hypertension, CV disease, DM2 and renal disease.

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:

- 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)

- 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 criterion

- Patient lost to follow-up

- Pregnancy

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

3.3.5.2 Incorrectly enrolled or randomised patients

Incorrectly randomised patients will continue to receive study treatment and assessment if, in the opinion of the investigator and/or study team physician, this is not consider to involve any risk or discomfort to the patient. There should be no attempt to switch treatments or change randomisation numbers.

If study medication is contraindicated, incorrectly randomised patients will be discontinue and contact to return study drug. However, the remaining visit and assessments most continue.

3.3.5.3 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

AstraZeneca will supply the investigational product. The study medication will consist of tablets of rosuvastatin (Crestor®, AstraZeneca) 10mg, and rosuvastatin 20 mg and tablets of placebo matching 10 and 20 mg of rosuvastatin as shown in Table 2.

Table 2 Dose and strength

Treatment	Presentation	Strength
Rosuvastatin	Bottle with 100 tabs	10 mg
Rosuvastatin	Bottle with 100 tabs	20 mg
Placebo	Bottle with 100 tabs	Matching 10 and 20 mg

AstraZeneca will package rosuvastatin and placebo by in high-density polyethylene (HDPE) bottles containing 100 tablets 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 visit 2.1 on which patients will be given two bottles. Each bottle will contain sufficient tablets and overage to finish study period (see Table 3).

At Visit 2.1 (week 0) following confirmation of eligibility, patients will be randomised to one of three treatment groups; rosuvastatin 10 mg, rosuvastatin 20 mg or placebo. Patients should take two tablets per day at the same day hour during 8 weeks (aprox 2 months). All study medication will be taken orally, with water if required, at any time of day or night.

Table 3 Visit schedule

Dispensing Visit	Number of weeks	Number of bottles	Number of tablets per bottle
2.1	8	2	100 (56 days treatment, 2 tablets per day + 44 days overage)

3.4.3 Labelling

All investigational product will be packaged and labeled 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 prescribing information (PI). 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 study coordinator).
- 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 be 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 CRFs
- The patient must return all unused investigational products to the investigator. The number of 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 for destruction. 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, 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) that 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 based on inclusion/exclusion criteria and were not randomised will **not** be allowed to re-enter the study.

The study doctor will establish patient eligibility before treatment randomisation. At Visit 2.1 (Week 0) patients who satisfy the entry criteria will be randomly assigned to receive either rosuvastatin 10 mg, rosuvastatin 20 mg or placebo 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 2.1).

At visit 2.1 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 Dummy methods and procedures for unbinding the study

3.6.1 Methods for ensuring blinding

The study employs a double blind, double dummy design. Medication for each treatment group will be supplied in identical bottles and will be labelled appropriately so as to maintain the study blind. Patients will receive 2 bottles, and should have on tablet of each bottle as a single dose a day. Patients will receive medication as follows:

a) For rosuvastatin 10 mg/day treatment arm: 1 bottle of rosuvastatin 10 mg + 1 bottle of placebo, matching rosuvastatin 20 mg.

b) For rosuvastatin 20 mg/day treatment arm: 1 bottle of rosuvastatin 20 mg + 1 bottle of placebo, matching rosuvastatin 10 mg.

c) For placebo treatment arm: 1 bottles of placebo matching rosuvastatin 10 mg + 1 bottle of placebo, matching rosuvastatin 20 mg.

All study personnel will be unaware of the randomised treatment until all decisions on the evaluability of the data from all patients have been made and documented.

Lipid profile results on visit 1 and 2 will be available for the investigator to made eligibility criteria.

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) using IVRS. Routines for this will be described in the IVRS manual that will be provided to each investigational centre.

AstraZeneca will not break treatment codes for the planned analyses of data until all decisions regarding the patients in each patient population have been made and documented.

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

Patients must not have been treated with any statin 6 months prior to Visit 1.

Patients must not have been treated with a lipid lowering therapy (other than statin) 6 months before visit 1.

All disallowed medications should be stopped on entry to the study (or 6 months before if it is a lipid-modifying drugs other than statins), 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. In particular there is a risk of myopathy with antibiotics, antifungals and immunosuppressants (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 CRF.

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
Antidiabetics	Insulin
	PPAR α/γ agonists (glitazones)
Lipid regulation	Gemfibrozil
	Fenofibrats
	Benzofibrats
	Niacin
	Ezetimibe
	Atorvastatin
	Lovastatin
	Pravastatin
	Rosuvastatin (except for study medication)
	Simvastatin
	Fluvastatin
	Omega 3
Immunosuppresants	Cyclosporin
	Lymphocyte immune globulin
	Rho(d) immune globulin
	Azathioprine sodium
	Muromonab-CD3
	Prograf (FK-506)
	Cellcept (mycophenolate mofetil)
	Oral or intravenous corticosteroids

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**

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.

3.8 Treatment compliance

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

$$\textbf{Compliance} = \frac{\text{(number of tablets dispensed-number of tablets return)}}{\text{Number of days between visit 2.1 and 3}} \times 100$$

Compliance will be checked at visit 3. For compliance patient should take more than 80% and less than 120% of the prescribed study medication.

4. MEASUREMENTS OF STUDY VARIABLES

4.1 Primary variable

The primary variable is the change TG from baseline to week 8.

4.2 Secondary variables

Secondary variables are: non-HDL-C; LDL-C; TC; HDL-C; ApoA1; ApoB levels; ApoB/ApoA1; non-HDL-C/HDL-C; LDL-C/HDL-C; TC/HDL-C and hsCRP.

4.3 Screening and demographic measurements

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

- Date of birth, sex and race

- Significant medical and surgical history

- Prior and concomitant medication
- Height, weight, waist circumference, vital signs and physical examination

4.4 Patient-Reported Outcomes (PROs) (Not applicable)

4.5 Health Economic measurements and variables (Not applicable)

4.6 Pharmacokinetic measurements and variables (Not applicable)

4.7 Efficacy and pharmacodynamic measurement and variables

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

Table 5 Efficacy variable(s)

Objective	Variable(s)
Primary	Percentage change in TG levels from baseline to week 8.
Secondary	
1st	Percentage change in non-HDL-C levels from baseline to week 8.
2nd	Percentage change in lipids and lipoproteins (different to TG and non-HDL-C) from baseline to week 8 (LDL-C, TC, HDL-C, ApoA1, ApoB, TC/HDL-C; LDL-C/HDL-C; nonHDL-C/HDL-C and ApoB/ApoA1 indexes)
3rd	Percent change of hsCRP from baseline to week 8.

4.7.1 Triglycerides levels

Triglycerides levels will be assessed from laboratory data.

4.7.1.1 Methods of assessment

Patients must fast for at least 12 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 12 hours before) then they must be asked to return within the visit windows for their fasting blood sample.

Fasting concentrations of TG will be determined at visit 1, 2 and 3.

4.7.2 Lipid assessments

Lipids and lipoproteins will be assessed from laboratory data.

4.7.2.1 Methods of assessment

Patients must fast for at least 12 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 12 hours before) then they must be asked to return within the visit windows for their fasting blood sample.

Fasting concentrations of nonHDL-C, LDL-C, HDL-C and TC will be determined at Visits 1, 2 and 3. 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 B and A-1 will be determined at Visits 2 and 3. The ApoB/ApoA-1 ratio will also be calculated at these visits.

The results of all lipid and lipoprotein levels measured at each visit will be revealed to the study centre personnel for randomisation.

All samples will be labelled with the patient initials, e-code and date of collection. A central laboratory will perform analyses of all laboratory samples. The central laboratory will be responsible for all lipid analysis and is certified for standardisation of lipid analysis by The College of American Pathologist. Further details of the central laboratory can be found in the central laboratory manual.

4.7.3 HDL-C assessment

HDL-C will be assessed by indirect precipitation method.

4.7.3.1 Methods of assessment

High Density Lipoproteins (HDL) can be separated by selectively precipitate low density and very low density lipoproteins (LDL and VLDL) adding Dextran sulphate in the presence of Mg++. In the remaining supernatant by centrifugation, which contains HDL can be then assay for cholesterol.

For further information please refer to the laboratory manual.

4.7.4 hsCRP assessment

hsCRP will be assessed from laboratory data.

4.7.4.1 Methods of assessment

hsCRP blood samples will be taken in the same conditions and the same moment than lipid blood samples.

hsCRP will be analysed at Visits 2 and 3.

4.8 Safety measurements and variables

The methods for collecting safety data are described below.

4.8.1 Adverse events

4.8.1.1 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 is 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 lead-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., lead-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)

The Clinical Study Team Physician will identify OAEs 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.

4.8.1.2 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 4.8.1.1. 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 National Medical Terminology Officially Accepted.

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 CRF 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 that 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.

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.

4.8.1.3 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** (ie, immediately but no later than the end of the next business day) of when he or she becomes aware of it.

The AstraZeneca representative will work with the investigator to compile all the necessary information and ensure that the AstraZeneca Drug Safety Department (ie, Clintrace Data

Entry Site) receives a report by **day one** for all fatal and life-threatening cases and by **day five** for all other SAEs.

The investigator must also reported follow-up information on SAEs within the same time frames.

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

All SAEs have to be reported, whether or not considered causally related to the investigational product. All SAEs will be recorded in the case report form. The investigator is responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

Subjects 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 SAEs he is aware of in the 30-day period following discontinuation of study treatment, on the AE CRF page and should report them to AstraZeneca in the usual manner.

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.

4.8.2 Laboratory safety measurements and variables

4.8.2.1 Methods of assessment

Laboratory analysis will be performed at Visits 1, 2 and 3.

For visit 1, 20ml of blood will be needed. In this visit, lipid profile, glucose, HbA_{1c}, urea, creatinine, reduced hepatic profile (ALT, AST and GGT) and CK will be performed. A TSH analysis will be done and patients with levels ≥1.5 ULN will be excluded of the trial. β-HCG will be performed to women with childbearing potential at visit 1.

For visit 2 and 3, 10 ml of blood will be needed. In these visits, lipid profile, apolipoproteins, hsCRP, glucose, urea, creatinine, complete hepatic profile and CK will be performed.

A 10 mL mid-stream urine sample will be collected for analysis at the central laboratory at visits 2 and 3. It 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.

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.

The volume of blood to be collected is detailed in section 4.9.

4.8.2.2 Derivation or calculation of outcome variables

The central laboratory (CARPERMOR) will perform all analysis.

Please refer to section 4.8.1.2 for details on how AEs based on laboratory assessments should be reported and recorded.

4.8.3 Vital signs and physical examination

4.8.3.1 Methods of assessment

Vital signs will be measured at visits 1, 2 and 3. This will include blood pressure, cardiac frequency and respiratory frequency.

The investigator will perform a full physical examination including weight and waist circumference at all visits. Height will additionally be measured at Visit 1.

4.8.3.2 Derivation or calculation of outcome variables

The patient should be requested to sit for 5 minutes before cardiac frequency; respiratory frequency and blood pressure are measured. These parameters will be recorded in the CRF.

4.9 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	3	30
Safety	HbA1c	4	1	4
	Clinical chemistry	7.5	3	22.5
	TSH	5	1	5
Total				61.5 mL

In addition, 2 urine samples (10 ml volume per sample) will be collected over the course of the study.

The total volume of blood associated with the scheduled protocol visits should not exceed 61.5 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.

4.9.1 Analysis of biological samples

4.9.1.1 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.

4.9.1.2 Pharmacokinetic samples (Not applicable)

5. DATA MANAGEMENT

Case Report Forms (CRFs) will be provided for the recording of data. The forms will be in triplicate with carbonless paper. Data will be recorded legibly on the record forms in ballpoint pen. If any data is not available, omissions will be indicated on the record forms. Corrections should be legible, initialled and dated. Correction fluid or covering labels should not be used. The original top copy of the CRF will be collected and returned to AstraZeneca or its

designee, the second copy is for the monitor and the investigator will retain the third copy. It is important to ensure that all CRF entries are also legible on the retained copy.

Data collected from the completed CRFs will be entered into the clinical database. Laboratory data will be electronically transferred into the clinical database. The processes will be documented into 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 National Medical Terminology Officially Accepted.

6. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

6.1 Statistical evaluation – general aspects

Statistical analysis will be performed by statistical personnel outsourced by AstraZeneca in accordance with a comprehensive Statistical Analysis Plan (SAP) that will be prepared before unblinding of the data.

6.2 Description of outcome variables in relation to objectives and hypotheses

Each outcome variable relates to the corresponding objective as described in Section 4.7.

Primary efficacy outcome variable

1. Percentage change in TG levels from baseline to week 8.

Secondary efficacy outcome variables

1. Percentage change in non-HDL-C levels from baseline to week 8.
2. Percentage change in lipids and lipoproteins (different to TG and non-HDL-C) from baseline to week 8 (LDL-C, TC, HDL-C, ApoA1, ApoB, TC/HDL-C; LDL-C/HDL-C; nonHDL-C/HDL-C and ApoB/ApoA1 indexes) .
3. Percent change of hsCRP from baseline to week 8.

Secondary safety outcome variables

1. 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 (i.e. patients taking lipid lowering therapy other tan study drugs).

Patients will be evaluated using randomised treatment/dose (i.e., rosuvastatin 10 mg, rosuvastatin 20 mg, or placebo) 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. 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 Triglycerides levels

The following analyses will be performed for TG:

- Last observation carried forward (LOCF) on the ITT (Intention to treat) population for primary and secondary endpoints at week 8. This will be the primary analysis.
- Observed data on the per Protocol (PP) population for primary and secondary endpoints at week 8.

Initially a Friedman analysis will be performed, then, for comparing each one of Rosuvastatin groups against placebo group at week 8 a U Man Whitney test will be done. Also, the percentage of reduction –week 8 minus basal- obtained in the placebo group will be contrasted against the percentage of reduction in each one of the Rosuvastatin groups using a U Man Whitney test. In all the cases a $p< 0.05$ will be considered significant.

6.4.1.2 Lipids and lipoproteins other than Triglycerids

Lipids (other than TGs), apolipoproteins and CRP comprising secondary endpoint (1, 2 and 3) will be analysed in a similar way.

6.4.2 Safety

Adverse events will be classified according to two definitions:

- Reported during the dietary lead-in period
- Treatment emergent. This is further categorised as:

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

– Starting during the randomised period. 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 the National Medical Terminology Officially Accepted and will be tabulated by treatment/dose.

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 TG levels from baseline to Week 8.

Hypothesis testing will be undertaken to assess whether this change from baseline in TG levels is significantly different from zero (i.e., testing for a positive effect compared to baseline) for each of the rosuvastatin 10 mg and rosuvastatin 20 mg treatment groups. Similar hypothesis testing will also be performed for the placebo 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. The required power is 90%.

Data taken from the literature suggest that an intervention with RSV will reduce TG levels between 22 and 25% average, with a maximum of 37% from baseline (expected p for sample 1(placebo):0.029; expected p for sample 2(RSV):0.229). We need a minimum of 67 fully evaluable patients per treatment arm to reach the 2-sided alpha 0.050 with a potency of 90% and a confident interval of 95%. Increasing sample size to 100 per arm increases potency to 97%.

As there are about 10 to15% patients that would probably not complete the 8 weeks treatment period (non-evaluable patients), we will increase the patients per treatment arm to 110 (a total of 330 randomised patients). As we have the facility of doing the trial in at least 10 centers, we can easily reach the target patients per treatment arm. Assuming a screen failure rate of 3:1 we will require approximately 990 patients to enter 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 CRFs, and that investigational product accountability checks are being performed

- Perform source data verification (a comparison of the data in the CRFs 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.

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 also by 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 by the regulatory authority.

The timetable for the study is as follows:

Estimated date of first patient enrolled	May 2007
Estimated date of last patient enrolled	October 2007
Estimated date of last patient completed	February 2008
Estimated recruitment period	6 months

Date of last patient completed is defined as the date of the last visit of the last patient

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 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 study team physician on the numbers shown below.

Role in the study	Name	Address & telephone number
ST Leader responsible for the protocol	Juan Carlos Osornio	AstraZeneca Lomas Verdes 67, Lomas Verdes; Naucalpan, Edo de Mex. CP 53120 Tel. (+5255) 5374-9600 ext 4251
ST Physician responsible for the protocol (24-hour emergency)	Ana Polanco	AstraZeneca Lomas Verdes 67, Lomas Verdes; Naucalpan, Edo de Mex. CP 53120 Tel. (+5255) 5374-9668 Cel. (04455) 1886-0723
Study Coordinator outside AstraZeneca	Juan Talavera	Aguayo No 35, Col del Carmen. Coyoacan, DF 04100 (+5255) 5627-6900 ext 21481
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 a SAE and should be reported as such, see Section 4.8.1.1.**

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. 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 CRFs 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 CRFs. 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 CRFs.

An overdose without associated symptoms should not be recorded as an AE in the CRFs. 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.

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.

10. REFERENCES

1. Cullen P. Evidence that triglycerides are an independent coronary heart disease risk factor. Am J Cardiol 2000; 86:943–949.

2. No authors listed. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA, 2001; 285(19):2486-97

3. Grundy S., et al. Diagnosis and Management of the Metabolic Syndrome. An American Heart Association/National Heart, Lung, and Blood Institute. Scientific Statement. Circulation 2005;112;2735-2752.

4. Paoletti R; et al. Metabolic syndrome, inflammation and Atherosclerosis. Vascular Health and Risk Management. 2006:2(2):145–152

5. Roseman HM et al. Progression from obesity to type 2 diabetes: Lipotoxicity, glucotoxicity, and implications for management. J Manag Care Pharm. 2005;11(6)(suppl s-b):s3-s11

6. Berneis KK, Krauss RM. Metabolic origins and clinical significance of LDL heterogeneity. J Lipid Res 2002;43:1363–79.

7. Shinji Koba. Significance of small dense low-density lipoprotein-cholesterol concentrations in relation to the severity of coronary heart diseases Atherosclerosis 2006. *in press.*

8. St-Pierre AC, Cantin B, Dagenais GR, et al. Low-density lipoprotein subfractions and the long-term risk of ischemic heart disease in men, 13-year follow-up data from the Qu´ebec cardiovascular study. Aretiroscler Thromb Vasc Biol 2005;25:553–9.

9. Rull, JA, et al. Epidemiology of Type 2 Diabetes in Mexico. Archives of Medical Research 36 (2005) 188–196

10. ENSA (Encuesta Nacional de Salud) 2000. Tomo 2. La salud de los Adultos. Cap 6 y 8. INSP, Mex, 2000.

11. Principales causas de mortalidad general, 2004. SSA; Mex; 2004. http://www.salud.gob.mx/

12. Carlos A. Aguilar-Salinas, High Prevalence of Metabolic Syndrome in Mexico. Archives of Medical Research 35 (2004) 76–81.

13. Barquera S, et al. Cholesterol, dyslipidemias and obesity in Mexico. *In press.*

14. The FIELD Investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet 2005; 366: 849–61.

15. Davidson MH, et al. Effects of Fenofibrate on Atherogenic Dyslipidemia in Hypertriglyceridemic Subjects Clin. Cardiol. 2006; 29: 268–273.

16. Wolffenbuttel, BHR; Franken, AAM and Vincent, HH. Cholesterol-lowering effects of rosuvastatin compared with atorvastatin in patients with type 2 diabetes – CORALL study. Journal of Internal Medicine 2005; 257: 531–539.

17. Ballantyne, CM: Bertolami, M; Hernandez-Garcia, HR; Nul, D; Stein, EA; Theroux, P; Weiss, R, Cain, VA and Raichlen, JS. Achieving LDL cholesterol, non-HDL cholesterol, and apolipoprotein B target levels in high-risk patients: Measuring effective reductions in cholesterol using rosuvastatin therapy (MERCURY) II. Am Heart J. 2006;151:975.e12975-e9

18. Jones, PH; Davidson, MH; Stein, EA; Bays, HE; McKenney, JM; Miller, E; Cain, VA and Blasetto, JW. Comparison of the Efficacy and Safety of Rosuvastatin Versus Atorvastatin, Simvastatin, and Pravastatin Across Doses (STELLAR* Trial). Am J Cardiol 2003;92:152–160

19. Stalenhoef1, AFH; Ballantyne, CM; Sarti, C; Murin, J; Tonstad, S; Rose, H and Wilpshaar, W. A Comparative study with rosuvastatin in subjects with metabolic syndrome: results of the COMETS study. European Heart Journal. 2005; 26, 2664–2672.

20. Hunninghake, DB; et al. Rosuvastatin improves the atherogenic and atheroprotective lipid profiles in patients with hypertriglyceridemia. Coronary Artery Disease. 2004; 15:115–123.

21. Mckenney, JM. Efficacy and safety of rosuvastatin in treatment of dyslipidemia. Am J Health-Syst Pharm. 2005; 62:1033-47.

22. Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. Lancet 2005; 366: 1267–78

23. Costa, J; Borges, M; David, C; Carneiro, AV. Efficacy of lipid lowering drug treatment for diabetic and non-diabetic patients: meta-analysis of randomised controlled trials. BMJ; 2006; 332:1115-1124

24. King H, Aubert R, Herman W. Global burden of diabetes, 1995–2025. Diabetes Care 1998; 21:1414–1431.