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**Clinical Study Protocol**

Drug Substance	Rosuvastatin calcium
Study Code	D3565C00003
Edition Number	2.0
Date	28 Mar 2018

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**A Randomized, Double-blind, Placebo-controlled, Multicenter Parallel Group Phase 3 Study Measuring the Effect of Rosuvastatin 20 mg on Carotid Intima-Media Thickness in Chinese Subjects**

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**Sponsor:**  
**AstraZeneca UK Limited, 600 Capability Green, Luton, LU1 3LU, UK**

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<b>Amendment No.</b>	<b>Date of Amendment</b>	<b>Local Amendment No:</b>	<b>Date of Local Amendment</b>
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## VERSION HISTORY

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## PROTOCOL SYNOPSIS

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### **A Randomized, Double-blind, Placebo-controlled, Multicenter Parallel Group Phase 3 Study Measuring the Effect of Rosuvastatin 20 mg on Carotid Intima-Media Thickness in Chinese Subjects**

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#### **Study site(s) and number of subjects planned**

Approximately 506 Chinese subjects will be randomized to study treatment. The study will be conducted across approximately 30 sites in China.

543 Chinese subjects were randomized into study when the recruitment was completed, these randomized patients were from 25 sites in China.

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<b>Study period</b>		<b>Phase of development</b>
Estimated date of first subject enrolled	3Q 2015	Phase 3
Estimated date of last subject completed	1Q 2019	Phase 3

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## Study design

This study is a randomized, double-blind, placebo-controlled, multicenter parallel group study assessing the effects of rosuvastatin 20 mg treatment for 104 weeks on the change in intima-media thickness (IMT) of the common carotid artery (CCA), carotid bulb, and internal carotid artery (ICA) in adult Chinese subjects with subclinical atherosclerosis.

## Objectives

<b>Primary Objective:</b>	<b>Outcome Measure:</b>
To assess the efficacy of rosuvastatin 20 mg compared to placebo on slowing progression of carotid intima-media thickness (CIMT) over 104 weeks in Chinese subjects with subclinical atherosclerosis	Annualized rate of change in mean of the maximum (MeanMax) CIMT measurements from each of the 12 carotid artery sites based on all scans performed during the 104-week study period

<b>Secondary Objective:</b>	<b>Outcome Measures:</b>
To assess the efficacy of rosuvastatin 20 mg compared to placebo over 104 weeks on slowing progression of intima-media thickness (IMT) in carotid artery segments and on blood lipids in Chinese subjects with subclinical atherosclerosis	<ul style="list-style-type: none"> <li>• Annualized rate of change in the MeanMax IMT of the near and far walls of the right and left CCA</li> <li>• Annualized rate of change in the MeanMax IMT of the near and far walls of the right and left carotid bulb</li> <li>• Annualized rate of change in the MeanMax IMT of the near and far walls of the right and left ICA</li> <li>• Annualized rate of change in the mean of the mean (MeanMean) IMT of the near and far walls of the right and left CCA</li> <li>• Change in low density lipoprotein cholesterol (LDL-C), total cholesterol, high density lipoprotein cholesterol (HDL-C), triglycerides, non-HDL-C, apolipoprotein (Apo) B, ApoA-I, non-HDL-C/HDL-C, and ApoB/ApoA-I</li> </ul>

<b>Safety Objective:</b>	<b>Outcome Measure :</b>
To assess the safety and tolerability of rosuvastatin 20 mg compared to placebo over 104 weeks in Chinese subjects with subclinical atherosclerosis	Safety assessments will include adverse events (AEs), serious adverse events (SAEs), AEs leading to discontinuation, changes in clinical laboratory analyses (chemistry, hematology, and urinalysis), vital signs, 12-lead electrocardiograms (ECGs), and physical examination

## **Target subject population**

The study population will consist of asymptomatic adult, male and female Chinese subjects with 10-year ischemic cardiovascular disease (ICVD) risk <10% based on the 2007 China Adult Dyslipidemia Management Guidelines. To qualify for entry into the study, men must be age  $\geq 45$  and <70 years, and women must be age  $\geq 55$  and <70 years, with HDL-C  $\leq 60$  mg/dL (1.6 mmol/L). At screening subjects must be asymptomatic.

Subjects with only hypertension and age as cardiovascular disease (CVD) risk factors or subjects without hypertension who have 3 or more other risk factors (including age) must have:

- Fasting LDL-C of  $\geq 120$  mg/dL (3.1 mmol/L) and <160 mg/dL (4.1 mmol/L).

Subjects without hypertension who have fewer than 3 other risk factors (including age) must have:

- Fasting LDL-C of  $\geq 120$  mg/dL (3.1 mmol/L) and <190 mg/dL (4.9 mmol/L).

Additionally, all subjects must have triglycerides <500 mg/dL (5.65 mmol/L) and a maximum IMT of  $\geq 1.2$  mm and <3.5 mm.

## **Duration of treatment**

Rosuvastatin or placebo will be administered once daily for a 104-week treatment period.

## **Investigational product, dosage and mode of administration**

The investigational product will be rosuvastatin 20 mg and placebo in oral tablet form for once daily use. Subjects will be encouraged to take the medication at the same time each day.

## **Statistical methods**

### Analysis sets

Three analysis sets will be used for data analysis:

- The intent-to-treat (ITT) population consists of all randomized subjects. Subjects will be analyzed according to the treatment randomized.
- The per-protocol (PP) population is a subset of the ITT population that includes subjects without any important protocol deviations. The criteria for important protocol deviations will be defined in the statistical analysis plan. Subjects will be analyzed according to the treatment actually received.
- The safety analysis set will consist of all subjects who take at least 1 dose of investigational product or placebo. Subjects will be analyzed according to treatment actually received. For subjects who received both treatments during the

study, the algorithm to be used for assignment of treatment will be detailed in the statistical analysis plan.

The ITT population will be the primary efficacy analysis population. The CIMT analysis will be performed based on both the ITT and PP populations, and lipid and apolipoprotein analyses will be performed on the ITT population only. Safety parameters will be summarized on the safety analysis set.

#### Methods for statistical analysis

A linear mixed-effects model will be used for the CIMT primary analysis to assess the difference in the annualized rate of change in the MeanMax CIMT measurements across 12 carotid artery sites between rosuvastatin 20 mg and placebo treatment over 104 weeks.

For the primary efficacy analysis, the dependent variable is the maximum CIMT measurement from 3 interrogation angles at each of the 12 carotid artery sites at each timepoint of CIMT measurement during the 104-week study period. The model includes fixed effects for treatment group, time, time by treatment interaction, ICVD risk (<5%/5% to 10%), age, sex, centre and scan reader, and random effects for the intercept and slope at the individual subject level and carotid artery site within subject. Ultrasound machine will be included as a fixed effect as well if different types of machines are deployed across sites. For time of CIMT measurement, the 2 pre-randomization visits and the final 2 visits at the end-of-study will be treated as separate time points. Details will be defined in the Statistical Analysis Plan. Time, as a continuous variable, is the interval from the date of randomization to the date of CIMT measurement. Differences in annualized change between rosuvastatin and placebo will be evaluated by testing the time-by-treatment interaction term.

The same statistical method used for the primary efficacy analysis will be applied to model the segment-specific secondary CIMT efficacy outcome measurements. The difference in the annualized rate of change between rosuvastatin and placebo for the secondary CIMT outcome measures will also be evaluated by testing the time-by-treatment interaction term in each model fitting.

Secondary lipid and lipoprotein outcome measures are the percentage change from baseline, which will be analyzed by analysis of covariance with terms for treatment in the model. For lipid measurements (LDL-C, total cholesterol, HDL-C, triglycerides, non-HDL-C, non-HDL-C/HDL-C), both the analysis of the percent change from baseline at the final visit and the analysis of the percent change from baseline to time-weighted average during treatment will be performed. In the evaluation of change from baseline to final visit, missing observations will be imputed by last observation carried forward (LOCF). The time-weighted average lipid value is defined as the lipid value multiplied by the number of days since the last lipid assessment, summed for all lipid observations, and divided by the sum of days between all visits. No imputation will be made for lipid missing values for the time-weighted average analysis. For apolipoprotein measurements (ApoB, ApoA-I, ApoB/ApoA-I), the analysis of the percent change from baseline to final visit (LOCF) will be performed.

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No multiplicity adjustment will be applied to the secondary efficacy analysis.

Safety outcome measures including AEs, SAEs, AEs leading to discontinuation, changes in clinical laboratory analyses (chemistry, hematology, and urinalysis), vital signs, 12-lead ECGs, and physical examination will be summarized descriptively for the safety analysis set. No formal statistical tests will be performed.

The study does not include any interim analysis.



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## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this Clinical Study Protocol.

<b>Abbreviation or special term</b>	<b>Explanation</b>
AE	Adverse event
ALT	Alanine aminotransferase
Apo	Apolipoprotein
AST	Aspartate aminotransferase
ATP	Adult Treatment Panel
CAD	coronary artery disease
CAI	Cholesterol-absorption inhibitor
CCA	Common carotid artery
CHD	Coronary heart disease
CIMT	Carotid intima-media thickness
CK	Creatine kinase
CVD	Cardiovascular disease
ECG	Electrocardiogram
eCRF	Electronic case report form
GCP	Good Clinical Practice
HDL-C	high-density lipoprotein cholesterol
HMG-CoA	Hydroxy-3-methylglutaryl coenzyme A
ICA	Internal carotid artery
ICH	International Conference on Harmonisation
ICVD	Ischemic cardiovascular disease
IMT	Intima-media thickness
INR	International normalized ratio
ITT	Intent-to-treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LDL-C	Low-density lipoprotein cholesterol
LOCF	Last observation carried forward
MeanMax	Mean of the maximum
MeanMean	Mean of the mean

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<b>Abbreviation or special term</b>	<b>Explanation</b>
MI	Myocardial infarction
National Coordinating Investigator	The National Coordinating Investigator is the investigator coordinating the investigators and/or activities.
NCEP	National Cholesterol Education Panel
PP	Per-protocol
SAE	Serious adverse event
Statin	HMG-CoA reductase inhibitor
TLC	Therapeutic Lifestyle Changes
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
WBDC	Web Based Data Capture

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## 1. INTRODUCTION

### 1.1 Background and rationale for conducting this study

Cardiovascular and cerebrovascular diseases caused by atherosclerosis are a serious problem in China. During the last 2 decades, the mortality and morbidity of coronary heart disease (CHD) has increased significantly in both cities and rural areas ([Zhu et al 2007](#)). Furthermore, the World Health Organization report in 1998 forecasted that the prevalence of CHD in China would increase 3.7-fold by the year 2030 compared with the year 2000 ([WHO 1998](#)).

Atherosclerosis has a silent course for several decades before symptoms and atherothrombotic complications occur ([Ross 1999](#)), by which time the disease already has major histopathological consequences that are poorly reversible. A 10-year follow-up study (CAFES-CAVES) showed the degree of atherosclerosis (assessed by carotid intima-media thickness [CIMT]) in low-risk, asymptomatic patients was strongly correlated with the 10-year incidence of cardiovascular events ([Belcaro et al 2001](#)). Three-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins), which are the most widely used prescription medications for the treatment of hypercholesterolemia, have emerged as among the most effective means of reducing the risk of cardiovascular diseases (CVDs) in both primary and secondary prevention settings. Statins have also been shown to slow the progression of, and even regress, atherosclerosis ([Crouse et al 2007](#), [Smilde et al 2001](#)). The antiatherosclerotic effect of statins has been demonstrated previously for carotid atherosclerosis as assessed via B-mode ultrasound measurement of CIMT and for coronary atherosclerosis as assessed by quantitative coronary angiography and intravascular ultrasound.

Increases in CIMT can be used to evaluate early stages of atherosclerosis in a noninvasive manner, as CIMT increases serve as an important hazard and predictive factor of CVD ([Onut et al 2012](#)). The ASAP trial demonstrated plaque regression from baseline in hypercholesterolemic patients treated with atorvastatin 80 mg compared to simvastatin 40 mg ( $-0.031$  mm vs  $0.036$  mm,  $p < 0.0005$  and  $p < 0.0017$ , respectively) ([Smilde et al 2001](#)). The ARBITER study similarly showed a reduction in CIMT by  $0.034$  mm with atorvastatin 80 mg vs  $0.025$  mm with pravastatin 40 mg after 12 months ( $p = 0.03$ ) ([Taylor et al 2002](#)). Extensive research has confirmed that the incidence of cardiovascular events increases when CIMT is elevated in type 2 diabetic patients ([Irie et al 2012](#)). Keo et al found that CIMT closely correlates with ischemic events in patients with atherosclerotic vascular disease ([Keo et al 2011](#)). In a meta-analysis, CIMT has been shown to be a reliable surrogate marker for cardiovascular events ([Espeland et al 2005](#)). For these reasons as well as the fact that there is regulatory precedence, CIMT has been increasingly used as an endpoint in clinical trials. Using CIMT measurement as a biomarker for atherosclerosis progression may accelerate drug development by facilitating efficacy assessments before the occurrence of endpoints, such as myocardial infarction (MI), stroke, and death ([Doneen and Bale 2013](#)). The 2010 China expert consensus on primary prevention of CVD indicated that CIMT can be used to assess overall cardiovascular risk ([Consensus on primary prevention of CVD 2010](#)). The major advantage of CIMT is that it is completely non-invasive and can be repeated as often as required. It provides a continuous measure, since all subjects have a measurable carotid wall.

It is also relatively inexpensive to perform, and the technology is widely available ([Onut et al 2012](#)).

CRESTOR™ (rosuvastatin) is effective at lowering low-density lipoprotein cholesterol (LDL-C) concentrations. In addition, rosuvastatin, like other statins, has favorable effects on other components of the lipid and lipoprotein profile, such as raising high-density lipoprotein cholesterol (HDL-C) and reducing levels of total cholesterol and triglycerides. The principal evidence supporting the anti-atherosclerotic effects of rosuvastatin is based on the findings of METEOR, the pivotal Phase 3 registration study that evaluated the effects of 2-year treatment with rosuvastatin 40 mg on the natural history of atherosclerosis of the carotid arteries ([Crouse et al 2007](#)). The study enrolled 984 patients with hypercholesterolemia who were randomized in a 5:2 ratio to active treatment or placebo (702 rosuvastatin, 282 placebo). Patients were at low risk (defined as 10-year Framingham Risk Index <10%) for CHD according to National Cholesterol Education Panel (NCEP) Adult Treatment Panel (ATP) III guidelines published in 2001 ([NCEP 2001](#)), and they were required to have evidence of subclinical atherosclerosis as assessed by CIMT. Over the 2-year course of the study, rosuvastatin significantly slowed the progression of atherosclerotic disease as compared to placebo. For the primary endpoint, there was a highly significant difference in the change in maximum CIMT across the 12 carotid sites relative to placebo (-0.0145 mm/year; 95% confidence interval for difference -0.0196, -0.0093;  $p < 0.0001$ ). Rosuvastatin also delayed the progression of atherosclerotic disease as evidenced by a negative rate of change across the 12 carotid sites over the 2-year study period (-0.0014 mm/year). This delay in disease progression among the rosuvastatin-treated patients over the 2-year course of the study is particularly noteworthy when viewed in the context of the observed placebo rate of progression of +0.0131 mm/year (95% confidence interval 0.0087, 0.0174;  $p < 0.0001$ ).

Several clinical trials have shown the ability of rosuvastatin therapy to slow the progression of atherosclerosis in Chinese and other Asian subjects. The REACH (Rosuvastatin Evaluation of Atherosclerotic Chinese Subjects) study showed that rosuvastatin therapy may induce a rapid and lasting decrease in carotid plaque lipid content as assessed by MRI in an average dose of 11 mg/day after a 104-week treatment period ([Du et al 2014](#)). A recent meta-analysis was conducted to determine the effect of rosuvastatin on regressing or slowing of the progression of carotid atherosclerosis in Chinese populations (1392 Chinese subjects treated with rosuvastatin from 28 studies) ([Feng et al 2014](#)). Rosuvastatin doses ranged from 5 mg/day to 20 mg/day, and with follow-up ranging from 6 to 12 months. Compared with control/active comparator groups, rosuvastatin treatment reduced intima-media thickness (IMT), plaque score, and plaque area, and was well tolerated in these studies. In addition, the COSMOS study showed significant regression of coronary artery atheroma volume (assessed by intravascular ultrasound) in a Japanese patient population after a 76-week rosuvastatin treatment period. In that study, rosuvastatin doses were titrated based on LDL-C reduction using the 2.5 to 20 mg dose range, resulting in an average of dose of 16.9 mg/day ([Takayama et al 2009](#)).

## 1.2 Rationale for study design, doses and control groups

The proposed study is designed to evaluate the effect of rosuvastatin versus placebo on progression of CIMT in asymptomatic Chinese subjects who have a 10-year ischemic cardiovascular disease (ICVD) risk <10%. The design is based on that of the pivotal METEOR study but includes only Chinese subjects.

The basic principle that guides cholesterol-lowering intervention is that the intensity of treatment is directly related to the degree of integrated risk for CVD (NCEP 2001). Cardiovascular disease risk results from the integration of multiple risk factors, and the concept of “integrated risk” evaluation is well recognized. Population-based risk algorithms, such as the Framingham Risk Score, which was also used in the pivotal study METEOR, are widely used to identify individuals at various risk levels of developing cardiovascular events and to determine the aggressiveness of preventive therapy. However, while the Framingham Risk Score is established to assess CHD risk, in China the risk factor patterns and the profile of CVD are different (Wu et al 2006). Stroke is twice as prevalent as CHD in China (Chinese Society of Cardiology 2011), so it is inappropriate to estimate the total cardiovascular risk on the basis of the risk of CHD alone without considering stroke.

Although CHD and stroke have some differences in origin, atherosclerosis is a common pathophysiological basis for both. Hypertension, hyperlipidemia, smoking, diabetes mellitus, obesity, age, and sex are widely accepted as major risk factors for atherosclerosis, CHD, and ischemic stroke (NCEP 2001). To properly consider the potential hazards of dyslipidemia on the Chinese population, Chinese scholars advocate using ICVD risk to represent integrated cardiovascular risk and Chinese prevalence characteristics (Wu et al 2004). The concept of integrating the risk of CHD and ischemic stroke into a single model and then using the resulting model in clinical practice is particularly valuable in countries where stroke risk is high, as it is in China. The 2007 China Adult Dyslipidemia Management Guidelines introduced a system of risk assessment that can be employed in subjects with/without existing CHD (or a CHD risk equivalent) and with/without hypertension by counting categorical risk factors (see Appendix F). Combining this risk assessment system with blood lipid levels allows CVD risk to be comprehensively estimated, allowing stratification of risk and guiding treatment. The risk stratification scheme singles out hypertension to reflect the characteristics of Chinese clinical practice.

In the present study, classification of patient risk and definition of therapeutic goals for LDL-C will be based on the 2007 China Adult Dyslipidemia Management Guidelines. The 10-year ICVD risk is equivalent to approximately 5% to 10% when fasting LDL-C is  $\geq 120$  mg/dL (3.1 mmol/L) and  $< 160$  mg/dL (4.1 mmol/L) for subjects with only hypertension (defined as blood pressure  $\geq 140/90$  mmHg or being on antihypertensive treatment) and age as CVD risk factors, and subjects without hypertension who have 3 or more other risk factors (including age). The 10-year ICVD risk is equivalent to  $< 5\%$  when LDL-C is  $\geq 120$  mg/dL (3.1 mmol/L) and  $< 190$  mg/dL (4.9 mmol/L) for subjects without hypertension who have fewer than 3 other risk factors (including age). The above-mentioned subjects will be the target patient population for current study.

This subject population largely overlaps with the subject population in the METEOR study, and the treatment recommendation/goals are similar, following the local guideline in Chinese and NCEP ATP III in METEOR.

The dose of 20 mg rosuvastatin has been selected for use in the present study as it is the maximum approved dose in China. In this Chinese study, the intent is to arrest the progression of atherosclerosis to the same degree as was demonstrated in the METEOR trial, which used a dose of 40 mg rosuvastatin.

This study is expected to evaluate whether similar CIMT findings will be found with rosuvastatin therapy in a Chinese population as were found in the METEOR study. Additionally, the study has been designed to comply with Chinese regulatory requirements by generating data from Chinese subjects.

### 1.3 Benefit/risk and ethical assessment

Clinical trials demonstrated that statin therapy is associated with a significant reduction in cardiovascular morbidity and mortality when used for either primary or secondary prevention of cardiovascular events (Collins et al 2003, Sever et al 2003, Baigent et al 2005). A meta-analysis by the Cholesterol Treatment Trialists shows that reduction of LDL-C with statin therapy significantly reduced the risk of major vascular events in individuals with a 5-year risk lower than 10%. Each 1 mmol/L reduction in LDL-C produced an absolute reduction in major vascular events of about 11 per 1000 over 5 years (CTT Collaborators 2012).

Additional evidence from imaging trials and epidemiologic studies suggests that initiation of statin therapy earlier in the course of atherosclerotic cardiovascular disease could more effectively prevent age-related progression of atherosclerosis. Strategies to improve primary prevention should be aimed at managing the overall burden of a disease. According to the American College of Cardiology/American Heart Association guidelines, statin treatment in the primary prevention setting is expected to benefit 40- to 75-year-old individuals who have LDL-C levels of 70 to 189 mg/dL, diabetes, or an estimated vascular risk  $\geq 7.5\%$  (Stone et al 2014).

Rosuvastatin has been available in China for approximately 10 years. In various populations, it has been shown to be the most effective statin in improving the serum lipid profile and achieving LDL-C goals (Davidson 2002, Jones et al 2003, Strandberg et al 2004, Lloret et al 2006). Prospective, randomized studies demonstrate the ability of rosuvastatin to reduce the risk of cardiovascular events and stabilize atherosclerosis in Western countries in a low risk population. The JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) study included 17,802 apparently healthy individuals with normal LDL-C ( $<130$  mg/dL), but increased high-sensitivity C-reactive protein ( $\geq 2$  mg/L) levels. In this population, rosuvastatin 20 mg resulted in a significant reduction of cardiovascular events (by 44 %) (Ridker et al 2008).

Regarding the safety of rosuvastatin, analysis in the JUPITER trial showed that myopathy, hepatic injury, and cancer did not occur more frequently with rosuvastatin 20 mg than with placebo during its median follow up of approximately 2 years of treatment. In our pivotal placebo-controlled METEOR study, rosuvastatin 40 mg was well-tolerated during the 2 years of treatment. No cases of hepatitis, rhabdomyolysis, or renal failure occurred. In addition, Chinese patients taking 20 mg or more of rosuvastatin reported adverse events (AEs) that were consistent with its known safety profile or with medical conditions expected in the target population. All the events are listed in the Chinese Package Insert and are consistent with the worldwide experience.

Overall, the benefit of rosuvastatin treatment in the prevention and management of atherosclerotic vascular disease appears to be greater than the risk of adverse effects. The design of this study in Chinese subjects is very similar to the global METEOR study, and the use of placebo in such low-risk subjects is considered as ethical according to the 2007 China Adult Dyslipidemia Management Guidelines. Also Therapeutic Lifestyle Changes (TLC) diet consultation will be provided in conjunction with study visits. Lipid values will be monitored throughout the study. Subjects will be monitored to ensure that they are within the entry

criteria limits for LDL-C throughout the study. Subjects with only hypertension (defined as blood pressure  $\geq 140/90$  mmHg or on antihypertensive treatment) and age and no other risk factors and subjects without hypertension who have 3 or more other risk factors (including age) will be discontinued from the treatment if their LDL-C levels are  $\geq 160$  mg/dL (4.1 mmol/L) on 2 consecutive visits during the study. Subjects without hypertension who have fewer than 3 other risk factors (including age) will be discontinued from the treatment if their LDL-C levels are  $\geq 190$  mg/dL (4.9 mmol/L) on 2 consecutive visits during the study and subsequent treatment will be advised by investigator based on local guideline.

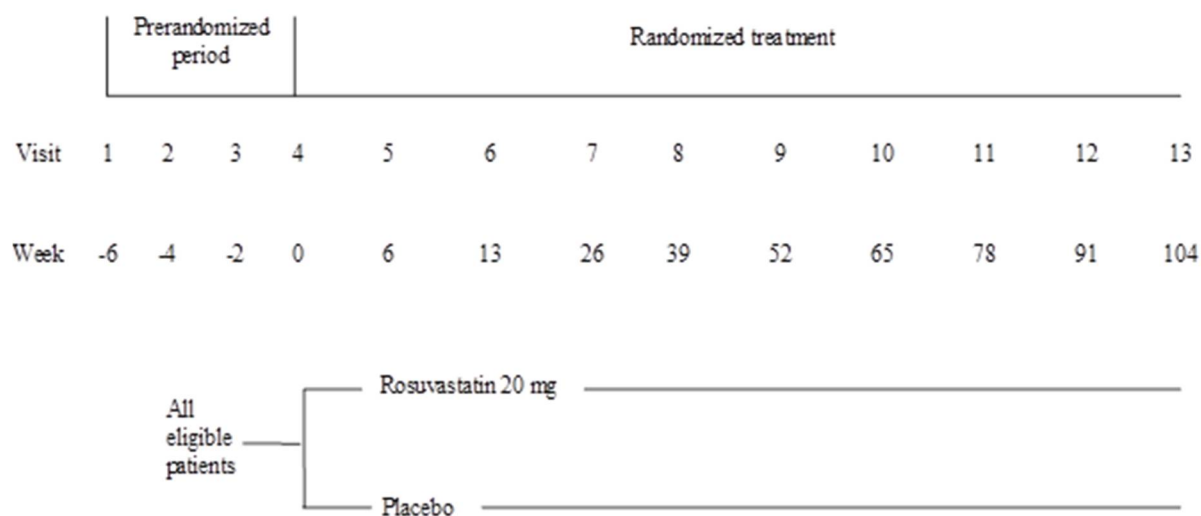
More detailed information about the known benefit and risks of rosuvastatin can be found in the Investigator’s Brochure.

## 1.4 Study Design

This study is a randomized, double-blind, placebo-controlled, multicenter parallel group study assessing the effects of rosuvastatin 20 mg treatment for 104 weeks on the change in IMT of the common carotid artery (CCA), carotid bulb, and internal carotid artery (ICA) in adult Chinese subjects with subclinical atherosclerosis. The study will be conducted across approximately 30 sites in China. The study design is illustrated in [Figure 1](#).

The study consists of 13 study visits: 3 for screening (Weeks -6 [Visit 1], -4 [Visit 2], -2 [Visit 3]), 1 baseline visit (Week 0, [Visit 4]), and 9 treatment visits (Weeks 6 [Visit 5], 13 [Visit 6], 26 [Visit 7], 39 [Visit 8], 52 [Visit 9], 65 [Visit 10], 78 [Visit 11], 91 [Visit 12], and 104 [Visit 13]). Visits 5-13 are to be conducted within  $\pm 7$  days of the scheduled time.

**Figure 1 Study flow chart**



## 2. STUDY OBJECTIVES

### 2.1 Primary objective

Primary Objective:	Outcome Measure:
To assess the efficacy of rosuvastatin 20 mg compared to placebo on slowing progression of carotid intima-media thickness (CIMT) over 104 weeks in Chinese subjects with subclinical atherosclerosis	Annualized rate of change in mean of the maximum (MeanMax) CIMT measurements from each of the 12 carotid artery sites based on all scans performed during the 104-week study period

### 2.2 Secondary objectives

Secondary Objective:	Outcome Measure :
To assess the efficacy of rosuvastatin 20 mg compared to placebo over 104 weeks on slowing progression of intima-media thickness (IMT) in carotid artery segments and on blood lipids in Chinese subjects with subclinical atherosclerosis	<ul style="list-style-type: none"> <li>• Annualized rate of change in the MeanMax IMT of the near and far walls of the right and left common carotid artery (CCA)</li> <li>• Annualized rate of change in the MeanMax IMT of the near and far walls of the right and left carotid bulb</li> <li>• Annualized rate of change in the MeanMax IMT of the near and far walls of the right and left internal carotid artery (ICA)</li> <li>• Annualized rate of change in the mean of the mean (MeanMean) IMT of the near and far walls of the right and left CCA</li> <li>• Change in LDL-C, total cholesterol, HDL-C, triglycerides, non-HDL-C, apolipoprotein (Apo) B, ApoA-I, non-HDL-C/HDL-C, and ApoB/ApoA-I</li> </ul>

### 2.3 Safety objectives

Safety Objective:	Outcome Measure :
To assess the safety and tolerability of rosuvastatin 20 mg compared to placebo over 104 weeks in Chinese subjects with subclinical atherosclerosis	Safety assessments will include AEs, serious adverse events (SAEs), AEs leading to discontinuation, changes in clinical laboratory analyses (chemistry, hematology, and urinalysis), vital signs, 12-lead electrocardiograms (ECGs), and physical examination

### **3. SUBJECT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL**

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

#### **3.1 Inclusion criteria**

For inclusion in the study, subjects should fulfill the following criteria:

1. Provision of informed consent prior to any study-specific procedures
2. Male aged  $\geq 45$  and  $< 70$  years or female aged  $\geq 55$  and  $< 70$  years
3. Subjects with only hypertension (as defined blood pressure  $\geq 140/90$  mmHg or on antihypertensive treatment) and age as CVD risk factors and subjects without hypertension who have 3 or more other risk factors (including age) must have:
  - Fasting LDL C of  $\geq 120$  mg/dL (3.1 mmol/L) and  $< 160$  mg/dL (4.1 mmol/L)Subjects without hypertension who have fewer than 3 other risk factors (including age) must have:
  - Fasting LDL-C of  $\geq 120$  mg/dL (3.1 mmol/L) and  $< 190$  mg/dL (4.9 mmol/L)
4. Triglycerides  $< 500$  mg/dL (5.65 mmol/L) at Visit 1 (Week -6)
5. HDL-C levels  $\leq 60$  mg/dL (1.6 mmol/L) at Visit 1 (Week -6)
6. Maximum IMT  $\geq 1.2$  mm and  $< 3.5$  mm at any location in the carotid ultrasound scans conducted at both Visit 2 (Week -4) and Visit 3 (Week -2)
7. Willing to follow all study procedures including study visits, fasting blood draws, and compliance with study treatment regimen

#### **3.2 Exclusion criteria**

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:

1. Use of pharmacologic lipid-lowering medications (eg, statins, fibrate derivatives, bile acid binding resins, niacin, or its analogues at doses  $> 400$  mg or prescribed Chinese traditional drugs), including cholesterol-absorption inhibitors (CAIs), and CAI/statin combination, within 12 months prior to Visit 1 (Week -6)
2. Current or recent (within 2 weeks of Visit 1, Week -6) use of supplements known to alter lipid metabolism (eg, soluble fibers [including  $> 2$  teaspoons Metamucil<sup>®</sup> or psyllium-containing supplement per day] or other dietary fiber supplements, marine



- oils, sterol/stanol products, or other supplement determined at the discretion of the investigator)
3. History of hypersensitivity reactions to other HMG-CoA reductase inhibitors
  4. Pregnant women, women who are breast-feeding, and women of childbearing potential who are not using chemical or mechanical contraception or who have a positive serum pregnancy test
  5. Clinical evidence of coronary artery disease (CAD) or any other atherosclerotic disease such as angina, MI, transient ischemic attack, symptomatic CAD, cerebrovascular accident, percutaneous coronary intervention, coronary artery bypass graft, peripheral arterial disease, abdominal aortic aneurysm
  6. History of cancer (other than basal cell carcinoma) in the past 2 years
  7. Uncontrolled hypertension defined as either a mean resting diastolic blood pressure of  $\geq 110$  mmHg or a resting systolic blood pressure of  $\geq 180$  mmHg recorded at any time during the screening period
  8. History of diabetes mellitus or current diabetes mellitus
  9. Uncontrolled hypothyroidism defined as a thyroid stimulating hormone (TSH)  $> 1.5$  times the upper limit of normal (ULN) at Visit 1 or subjects whose thyroid replacement therapy was initiated within the last 3 months
  10. History of heterozygous or homozygous familial hypercholesterolemia or known hyperlipoproteinemia Types I, III, IV, or V (familial dysbetalipoproteinemia)
  11. Use of the disallowed concomitant medications (see Section 7.7.1, except “food supplement taken specifically for lipid lowering”) within 12 months prior to Visit 1 (Week -6)
  12. History of alcohol and/or drug abuse within the past 5 years, that in the investigator’s opinion would jeopardize the patient’s participation in the study or interpretation of the data
  13. Active liver disease or hepatic dysfunction as defined by elevations of  $\geq 1.5$  x ULN at Visit 1 (Week -6) in any of the following liver function tests: alanine aminotransferase (ALT), aspartate aminotransferase (AST), or bilirubin
  14. Serum creatine kinase (CK)  $> 3$  x ULN at Visit 1 (Week -6)
  15. Serum creatinine  $> 2.0$  mg/dL (177 mmol/L) recorded during the screening period
  16. Participation in another investigational drug study, and having ingested investigational drug  $\leq 4$  weeks before enrollment in the screening period

17. Previous randomization in the present study
18. History of a significant medical or psychological condition that, in the opinion of the investigator, would compromise the subject's safety or successful participation in the study
19. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)


For the procedures for withdrawal of incorrectly enrolled subjects, see Section 3.4.

### 3.3 Subject enrollment and randomization

Investigator(s) should keep a record, the subject screening log, of subjects who entered prestudy screening.

The investigator(s) will:

1. Obtain signed informed consent from the potential subject before any study-specific procedures are performed.
2. Assign each potential subject a unique enrollment number, beginning with "E#" via interactive web/voice response system (IWRS/IVRS).
3. Determine subject eligibility; see Sections 3.1 and 3.2.
4. Assign each eligible subject a unique randomization code via IWRS/IVRS.

At the start of the screening period, each subject must be allocated an enrollment code (E-code) **CC/** 

At the end of the screening period, subjects who satisfy the entry criteria will be randomly assigned in a 1:1 ratio to 1 of the following 2 treatment groups: rosuvastatin 20 mg or placebo (see Section 3.5). Randomization codes will be assigned strictly sequentially as subjects become eligible for randomization. If a subject withdraws from participation in the study, then his/her enrollment/randomization code cannot be reused. Once a randomization number has been assigned, no attempt should be made to use that number again.

### 3.4 Procedures for handling incorrectly enrolled or randomized subjects

Incorrectly enrolled or randomized subjects will be discontinued from further study treatment and assessments. Subjects who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive investigational product. There can be no exceptions to this rule. Subjects who are enrolled, but subsequently found not to meet all the eligibility

criteria must not be randomized or initiated on treatment, and must be withdrawn from the study.

Where a subject does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the investigator regarding whether to continue or discontinue the subject from treatment. The AstraZeneca study physician must ensure all decisions are appropriately documented.

### 3.5 Methods for assigning treatment groups

**CCI**  
[Redacted text block]

### 3.6 Methods for ensuring blinding

Subjects, the investigator, study site personnel, and Sponsor personnel involved with data review and analysis will remain blinded to study treatment throughout the study.

The study treatment will be blinded by providing rosuvastatin and matching placebo tablets, which are indistinguishable from each other in appearance and will be presented in the same packaging.

Medication will be labelled using a unique kit ID number, which is linked to the randomization scheme. IVRS/IWRS will allocate randomization numbers sequentially when sites call the IVRS/IWRS to randomize an eligible subject. IVRS/IWRS will also allocate the kit ID number to be dispensed to the subject.

The treatment codes will be kept strictly within AstraZeneca to safeguard the integrity of the blind of investigator and subjects and hence to minimize any possible bias in data handling.

AstraZeneca patient safety only has access in the cases of emergency whereas AstraZeneca drug supply chain has access to enable investigational product supply. The central laboratory vendor will remain unblinded to the results of all laboratory tests. After screening, subjects and investigational site personnel will be blinded to blood lipid levels. A flag placed by the central laboratory on laboratory reports will alert site personnel that further action is indicated.

### **3.7 Methods for unblinding**

The treatment code should not be broken except in medical emergencies when the appropriate management of the subject requires knowledge of the treatment randomization. Only in the case of a medical emergency, individual treatment codes, indicating the treatment randomization for each randomized subject, will be available to the investigator(s) or pharmacists from the IVRS/IWRS.

Routines for unblinding in the case of an emergency will be described in the IVRS/IWRS user manual that will be provided to each center. The investigator will document and report the action to AstraZeneca, without revealing the treatment given to the subject to the AstraZeneca staff.

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

### **3.8 Restrictions**

Beginning at the screening visit, all subjects will undergo a diet and lifestyle stabilization period, and will receive counselling regarding the 2007 China Adult Dyslipidemia Management Guidelines TLC diet (see Appendix E). The following restrictions will be applied to subjects in this study:

- Subjects who were blood donors are not to donate blood during the study or for 3 months following their last dose of study treatment.
- Subjects will fast (water is permitted) and refrain from alcohol consumption for 8 hours before visits requiring blood collection.
- Subjects should refrain from cigarette smoking on the morning of each visit.
- Subjects should be advised to maintain their normal physical activities or exercise routines during the trial.

- Subjects should alert the investigator regarding any elective planned surgery or extended travel.

### **3.9 Discontinuation of investigational product**

Subjects may be discontinued from investigational product in the following situations, at the discretion of the investigator(s):

- Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment.
- An AE that in the opinion of the investigator warrants subject withdrawal.
- Severe non-compliance with the study protocol.
- Withdrawal of informed consent.
- CK >10 x ULN accompanied by muscle pain, tenderness, or weakness; see Appendix D for management of increased creatine kinase.
- ALT or AST >3 x ULN; see Appendix C for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.
- Deterioration in the subject's condition that in the opinion of the investigator warrants subject withdrawal.
- At investigator's discretion.
- Development of a condition that made the subject high-risk, such as clinical atherosclerotic disease (MI, transient ischemic attack, stroke, angina pectoris, symptomatic CAD, peripheral arterial disease, abdominal aortic aneurysm) or diabetes mellitus.

Subjects will be monitored to ensure that they are within the entry criteria limits for LDL-C throughout the study. Subjects will be discontinued from the treatment in 1 of 2 circumstances based on a subject's inclusion criteria:

1. Subjects with no additional CVD risk factors other than age and hypertension, and subjects without hypertension who have 3 or more other risk factors (including age) will be discontinued from the treatment if their LDL-C levels are  $\geq 160$  mg/dL (4.1 mmol/L) on 2 consecutive visits during the study.
2. Subjects without hypertension who have fewer than 3 other risk factors (including age) will be discontinued from the treatment if their LDL-C levels are  $\geq 190$  mg/dL (4.9 mmol/L) on 2 consecutive visits during the study.

The results of the LDL-C determinations will remain unblinded to the central laboratory but will be blinded to the investigator and site personnel after screening. A flag on the central laboratory report will notify the investigator that the subject should be removed from the study. The subject will be discontinued from the study and complete the Early Termination visit procedures. Subsequent treatment will be advised by the investigator based on local guidelines.

If the subject is discontinued from investigational product, the principal investigator/sub-investigator will perform the best possible observation(s), test(s) and evaluation(s) as well as give appropriate medication and all possible measures for the safety of the subject. The subject will be required to attend the Early Termination visit (see Section 4.2.11) and to return all study medication.

In cases where a subject has been removed from study treatment for 2 weeks or longer, the AstraZeneca physician or designee needs to be contacted prior to any decision to permanently withdraw or resume investigational product.

### **3.9.1 Procedures for discontinuation of a subject from investigational product**

At any time, subjects are free to discontinue investigational product or withdraw from the study (ie, investigational product and assessments – see Section 3.10), without prejudice to further treatment. A subject who decides to discontinue investigational product will always be asked about the reason(s) for discontinuation and the presence of any AEs. If possible, the subject will be seen and assessed by an investigator(s). All AEs will be followed up (see Section 6), and all investigational products should be returned by the subject.

Subjects who discontinue from the investigational product should complete the Early Termination visit procedures.

## **3.10 Criteria for withdrawal**

### **3.10.1 Screen failures**

Screening failures are subjects who do not fulfill the eligibility criteria for the study, and therefore, must not be randomized. These subjects should have the reason for study withdrawal recorded as ‘Incorrect Enrollment’ (ie, subject does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomized subjects).

### **3.10.2 Withdrawal of the informed consent**

Subjects are free to withdraw from the study at any time (investigational product and assessments), without prejudice to further treatment.

A subject who withdraws consent will always be asked about the reason(s) and the presence of any AE. The investigator will follow up AEs outside of the clinical study.

If a subject withdraws from participation in the study, then his/her enrollment/randomization code cannot be reused. Withdrawn subjects will not be replaced.

When a subject is lost to follow-up (ie, fails to return for study visits), a reasonable effort (eg, documented by receipts for certified mailings) will be made to contact the subject to determine why the subject failed to return and to attempt to schedule the Early Termination visit (see Section 4.2.11).

### **3.11 Discontinuation of the study**

The study may be stopped if, in the judgment of AstraZeneca, trial subjects are placed at undue risk because of clinically significant findings that:

- meet individual stopping criteria or are otherwise considered significant
- are assessed as causally related to investigational product
- are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the subject at the time of discontinuation of follow-up must be recorded in the eCRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the subjects' interests.

## **4. STUDY PLAN AND TIMING OF PROCEDURES**

A schedule of trial procedures showing the timing of events is presented in [Table 1](#).

**Table 1 Study plan**

Study plan	Screening			Treatment									
	1	2	3	4	5	6	7	8	9	10	11	12	13/ET <sup>a</sup>
Week number*	-6	-4	-2	0	6	13	26	39	52	65	78	91	104
Informed consent	√												
Randomization				√									
Vital signs	√			√	√	√		√		√		√	√
Height	√												
Body weight	√			√									√
Adverse events	√	√	√	√	√	√	√	√	√	√	√	√	√
Concomitant medications	√			√	√	√	√	√	√	√	√	√	√
Medical history	√												
Physical examination				√									√
ECG				√									√
Chemistry panel	√ <sup>b</sup>			√	√	√		√ <sup>c</sup>		√ <sup>c</sup>		√ <sup>c</sup>	√
Pregnancy test <sup>d</sup>	√												
Hematology				√									√
Urine sample <sup>e</sup>				√									√
Serum lipid profile	√			√	√	√		√		√		√	√
ApoA-I and ApoB				√									√
Risk assessment	√												
IMT		√ <sup>f</sup>	√ <sup>f</sup>				√		√		√		√ <sup>g</sup>
Dispense investigational product				√		√	√	√	√	√	√	√	
Investigational product compliance					√	√	√	√	√	√	√	√	√
TLC counselling <sup>h</sup>	√			√	√	√	√	√	√	√	√	√	

ALP Alkaline phosphatase; ALT Alanine aminotransferase; Apo Apolipoprotein; AST Aspartate aminotransferase; CK Creatine kinase; ECG Electrocardiogram; ET Early termination; IMT Intima-media thickness; TLC Therapeutic Lifestyle Changes; TSH Thyroid stimulating hormone.

\* Note: The visit window for visits 5-13 is ±7 days.

<sup>a</sup> In the event of early termination, all non-IMT procedures scheduled for Visit 13 (Week 104) are to be conducted. A single IMT is to be performed on any subject who withdraws after 26 weeks.

<sup>b</sup> Including TSH at Visit 1.

<sup>c</sup> Abbreviated chemistry panel including liver function tests (ALT, AST, bilirubin, ALP), serum creatinine, and CK only.

<sup>d</sup> Urine pregnancy test conducted at study site. Required only for premenopausal females. Those with amenorrhea for at least 1 year are exempt.

<sup>e</sup> For complete urinalysis.



- f IMT measurements at Visit 2 (Week -4) and Visit 3 (Week -2) must meet inclusion criteria of maximum IMT  $\geq 1.2$  mm and  $< 3.5$  mm.
- g Final IMT procedures will be scheduled before discontinuation of study treatment. The second and final IMT procedure should occur at or before Visit 13 (Week 104), at the time of discontinuation of the study treatment. The 2 IMT procedures for Visit 13 should be performed on different days when possible.
- h TLC counselling is to be reinforced at each clinic visit.

## 4.1 Screening period

Procedures will be performed according to the Study Plan shown in [Table 1](#). At screening, consenting subjects are assessed to ensure that they meet eligibility criteria. Subjects who do not meet these criteria must not be enrolled in the study. All the assessments and procedures for screening period should be performed after informed consent and within 6 weeks prior to subject randomization.

### 4.1.1 Visit 1 (Week -6)

Subjects will be required to fast for 8 hours (water permitted) prior to Visit 1 (Week -6). Those subjects who have failed to fast for 8 hours should return for their blood draw following an 8-hour fasting period. At the visit, the following procedures will be performed:

- Informed consent
- Recording of vital signs
- Measurement of height
- Measurement of body weight
- Recording of AEs
- Review of prior and concomitant medications
- Medical history
- Chemistry panel, including TSH
- Pregnancy test for premenopausal females only. Those with amenorrhea for at least 1 year are exempt.
- Serum lipid profile
- Risk assessment, including calculation of body mass index
- TLC counselling

#### **4.1.2 Visit 2 (Week -4) and Visit 3 (Week -2)**

At Visits 2 and 3, IMT will be performed. Intima-media thickness measurements at both of these visits must meet the inclusion criteria of maximum IMT  $\geq 1.2$  mm and  $< 3.5$  mm, or the subject is not eligible for the study.

IMT measurements at Visit 2 and Visit 3 are not mandatory to be performed on Weeks -4 and -2, respectively, as long as they are performed on different days after Visit 1, and within 6 weeks prior subject randomization. IMT measurement in Visit 3 is to be conducted after Visit 2 IMT measurement result meets inclusion criteria.

AE needs to be recorded in Visit 2 and Visit 3.

## **4.2 Treatment period**

During the Treatment Period, the procedures will be performed according to the Study Plan shown in [Table 1](#). There will be 10 visits during the 104-week treatment period (Visits 4, 5, 6, 7, 8, 9, 10, 11, 12, and 13 at Weeks 0, 6, 13, 26, 39, 52, 65, 78, 91, and 104, respectively). Visits 5-13 will have a visit window of  $\pm 7$  days.

#### **4.2.1 Visit 4 (Week 0; Baseline)**

Visit 4 at Week 0 is the Baseline visit. Subjects will be required to fast for 8 hours (water permitted) prior to Visit 4 (Week 0). Those subjects who have failed to fast for 8 hours should return for their blood draw following an 8-hour fasting period. At the visit, the following procedures will be performed:

- Randomization
- Recording of vital signs
- Measurement of body weight
- Recording of AEs
- Recording of concomitant medications
- Physical examination
- Electrocardiogram (ECG)
- Chemistry panel
- Hematology
- Urine sample for complete urinalysis
- Serum lipid profile

- ApoA-I and ApoB
- Dispense investigational product
- TLC counselling

#### **4.2.2 Visit 5 (Week 6)**

Subjects will be required to fast for 8 hours (water permitted) prior to Visit 5 (Week 6). Those subjects who have failed to fast for 8 hours should return for their blood draw following an 8-hour fasting period. At the visit, the following procedures will be performed:

- Recording of vital signs
- Recording of AEs
- Recording of concomitant medications
- Chemistry panel
- Serum lipid profile
- Investigational product compliance
- TLC counselling

#### **4.2.3 Visit 6 (Week 13)**

Subjects will be required to fast for 8 hours (water permitted) prior to Visit 6 (Week 13). Those subjects who have failed to fast for 8 hours should return for their blood draw following an 8-hour fasting period. At the visit, the following procedures will be performed:

- Recording of vital signs
- Recording of AEs
- Recording of concomitant medications
- Chemistry panel
- Serum lipid profile
- Dispense investigational product
- Investigational product compliance
- TLC counselling

#### **4.2.4 Visit 7 (Week 26)**

At Visit 7 at Week 26, the following procedures will be performed:

- Recording of AEs
- Recording of concomitant medications
- IMT
- Dispense investigational product
- Investigational product compliance
- TLC counselling

#### **4.2.5 Visit 8 (Week 39)**

Subjects will be required to fast for 8 hours (water permitted) prior to Visit 8 (Week 39). Those subjects who have failed to fast for 8 hours should return for their blood draw following an 8-hour fasting period. At the visit, the following procedures will be performed:

- Recording of vital signs
- Recording of AEs
- Recording of concomitant medications
- Chemistry panel including liver function tests (ALT, AST, bilirubin, ALP), serum creatinine, and CK only
- Serum lipid profile
- Dispense investigational product
- Investigational product compliance
- TLC counselling

#### **4.2.6 Visit 9 (Week 52)**

At Visit 9 at Week 52, the following procedures will be performed:

- Recording of AEs
- Recording of concomitant medications
- IMT

- Dispense investigational product
- Investigational product compliance
- TLC counselling

#### **4.2.7 Visit 10 (Week 65)**

Subjects will be required to fast for 8 hours (water permitted) prior to Visit 10 (Week 65). Those subjects who have failed to fast for 8 hours should return for their blood draw following an 8-hour fasting period. At the visit, the following procedures will be performed:

- Recording of vital signs
- Recording of AEs
- Recording of concomitant medications
- Chemistry panel including liver function tests (ALT, AST, bilirubin, ALP), serum creatinine, and CK only
- Serum lipid profile
- Dispense investigational product
- Investigational product compliance
- TLC counselling

#### **4.2.8 Visit 11 (Week 78)**

At Visit 11 at Week 78, the following procedures will be performed:

- Recording of AEs
- Recording of concomitant medications
- IMT
- Dispense investigational product
- Investigational product compliance
- TLC counselling

#### **4.2.9 Visit 12 (Week 91)**

Subjects will be required to fast for 8 hours (water permitted) prior to Visit 12 (Week 91). Those subjects who have failed to fast for 8 hours should return for their blood draw following an 8-hour fasting period. At the visit, the following procedures will be performed:

- Recording of vital signs
- Recording of AEs
- Recording of concomitant medications
- Chemistry panel including liver function tests (ALT, AST, bilirubin, ALP), serum creatinine, and CK only
- Serum lipid profile
- Dispense investigational product
- Investigational product compliance
- TLC counselling

#### **4.2.10 Visit 13 (Week 104)**

Subjects will be required to fast for 8 hours (water permitted) prior to Visit 13 (Week 104). Those subjects who have failed to fast for 8 hours should return for their blood draw following an 8-hour fasting period. If, at the final visit, the subject has failed to fast, the subject should remain on investigational product until the blood samples have been drawn.

At this last visit during the treatment period (Visit 13), the following procedures will be performed:

- Recording of vital signs
- Measurement of body weight
- Recording of AEs
- Recording of concomitant medications
- Physical examination
- ECG
- Chemistry panel
- Hematology

- Urine sample for complete urinalysis
- Serum lipid profile
- ApoA-I and ApoB
- IMT (2 IMT procedures for Visit 13 are to be performed on different days when possible with the second IMT procedure occurring on or before Visit 13)
- Investigational product compliance

The final 2 IMT procedures will be scheduled before discontinuation of study treatment. The second of the final 2 IMT procedures will occur at or before Visit 13 (Week 104), at the time of discontinuation of the study treatment.

#### **4.2.11 Early Termination Visit**

The term "early termination" refers to a subject's non-completion of a study whether by his or her own choice or the investigator's decision or due to discontinuation of the study by the Sponsor.

In the absence of a medical contraindication or significant protocol violation, every effort will be made by the principal investigator to keep the subject in the study. Should the subject decide to withdraw, an attempt will be made to conduct an Early Termination (ET) Visit within 1 week of discontinuation of study treatment. The ET visit will include all procedures normally done at Visit 13 (Week 104) except the IMT procedures. A single IMT is to be performed on any subject who withdraws after 26 weeks.

The primary reason for a subject withdrawing prematurely should be recorded on the eCRF.

The investigator should notify the Study Physician promptly when a subject is withdrawn, or if the study is stopped at their site by the Independent Ethics Committee/Institutional Review Board, or if the investigator elects to stop the study.

### **4.3 Follow-up period**

A follow-up period is not planned for this study.

## **5. STUDY ASSESSMENTS**

The Rave Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the eCRF as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The

investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

## 5.1 Efficacy assessments

### 5.1.1 IMT Assessment

IMT assessment will be conducted at the times indicated in the Study Plan shown in [Table 1](#). The images will be centrally evaluated at **CCI** or **CCI**.

Intima-media thickness measurements will be made from ultrasound images of the carotid arteries. The thickness of the intima and media is determined as the distance from the interface between the vessel lumen and the intima, to the interface between the media and the adventitia. At each imaging visit, subjects will lie in a supine position with their head turned to the opposite side away from the artery that is being examined. Images will be made of the near and far walls of the CCA, the carotid bulb, and the ICA segments of the right and left carotid arteries. The standard protocol requires each of these 12 artery segments to be imaged from 3 interrogation angles, each of which differs from the adjacent orientation by 30° of angulation (see Appendix G). The images will be recorded and sent to **CCI** for evaluation.

For each carotid artery segment, the images recorded at the various interrogation angles will be measured to determine the largest IMT in each image. The maximum IMT measured from the individual interrogation angles will be entered as the IMT value for that arterial segment. This process is repeated for the 12 carotid arterial segments: the near and far walls of the CCA, the carotid bulb, and the ICA segments of the right and left carotid arteries.

### 5.1.2 Lipid parameters

Blood samples for analysis of lipid parameters will be collected at the times indicated in the Study Plan shown in [Table 1](#).

Subjects must fast for at least 8 hours and must have been sitting for at least 5 minutes before blood samples are taken for lipid assays. If a subject attends a study visit without having fasted for 8 hours, he or she must be asked to return at another time within the visit window for the study visit.

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. A central laboratory manual providing detailed instructions will be provided to each investigational site before trial start.

The principal investigator will ensure that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix B. Any samples identified as Infectious Category A materials are not to be



shipped, and no further samples will be taken from the subject unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

Sample analysis will be carried out in the central laboratory.

## **5.2 Safety assessments**

Safety will be assessed by the incidence of AEs, SAEs, AEs leading to discontinuation, changes in clinical laboratory analyses (chemistry, hematology, and urinalysis), vital signs, 12-lead ECGs, and physical examination during treatment with rosuvastatin. The collection of AEs is described in Section 6 and the other safety assessments are detailed below.

### **5.2.1 Laboratory safety assessments**

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in the Study Plan in Table 1. A full clinical chemistry will be performed at Visit 1 (Week -6), Visit 4 (Week 0), Visit 5 (Week 6), Visit 6 (Week 13), and Visit 13 (Week 104), and an abbreviated chemistry panel including liver function tests (ALT, AST, bilirubin and ALP), serum creatinine, and CK only will be performed at Visit 8 (Week 39), Visit 10 (Week 65), and Visit 12 (Week 91). Additional safety samples may be collected if clinically indicated at the discretion of the investigator. The date and time of collection will be recorded on the appropriate eCRF.

All safety laboratory analyses, other than urine pregnancy tests, will be performed by a central laboratory. The safety laboratory samples will be disposed of after analysis. The central laboratory will provide all collection materials and instructions for sample collection, packaging, and shipment. Urine pregnancy tests will be performed at the clinical sites.

The laboratory variables shown in Table 2 will be measured.

**Table 2 Laboratory Safety Assessments**

<b>Hematology (whole blood)</b>	<b>Clinical Chemistry (serum or plasma)</b>	<b>Urinalysis</b>
Hemoglobin	Alanine aminotransferase	Color
Erythrocytes	Aspartate aminotransferase	Appearance
Hematocrit	Creatine kinase	Specific gravity
Leukocyte cell count	Gamma-glutamyltransferase	Urine reaction pH
Platelet count	Alkaline phosphatase	Glucose
Red cell distribution width	Total bilirubin	Protein (qualitative)
Mean corpuscular volume	Sodium	Ketones
Mean corpuscular hemoglobin	Potassium	Bilirubin
Mean corpuscular hemoglobin concentration	Calcium	Occult blood
Percentage differential leukocyte count	Total protein	Microscopic analysis of any formed elements
	Phosphate	
	Albumin	
	Creatinine	
	Fasting blood glucose	

The investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at the center as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3.

Note: If CK is  $\geq 5$  x ULN, see Appendix D.

Note: If a subject has ALT or AST  $>3$  x ULN, it is recommended to discontinue the investigational product. See Appendix C for further instruction on cases of increases in liver biochemistry values and evaluation of Hy's Law.

### 5.2.2 Medical history and physical examination (including height and weight)

A detailed medical history, including family history of hyperlipidemia, alcohol intake, use of other medications or drugs, as well as CHD, and risk factors such as smoking, diabetes mellitus, and a family history of premature CHD will be recorded on the eCRF at Visit 1 (Week -6).

A full physical examination (including stigmata of hyperlipidemia) including cardiovascular system, respiratory system, central nervous system, skin, gastrointestinal system, musculoskeletal system, endocrine system, ears, nose and throat, eyes, and lymph nodes will be recorded at the times indicated in the Study Plan in Table 1. Weight will be recorded at Visit 1 (Week -6), Visit 4 (Week 0), and Visit 13 (Week 104), and height will be recorded only at Visit 1 (Week -6).

### **5.2.3 ECG**

A 12-lead ECG will be performed after the subject has been lying down for 5 minutes at the times indicated in the Study Plan in [Table 1](#). Heart rate, P and QRS durations, PR, QT and QTc intervals will be recorded from standard lead of the computerized quantitative 12-lead ECG.

For information on how AEs based on ECGs should be recorded and reported, see [Section 6.3](#).

### **5.2.4 Vital signs**

Blood pressure and resting heart rate will be measured at the times indicated in the Study Plan in [Table 1](#). Blood pressure will be measured after the subject has been resting for 5 minutes, using a standard non-invasive equipment and recorded. Heart rate will be taken manually from the radial pulse.

For information on how AEs based on vital signs should be recorded and reported, see [Section 6.3](#).

## **5.3 Other assessments**

### **5.3.1 Risk assessment**

During the screening period at Visit 1 (Week -6), subjects will be evaluated using the risk assessment introduced in the 2007 China Adult Dyslipidemia Management Guidelines (see [Appendix F](#)). Patients with existing CHD (or a CHD risk equivalent) are at the highest risk and will be excluded from participation. According to the guideline, hypertension plays a role equal to that of any 3 other risk factors. Thus, subjects with hypertension and 3 or more additional CVD risk factors will be regarded as at high risk and will be excluded from participation. The risk assessment will be determined according to the counting of categorical CVD risk factors of age, hypertension, smoking, obesity, family history of premature CHD, and HDL-C (see [Appendix F](#)).

### **5.4 Pharmacokinetics**

Pharmacokinetic samples will not be taken during the study.

### **5.5 Pharmacodynamics**

Pharmacodynamic samples will not be taken during the study.

### **5.6 Pharmacogenetics**

Pharmacogenetic samples will not be taken during the study.

### **5.7 Biomarker analysis**

Biomarkers will not be assessed in this study.

## **6. SAFETY REPORTING AND MEDICAL MANAGEMENT**

The principal investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

### **6.1 Definition of adverse events**

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). 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.

The term AE is used to include both serious and non-serious AEs.

### **6.2 Definitions of serious adverse event**

A serious adverse event is an AE occurring during any study phase (ie, screening, treatment, follow-up), that fulfills one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above

For further guidance on the definition of an SAE, see Appendix A.

### **6.3 Recording of adverse events**

#### **6.3.1 Time period for collection of adverse events**

All AEs, including SAEs, will be collected from the time of signature of the informed consent throughout the treatment period and within 10 days after last dose of study drug.

#### **6.3.2 Follow-up of unresolved adverse events**

Any AEs that are unresolved at subject's last visit/ contact in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF.

AstraZeneca retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

### **6.3.3 Variables**

The following variables will be collected for each AE:

- AE (verbatim)
- Date and time when the AE started and stopped
- Maximum intensity (mild, moderate, or severe)
- Whether the AE is serious or not
- Investigator causality rating against the investigational product (yes or no)
- Action taken with regard to investigational product
- AE caused subject's withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date investigator became aware of serious AE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Description of AE

The investigator will rate the intensity of AEs using 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)

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 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Section 6.2.

#### **6.3.4 Causality collection**

The investigator will assess causal relationship between investigational product and each AE, and answer “yes” or “no” to the question “Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?”

For SAEs, causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as ‘yes.’

For a guide to the interpretation of the causality question, see Appendix A.

#### **6.3.5 Adverse events based on signs and symptoms**

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: “Have you had any health problems since the previous visit?” or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

#### **6.3.6 Adverse events based on examinations and tests**

The results from protocol-mandated laboratory tests and vital signs will be summarized in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, and ECGs should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign/ECG is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible, the reporting investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

### 6.3.7 Hy's Law

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT  $\geq 3$  x ULN together with total bilirubin  $\geq 2$  x ULN will need to be reported as SAEs. See Appendix C for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

## 6.4 Reporting of serious adverse events

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

If any SAE occurs in the course of the study, then investigators or other site personnel inform the appropriate AstraZeneca representatives within 1 day (ie, immediately but **no later than 24 hours**) of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day (ie, immediately but **no later than 24 hours**) of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the investigator or other study site personnel reports an SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the investigator/study site personnel how to proceed.

## 6.5 Overdose

There is no specific antidote to rosuvastatin.

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

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module
- An overdose without associated symptoms is only reported on the Overdose eCRF module

If an overdose on an AstraZeneca investigational product occurs in the course of the study, then the investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with an SAE, the standard reporting timelines apply; see Section 6.4. For other overdoses, reporting must occur within 30 days.

## 6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca.

### 6.6.1 Maternal exposure

If a subject becomes pregnant during the course of the study, the investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representative within 1 day (ie, immediately but **no later than 24 hours**) of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.



### 6.6.2 Paternal exposure

Male subjects should refrain from fathering a child or donating sperm during the study and 3 months following the last dose.

## 6.7 Management of investigational product-related toxicities: Dose reductions

Dose reductions are not permitted in this study.

## 7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

### 7.1 Identity of investigational product(s)

All investigational products will be supplied to the investigator by AstraZeneca in tablet formulation for oral use.

Investigational product	Dosage form and strength	Manufacturer
Rosuvastatin	20 mg tablets <sup>a</sup>	AstraZeneca
Placebo	Matching placebo tablets <sup>a</sup>	AstraZeneca

a. The lot number will be identified in the clinical study report. Rosuvastatin (CRESTOR) Clinical tablets for use in clinical trials are identical to CRESTOR commercial tablets in all aspects with the exception of the tablet markings. CRESTOR Clinical tablets are plain (unmarked), while commercial tablets are marked (intagliated).

### 7.2 Dose and treatment regimens

At Visit 4 (Week 0), the subject will be randomized to either rosuvastatin 20 mg or placebo. Beginning at Visit 4, subjects will take the investigational product orally with water once daily for the duration of the 104-week treatment period. Each dose will consist of 1 tablet. The subject should be encouraged to take the investigational product at the same time each day.

### 7.3 Labelling

The investigational product will be supplied in subject-specific labelled bottles. Each labelled bottle will contain sufficient medication for at least each treatment period plus overage.

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements for labelling. Label text will be translated into local language.

### 7.4 Storage

All investigational products must be kept in a secure place under appropriate storage conditions, as specified on the investigational product label on each bottle.

The investigational product must be stored in its original container in a lockable storage facility until dispensed to the subjects and should be protected from light and moisture. The investigational product must be stored below 25°C and should not be frozen.

## 7.5 Compliance

Subjects must return all unused medications and empty containers to the investigator. The number of tablets returned at Visits 5 (Week 6), 6 (Week 13), 7 (Week 26), 8 (Week 39), 9 (Week 52), 10 (Week 65), 11 (Week 78), 12 (Week 91) and 13 (Week 104) must be checked against the number of tablets dispensed to determine subject compliance.

Compliance will be calculated, as follows:

$$\% \text{ Compliance} = \frac{\# \text{ of tablets dispensed} - \# \text{ of tablets returned}}{\# \text{ of days between visits} \times \# \text{ of tablets per daily dose}} \times 100$$

A subject should be counselled on the importance of taking his or her medication as prescribed. Any subject taking less than 80% of the prescribed investigational product at 2 consecutive visits will be considered non-compliant. The subject will continue in the study but will be counselled on the importance of taking his or her medication regularly.

In cases where a subject is removed from treatment for 2 weeks or longer, the AstraZeneca physician must be contacted prior to resuming therapy.

## 7.6 Accountability

The investigational products provided for this study will be used only as directed in the study protocol. The investigational products are to be prescribed only by the investigator or his or her designee.

Subjects must return all unused medications and empty containers to the investigator. The study personnel will account for all investigational products dispensed to and returned from the subject.

The investigator must maintain accurate records to account for the receipt of the investigational materials. This record keeping consists of a dispensing record that includes the identification of the person receiving the medication, the date of dispensing, and any unused medication returned to the investigator. The dispensing record, in addition to any drug accountability information, must be recorded on the eCRFs. The delivery records must be able to be reconciled with records of usage and returned stocks. Any discrepancies must be reconciled. Certificates of delivery and returns must be signed by the investigator or responsible person.

The investigator will retain the returned medication until AstraZeneca-authorized personnel collect it, along with any trial treatments not dispensed. An AstraZeneca monitor will account for all investigational products received at the center, unused investigational products, and

appropriate destruction (according to local procedures). Certificates of destruction and/or return should be signed.

## 7.7 Concomitant and other treatments

The administration of all medication (including investigational products) must be recorded in the appropriate sections of the eCRF. Introduction of new concomitant drugs should be recorded throughout the trial.

Other medication that is considered necessary for the subject's safety and well-being may be given at the discretion of the investigator and are acceptable, provided that these medications do not conflict with the exclusion criteria (Section 3.2).

Subjects must follow the medication restrictions outlined in the inclusion and exclusion criteria (Section 3.1 and Section 3.2, respectively) during the study.

### 7.7.1 Prohibited medications

With the exception of lipid-regulating drugs, the only other disallowed drugs will be cyclosporine and tacrolimus, azathioprine sodium, and other potent immunosuppressants as listed in Table 3 since use of these agents may increase the risk of AEs during treatment with rosuvastatin.

**Table 3 Disallowed concomitant medications**

<b>Class of drug</b>	<b>Generic name</b>
Lipid Regulation	niacin/nicotinic acid (includes vitamins/supplements with >50mg/day niacin/nicotinic acid) bile acid sequestrant probucol clofibrate fenofibrate gemfibrozil (and other fibrates) all statins, such as (but not exclusively) atorvastatin, lovastatin, pravastatin, rosuvastatin (except for study medication), simvastatin, and fluvastatin cholesterol-absorption inhibitor/ezetimibe cholestyramine cholesterol-absorption inhibitor and statins combination/vytorin any other prescription medicine given to treat dyslipidemia any other prescription medicine given for lipid lowering any food supplement taken specifically for lipid lowering
Immunosuppressants	azathioprine sodium tacrolimus cyclosporine
Protease inhibitors	all protease inhibitors

### **7.7.2 Warfarin (including warfarin derivatives and Coumadin)**

In 2 clinical studies, one in normal volunteers and the other in subjects receiving a coumarin anticoagulant, rosuvastatin potentiated the effect of the coumarin anticoagulant. With rosuvastatin and other HMG-CoA reductase inhibitors, clinically evident bleeding and/or increased prothrombin time has been reported in a few subjects taking coumarin anticoagulants concomitantly.

For this reason, careful monitoring of international normalized ratio (INR) is required when warfarin and blinded investigational product are co-administered at any time during the subject's participation during this trial. It is suggested that the investigators should, in accordance with usual practice, measure INR frequently until warfarin dose stabilization is achieved, and periodically thereafter in the following situations:

- when starting warfarin therapy in a randomized subject
- when a subject already receiving warfarin begins randomized trial treatment

To provide current information and advice, investigators should telephone their study monitor to discuss the situation with the AstraZeneca Study Team Physician.

### **7.7.3 Other concomitant treatment**

Other medication other than that described above, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

## **8. STATISTICAL ANALYSES**

### **8.1 Statistical considerations**

All personnel involved with the analysis of the study will remain blinded until database lock and protocol violators are identified.

Analyses will be performed by AstraZeneca or its representatives.

A comprehensive Statistical Analysis Plan will be prepared and any subsequent amendments will be documented, with final amendments completed prior to unblinding of the data.

### **8.2 Sample size estimate**

CCI



## 8.3 Definitions of analysis sets

### 8.3.1 Efficacy analysis sets

Two analysis sets will be used for efficacy evaluation:

- The Intent-to-Treat (ITT) population consists of all randomized subjects. Subjects will be analyzed according to the treatment randomized.
- The per-protocol (PP) population is a subset of the ITT population that includes subjects without any important protocol deviations. The criteria for important protocol deviations will be defined in the statistical analysis plan. Subjects will be analyzed according to the treatment actually received.

The ITT population will be the primary efficacy analysis population. The CIMT analysis will be performed based on both the ITT and PP populations, and lipid and apolipoprotein analyses will be performed on the ITT population only.

### 8.3.2 Safety analysis set

The safety analysis set will consist of all subjects who took at least 1 dose of investigational product or placebo. Subjects will be analyzed according to treatment actually received, and data in this population will be presented based on treatment actually received. For subjects who received both treatments during the study, the algorithm to be used for assignment of treatment will be detailed in the Statistical Analysis Plan.

## 8.4 Outcome measures for analyses

### 8.4.1 Primary variable

Maximum CIMT measurements from 3 different angles (Max CIMT) obtained at each of the 12 carotid artery sites at each measuring timepoint will be provided by the imaging center. Max CIMT measurement will be analyzed for estimation of the annualized rate of change in MeanMax of the 12 carotid artery sites during the 104-week study period. The 12 carotid artery sites include the near and far walls of the right and left CCA, carotid bulb, and ICA.

### 8.4.2 Secondary variables

The secondary efficacy variables are as follows:

- Max CIMT of the near and far walls of the right and left CCA

- Max CIMT of the near and far walls of the right and left carotid bulb
- Max CIMT of the near and far walls of the right and left ICA
- Mean CIMT (mean value of 3 CIMT measurements from the 3 angles) of the near and far walls of the right and left CCA.
- Percentage change from baseline in LDL-C, total cholesterol, HDL-C, triglycerides, non-HDL-C, Apo B, ApoA-I, non-HDL-C/HDL-C, and ApoB/ApoA-I
- Segment specific Max CIMT or Mean CIMT measurement will be analyzed for the estimation of the corresponding annualized rate of change as secondary efficacy evaluation.

#### **8.4.3 Safety variables**

Safety variables are AEs, SAEs, AEs leading to discontinuation, changes in clinical laboratory analyses (chemistry, hematology, and urinalysis), vital signs, 12-lead ECGs, and physical examination.

### **8.5 Methods for statistical analyses**

All efficacy measures will be summarized by randomized treatment group using descriptive statistics or frequency distributions (whichever is appropriate) for the raw data. For variables subject to formal statistical analysis, such as hypothesis testing and statistical modeling, the results of the analysis will be presented and interpreted.

#### **8.5.1 Analysis of the primary efficacy variable**

A linear mixed-effects model will be used for the primary analysis to assess the difference in the annualized rate of change in the CIMT measurements across 12 carotid artery sites between rosuvastatin 20 mg and placebo treatment over 104 weeks.

For the primary efficacy analysis, the dependent variable is the maximum CIMT measurement from 3 interrogation angles at each of the 12 carotid artery sites at each timepoint of CIMT measurement during the 104-week study period. The model includes fixed effects for treatment group, time, time by treatment interaction, ICVD risk stratification (<5%/5% to 10%), age, sex, centre and scan reader, and random effects for the intercept and slope at the individual subject level and carotid artery site within subject. Ultrasound machine will be included as a fixed effect as well if different types of machines are deployed across sites. For time of CIMT measurement, the 2 pre-randomization visits and the final 2 visits at the end-of-study will be treated as separate time points. Details will be defined in the Statistical Analysis Plan. Time, as a continuous variable, is the interval from the date of randomization to the date of CIMT measurement. Differences in annualized change between rosuvastatin and placebo will be evaluated by testing the time-by-treatment interaction term.

In the analysis, let  $\beta_1$  and  $\beta_2$  represent respectively the coefficient parameters for time and time by treatment interaction in the mixed effect model. The annualized rate of change (slope) in MeanMax CIMT in placebo will be estimated by the coefficient parameter  $\beta_1$ , the annualized rate of change (slope) in MeanMax CIMT in rosuvastatin will be estimated by  $\beta_1 + \beta_2$ , and the difference of annualized rate (slope) of change between 2 groups will be estimated by  $\beta_2$ . Then, the null and the alternative primary hypothesis can be expressed as  $H_0: \beta_2 = 0$  vs.  $H_a: \beta_2 \neq 0$  at a significance level of 0.05 two-sided.

### 8.5.2 Analysis of the secondary efficacy variables

The same statistical method used for the primary CIMT efficacy analysis will be applied to model the segment-specific secondary CIMT efficacy outcome measurements. The difference in the annualized rate of change between rosuvastatin and placebo for the secondary CIMT outcome measures will also be evaluated by testing the time-by-treatment interaction term in each model fitting.

Secondary lipid and lipoproteins outcome measures are the percentage change from baseline, which will be analyzed by analysis of covariance with terms for treatment in the model. For lipid measurements (LDL-C, total cholesterol, HDL-C, triglycerides, non-HDL-C, non-HDL-C/HDL-C), both the analysis of the percent change from baseline at final visit, and the analysis of the percent change from baseline to time-weighted average during treatment will be performed. In the evaluation of change from baseline to final visit, missing observations will be imputed by last observation carried forward (LOCF). The time-weighted average lipid value is defined as the lipid value multiplied by the number of days since the last lipid assessment, summed for all lipid observations and divided by the sum of days between all visits. No imputation will be made for lipid missing values for time-weighted average analysis. For apolipoprotein measurements (ApoB, ApoA-I, ApoB/ApoA-I), the analysis of the percent change from baseline to final visit (LOCF) will be performed.

No multiplicity adjustment will be applied to the secondary efficacy analysis.

### 8.5.3 Safety Analysis

Safety outcome measures including incidence of AEs (including SAEs and AEs leading to discontinuation), changes in clinical laboratory analyses (chemistry, hematology, and urinalysis), vital signs, 12-lead ECGs, and physical examination will be summarized descriptively. Safety analysis will be conducted using the safety analysis set. No formal statistical test will be performed.

AEs will be categorized according to 2 definitions:

- AEs reported during the screening phase
- Treatment-emergent AEs

AEs will be reported according to a standard dictionary for body system and preferred term.

#### **8.5.4 Demographics and baseline data**

Descriptive statistics of demographic and other baseline characteristics will be provided.

#### **8.5.5 Subgroup analysis**

Subgroup analysis of the primary efficacy measurement will be specified in detail in Statistical Analysis Plan.

#### **8.5.6 Interim analysis**

No interim analysis is planned.

#### **8.5.7 Sensitivity analysis**

Analysis of CIMT data on the PP population will be performed as a check of the robustness of the analysis on the ITT population.

### **9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA**

#### **9.1 Training of study site personnel**

Before the first subject is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study-specific procedures and system(s) utilized.

The principal investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The principal investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

IMT sonographers from each study center must participate in a uniform training and certification program coordinated by **CCI**.

Documentation related to certification is maintained at **CCI**.

#### **9.2 Monitoring of the study**

During the study, an AstraZeneca representative 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 and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual. and that investigational product accountability checks are being performed.
- Perform source data verification (a comparison of the data in the eCRF with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts).
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

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

#### **9.2.1 Source data**

Refer to the Clinical Study Agreement for location of source data.

#### **9.2.2 Study agreements**

The principal investigator at each center should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

Agreements between AstraZeneca and the principal investigator should be in place before any study-related procedures can take place, or subjects are enrolled.

#### **9.2.3 Archiving of study documents**

The investigator follows the principles outlined in the Clinical Study Agreement.

### **9.3 Study timetable and end of study**

The end of the study is defined as 'the last visit of the last subject undergoing the study'.

The study is expected to start in 3Q 2015 and to end by 1Q 2019.

The study may be terminated at individual centers if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with rosuvastatin.

## **9.4 Data management by AstraZeneca**

Data management will be performed by AstraZeneca Data Management Center staff, according to the Data Management Plan. AEs and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities. Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by the Medical Coding Team at the AstraZeneca Data Management Center.

The data collected through third-party sources will be obtained and reconciled against study data.

Data queries will be raised for inconsistent, impossible, or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

When all data have been coded, validated, and locked, a clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

### **Serious Adverse Event (SAE) Reconciliation**

SAE reconciliation reports are produced and reconciled with the Patient Safety database and/or the investigational site.

## **10. ETHICAL AND REGULATORY REQUIREMENTS**

### **10.1 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 International Conference on Harmonisation (ICH)/GCP, applicable regulatory requirements, and the AstraZeneca policy on Bioethics and Human Biological Samples.

### **10.2 Subject data protection**

The 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.

### **10.3 Ethics and regulatory review**

An Ethics Committee should approve the final study protocol, including the final version of the informed consent form and any other written information and/or materials to be provided to the subjects. The investigator will ensure the distribution of these documents to the applicable Ethics Committee and to the study site staff.

The opinion of the Ethics Committee should be given in writing. The investigator should submit the written approval to AstraZeneca before enrollment of any subject into the study.

The Ethics Committee should approve all advertising used to recruit subjects for the study.

AstraZeneca should approve any modifications to the informed consent form that are needed to meet local requirements.

Before enrollment of any subject into the study, the final study protocol, including the final version of the informed consent form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, Ethics Committees, and principal investigators with safety updates/reports according to local requirements.

Each principal investigator is responsible for providing the Ethics Committees/Institutional Review Board 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 so that he/she can meet these reporting requirements.

### **10.4 Informed consent**

The principal investigator(s) at each center will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study.
- Ensure each subject is notified that he/she is free to discontinue from the study at any time.
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided.
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study.

- Ensure the original, signed informed consent form(s) is/are stored in the investigator's Study File.
- Ensure a copy of the signed informed consent form is given to the subject.
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

## **10.5 Changes to the protocol and informed consent form**

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

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each principal investigator(s). For distribution to the Ethics Committee, see Section 10.3.

If a protocol amendment requires a change to a center's informed consent form, AstraZeneca and the center's Ethics Committee are to approve the revised informed consent form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

## **10.6 Audits and inspections**

Authorized representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the center.

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Study Code D3565C00003  
Edition Number 2.0  
Date 28 Mar 2018

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## **12. APPENDIX**

## **12.1 Appendix A 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**

Outpatient 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**

When making an assessment of causality consider the following factors 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?
- De-challenge 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.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

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

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of ‘related’ is made if following a review of the relevant data, there is evidence for a ‘reasonable possibility’ of a causal relationship for the individual case. The expression ‘reasonable possibility’ of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as ‘not related’.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

## **12.2 Appendix B International Airline Transportation Association (IATA) 6.2 Guidance Document**

## **LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES**

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

**Category A Infectious Substances** are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

**Category B Infectious Substances** are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

**Exempt** - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

### **12.3 Appendix C Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law**

### 12.3.1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug induced liver injury (DILI) caused by the investigational medicinal product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting adverse events (AE) and serious adverse events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

### 12.3.2 Definitions

#### Potential Hy's Law (PHL)

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT)  $\geq 3x$  upper limit of normal (ULN) **together with** total bilirubin (TBL)  $\geq 2x$ ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

#### Hy's Law (HL)

AST or ALT  $\geq 3x$  ULN **together with** TBL  $\geq 2x$ ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e. on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

### 12.3.3 Identification of potential hy's law cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT  $\geq 3x$ ULN
- AST  $\geq 3x$ ULN



- $TBL \geq 2xULN$

When a patient meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the patient meets PHL criteria (see Section 12.3.2 of this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

#### **12.3.4 Follow-up**

##### **12.3.4.1 Potential Hy's Law Criteria not met**

If the patient does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the patient has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

##### **12.3.4.2 Potential Hy's Law Criteria met**

If the patient does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated

- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician.
- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

### **12.3.5 Review and Assessment of potential hy's law cases**

The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term ‘Potential Hy’s Law’) applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

### **12.3.6References**

FDA Guidance for Industry (issued July 2009) ‘Drug-induced liver injury: Premarketing clinical evaluation’:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>

## **12.4 Appendix D Guidance for Management of Muscle Symptoms and Increased Creatine Kinase (CK)**

## **GUIDANCE FOR 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.
- If CK is found to be elevated  $\geq 5 \times \text{ULN}$  on routine testing, the subject should be questioned about muscle symptoms.
- A suitably-experienced physician should be involved in deciding appropriate management for the subject. The physician should be alerted to the occurrence of unexplained muscle symptoms, and any CK values  $\geq 5 \times \text{ULN}$  and must take immediate action if CK  $> 10 \times \text{ULN}$ .
- For CK  $> 10 \times \text{ULN}$  with or without muscle symptoms, discontinue study drug.
- For CK 5-10xULN:
  - If symptomatic and no alternative explanation exists, withhold therapy
  - If asymptomatic, or if symptomatic but alternative explanation exists, follow symptoms and CK levels weekly until there is no longer medical concern or symptoms worsen and meet criteria above
- The following questioning and follow-up investigations should be considered:
  - Clarify the nature, duration and intensity of relevant symptoms
  - Clarify and document whether the patient was taking study treatment at the time of the event, or when the last dose of study treatment was taken. Document dosing information in source and report if appropriate (eg, if considered an SAE).
  - Review possible predisposing factors, such as: unaccustomed exercise (including decorating, gardening, etc.), heavy alcohol intake, viral illness (consider performing serology), concomitant medications (e.g. anesthetics, cholesterol -lowering agents – niacin, clofibrate, statins, ezetimibe, glucocorticoids, narcotics, chloroquine, etc.) 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
- Myopathy is defined as muscle aches or weakness in association with CK increased to  $>10 \times \text{ULN}$ . If myopathy occurs 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 AstraZeneca representative must be informed.
- If study treatment is temporarily disrupted, it is suggested that the AstraZeneca representative be consulted before restarting study treatment.
- The AstraZeneca representative should be consulted prior to permanently withdrawing a patient.

## **12.5 Appendix E Therapeutic Lifestyle Changes (TLC) Diet**

## **THERAPEUTIC LIFESTYLE CHANGES (TLC) DIET**

2007 China adult dyslipidemia management guidelines recommend a multifaceted lifestyle approach to reduce the risk of cardiovascular disease.

The recommended essential elements of TLC are listed in the Table below.

### **Essential elements of the Therapeutic Lifestyle Changes Diet**

<b>Essential element</b>	<b>Recommendation</b>
Reduce the nutrient that elevates the LDL-C	
Saturated Fatty Acids	<7% of total calories
Dietary Cholesterol	<200mg/d
Increase the dietary component that lowers LDL-C	
Phytosterols	2g/d
Soluble Cellulose	10~25g/d
Total Calories	Balance energy intake and expenditure to maintain desirable body weight/prevent weight gain
Physical Activity	Including enough moderate exercise, obliterate more than 200kcal of energy per day.

Note: Trans-Fatty Acids also increase the LDL-C. It is unfavourable to intake more



## **12.6 Appendix F Definition of China Adult Dyslipidemia Management Guidelines Risk Factors**

## **DEFINITION OF CHINA ADULT DYSLIPIDEMIA MANAGEMENT GUIDELINES RISK FACTORS**

- Hypertension (as defined:  $BP \geq 140/90$  or on antihypertensive treatment)
- Smoking
- HDL-C  $< 40$  mg/dL
- Obesity (body mass index  $\geq 28$  kg/m<sup>2</sup>)
- Family history of premature CHD (CHD in male first degree relative  $< 55$  years of age; CHD in female first degree relative  $< 65$  years of age)
- Age (Male  $\geq 45$  years, Females  $\geq 55$  years)

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Subtract one (1) risk factor if HDL-C  $\geq 60$  mg

## **12.7 Appendix G Carotid Ultrasound Process**

Clinical Study Protocol  
Drug Substance  
Study Code  
Edition Number 2.0  
Date 28 Mar 2018

# **Carotid Ultrasound Protocol & Quality Assurance Manual**

Version 1.0

## List of Abbreviations

BIF or BIFUR	Bifurcation
CCA	Common carotid artery
CIMT	Carotid intima-media thickness
DICOM	Digital Imaging and Communications in Medicine
DVD	Digital video disk
ECA	External carotid artery
ECG	Electrocardiogram
ICA	Internal carotid artery
ID	Identification
IMT	Intima-media thickness
LA	Left arm
LT	Left
OAI	Optimal anatomical interrogation angle
QA	Quality assurance
QC	Quality control
RA	Right arm
RL	Right leg
RT	Right
SOP	Standard Operating Procedure
TFD	Tip of flow divider
USB	Universal serial bus

## **12.7.1 Ultrasound Training and Certification**

### **12.7.1.1 Introduction**

The responsibilities of the research sonographer in this study differ significantly from those normally assumed by the clinical sonographer. The off-line reading of the B-mode images also requires skills that differ significantly from the routine clinical approach to image interpretation and measurement. Consequently, all sonographers and readers must participate in a uniform training and certification program coordinated by the QC Center(s). Documentation related to certification is maintained at the QC Center(s).

### **12.7.1.2 Training**

Each sonographer and reader first completes a didactic ultrasound training session lead by QC Center staff and representatives of equipment manufacturers, as appropriate. A set of pre-training materials providing a common background on CIMT measurements and an overview of the study specific CIMT scan protocol will be provided to each Imaging Center approximately one month before the CIMT carotid ultrasound protocol training session is conducted. The primary objective of the central training session is to familiarize the sonographer with the general operation of the selected ultrasound instrument with emphasis on the use of each important control used in this study protocol and its function. Standardization of the equipment settings is stressed. Detailed instruction on scanning of the carotid arteries is provided. The specific research scanning protocol is demonstrated to all sonographers and readers. Supervised practice of the scanning protocol is conducted on volunteers during the training by QC Center personnel.

Following the central training, the sonographers continue scanning practice at their respective Imaging Center in order to complete the certification requirements as soon as possible. This typically takes two to eight weeks depending upon the experience and effort commitment of the sonographer to the study. Ideally, sonographers should practice the protocol for a period of two hours per day immediately following the conclusion of the initial training session.

### **12.7.1.3 Sonographer Certification**

The sonographer certification requirements consist of submitting a total of up to 20 good quality protocol scans on volunteers. We recommend that the last five of these 20 scans are done on volunteers in the age group of the study population. These scans are reviewed and critiqued by QC Center staff and must demonstrate a high level of proficiency in the carotid ultrasound protocol. Each sonographer after completion of the scan carefully reviews the recorded images for each certification examination and completes a standard review form (see Carotid Ultrasound Training Manual). This is to ensure that images and annotations are correctly recorded and to permit a careful self-evaluation of adherence to the scanning protocol before sending the scans and forms to the QC Center(s). The QC Center staff will evaluate the scans again, and observations and critiques are returned by e-mail within five working days after receipt of the ultrasound material to each sonographer to indicate the quality of performance and suggestions for improvement. The expectation is that 20 scans are needed to demonstrate a high level of proficiency in the performance of the protocol. Less than 20 scans are possible when a sufficiently high level of performance is achieved more

rapidly or for sonographers experienced in similar protocols. At least three consecutive scans (graded as level A) are needed for a sonographer to receive initial certification.

#### **12.7.1.4 Reader Certification**

The ultrasound readers receive instruction on the operation of the reading station instrumentation located at the QC Center(s) and on the performance of the B-mode image reading protocol. Readings are then performed on the recordings from the volunteer studies submitted for sonographer certification. After completion of 10 satisfactory readings on these scans in duplicate that demonstrate a high level of proficiency in the performance of the protocol, each reader receives initial certification. Outcome variable data including within-reader and between-reader reproducibility are of primary importance in the certification process. In general, we aim at having an intra-class correlation coefficient for between readings of 0.75 or higher. Certification of readers may be achieved based on less than 10 readings if a sufficiently high level of performance is demonstrated more rapidly. This may be relevant especially for experienced readers, i.e., those who have worked with a similar reading protocol in previous studies and have shown in these previous studies to read in a consistent and reproducible manner.

#### **12.7.1.5 Performance and Maintenance of Equipment**

It is the primary responsibility of the sonographer and reader to assure that the ultrasound or reading equipment is performing optimally prior to each exam or reading. Routine preventive maintenance must be provided at the interval recommended by the manufacturer. Any service related problems that could reduce data quality during the examination should be documented in a service log and rapidly resolved by the equipment manufacturer. The QC Center(s) and study sponsor must approve all upgrades, to hardware and software in advance in writing. In addition, documentation must be made in the service log. Modification of the scanning or reading hardware and software can only be made during the course of the study with prior written approval of the QC Center(s) and sponsor to maintain standardization throughout the study.

#### **12.7.1.6 Image Data Recording**

This study will record digital image data in DICOM format for off-line analysis. The digital files may be uploaded directly over the internet or recorded on a digital media (e.g., video disk [DVD] or universal serial bus [USB] for transfer to the QC Center[s]). Several scans may be recorded on a single DVD or USB. Numbered labels will be used to facilitate tracking of digital media. Detailed instructions of imaging uploading will be provided in the carotid ultrasound training manual.

#### **12.7.1.7 Contact Addresses**

Clinical/imaging sites should refer questions, comments and suggestions related to the Carotid Ultrasound Protocol to:

**PPD**



Clinical Study Protocol  
Drug Substance  
Study Code  
Edition Number 2.0  
Date 28 Mar 2018

**PPD**  
[Redacted text block]

**PPD**  
[Redacted text block]



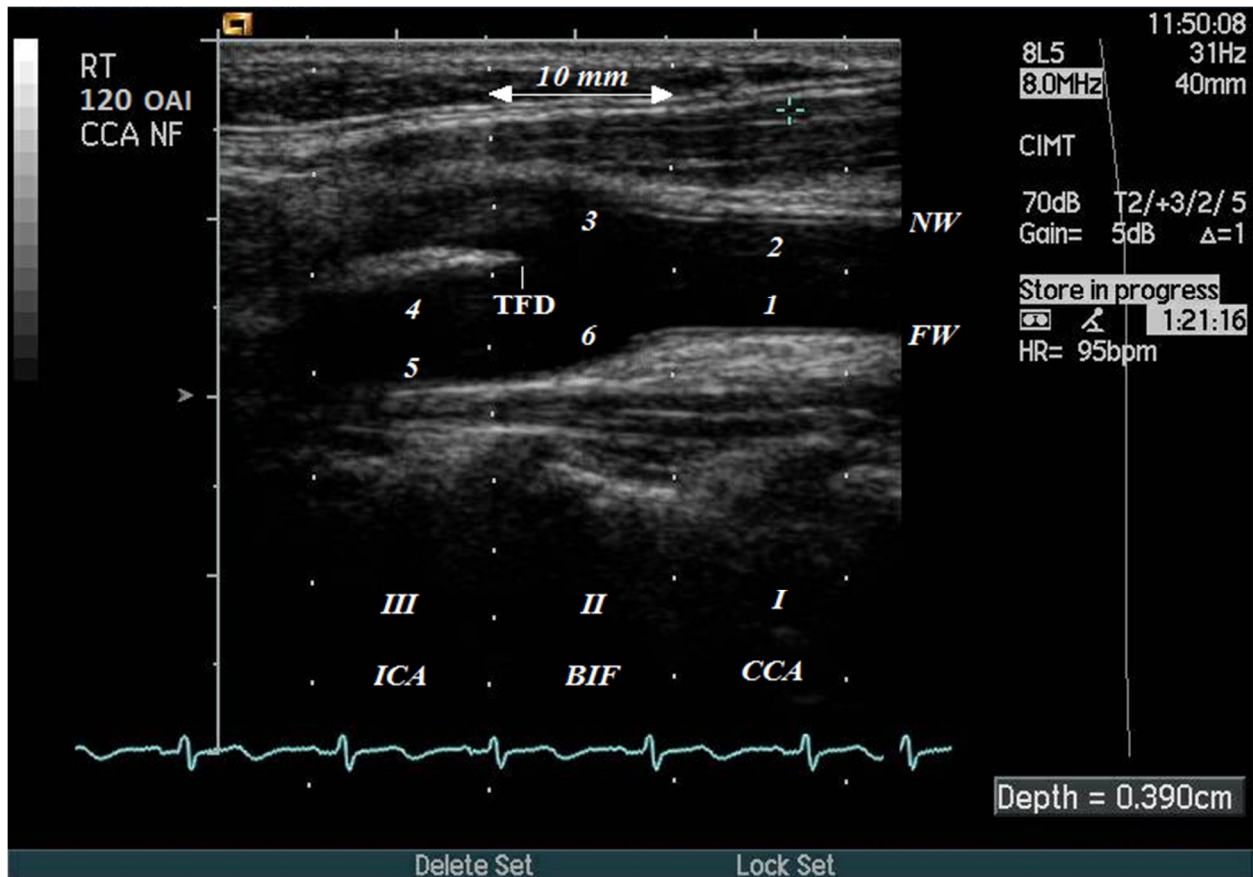
## 12.7.2 Ultrasound Exam Summary

The ultrasound scanning protocol describes a standardized examination of the right and left carotid arteries including the common carotid artery, the carotid bifurcation and the internal carotid artery. After proficiency has been developed in performing the protocol, the duration of the examination of both sides should not exceed 30 minutes. All Imaging Centers will use an approved ultrasound scanner with uniform image settings that will be indicated in the carotid ultrasound training manual. For off-line analysis, real time DICOM image clips will be stored on digital media or uploaded via the internet. Copies of digital image files will be stored at the Clinical/Imaging Centers and/or at the QC Center(s). **Extensive Carotid Disease**

This research protocol has been developed to meet specific research objectives in the study, and the protocol differs significantly from the routine clinical examination of the carotid arteries performed in clinical subjects. If, as a result of the performance of this research scan protocol, severe and/or extensive carotid artery disease is discovered in a participant, this information is communicated by the sonographer to the clinical site principal investigator or a designated co-investigator. A more detailed medical history may be obtained on these subjects and the extent of follow-up will be determined by the local clinical site principal investigator.

### 12.7.2.2 Carotid Segments

The primary objective of the carotid ultrasound scanning protocol is to acquire high quality standardized longitudinal B-mode images in 12 well defined arterial wall segments in both the right and left carotid arteries. Each carotid artery has been divided into 3 segments (CCA, BIF, ICA) with 6 walls (near wall and far wall of each segment) as shown in [Figure 2](#). The tip of the carotid flow divider is an important landmark for the standardization of the horizontal positioning of the artery and the definition of the segments. The position of each segment is defined relative to this tip of the flow divider (TFD), which is normally the most clearly defined anatomical reference in the proximity of the carotid bifurcation. The three segments are defined as: the near wall and far wall of the arterial segment extending from 10 mm to 20 mm proximal to the tip of the flow divider into the common carotid artery (CCA); the near wall and far wall of the carotid bifurcation beginning at the tip of the flow divider and extending 10 mm proximal to the flow divider tip (BIF); and the near wall and far wall of the 10 mm of the internal carotid artery (ICA) distal to the tip of the flow divider. Since the specific internal anatomy of an individual subject is variable, the near walls and far walls may correspond to different anatomical sites. Markers on the ultrasound screen will facilitate the correct placement of the segments.

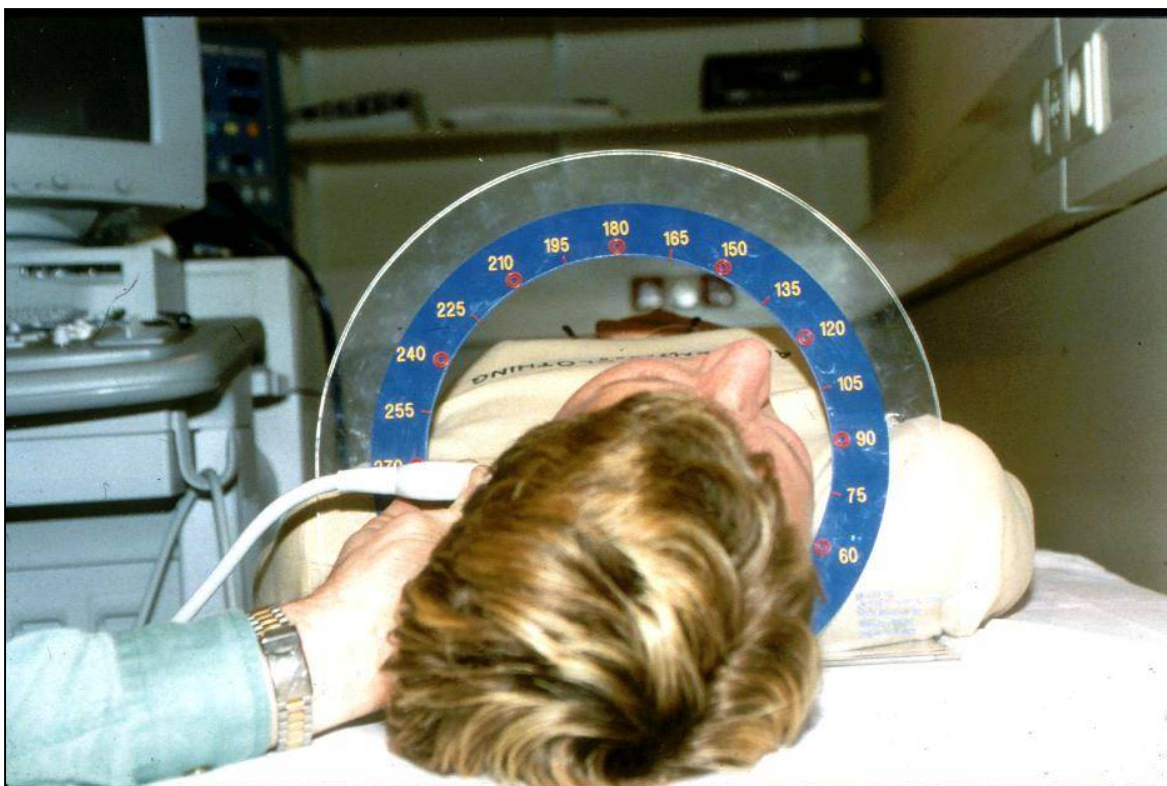


**Figure 2** Three 10 mm segments (CCA/BIF/ICA), the tip of the flow divider (TFD) and the 6 boundaries. Gridlines were used to indicate the segments and to position the TFD in a standard way

In many participants, it is often difficult to obtain good images of the internal carotid artery further than 10 mm distal to the tip of the flow divider. The length of the bifurcation varies significantly between subjects, and 10 mm is an approximate average length. The segment containing the common carotid is limited to 10 mm in length so that the segment can be imaged with high quality while maintaining the level of the flow divider tip at the appropriate gridline.

### 12.7.2.3 Standardized Interrogation Angles

Besides the standardization of the left-right placement of the artery and clear definition of the segments, the angle of interrogation has also been standardized. To achieve this objective a carotid arc (Meijer's Carotid Arc) is used as a reference for the interrogation angle as shown [Figure 3](#). Carotid images are selected at 3 predefined angles with 30 degrees increments on both sides: 90;120;150 for the right side and 210;240;270 for the left side.



**Figure 3**            **The Meijer's Carotid Arc is used to position the transducer at the 6 predefined angles**

#### **12.7.2.4            Instrumentation**

Each participating site will work with the sponsor and appropriate QC Center(s) to identify one or more approved ultrasound systems that may be used for study examinations. In some cases, approved equipment may be purchased or leased specifically for study use. Factors considered in the ultrasound equipment approval process will include: year of manufacturing, axial and lateral resolution, image field of view and distortion, transducer dimensions and weight, ease of use by sonographers, quality control standardization, data storage and recording methods, Doppler mode capabilities, engineering staff quality, digital recording capabilities (including audio) and service frequency and response time. We anticipate that images will be recorded on digital media to support off-line image frame selection and measurement of CIMT. Since even subtle between system differences in performance and calibration can inflate the variability of estimated rates of change in CIMT, care should be taken to minimize the number of different systems approved for study use. Ideally uniform equipment is selected to ensure the highest quality of the carotid IMT image and reading process.

#### **12.7.2.5 Personnel**

Two part-time sonographers are required to perform the ultrasound scanning duties at each Imaging Center. All sonographers must complete a uniform CIMT training program conducted at the central training meeting. Sonographers are certified upon satisfactory documented completion of the training and certification program. Sonographers should equally share the scanning responsibilities during the course of the study to maintain a high skill level and certification requirements. The concept of a “primary” and a “back-up” sonographer in longitudinal studies of this type is inappropriate since the skills must be practiced on a regular basis by each sonographer to maintain a high skill level.

#### **12.7.2.6 Administration of Image Data**

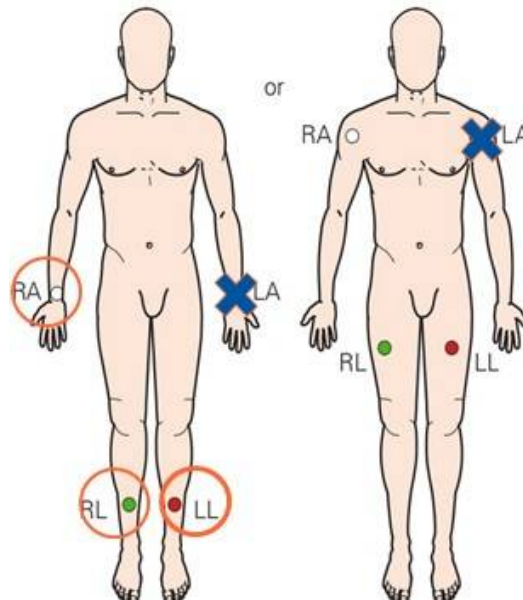
Numbered labels will be used to keep record of the participant examination data and to track media used to store and transfer digital image files. All administrative issues and the procedures related to the labeling and transfer of the digital media will be described in detail in the carotid ultrasound training manual.

#### **12.7.2.7 Exclusion Guidelines Based On Carotid Ultrasound**

The subjects recruited for this study are asymptomatic adults with evidence of early carotid atherosclerosis (a maximum intima-media thickness of at least 1.2 mm [subject to any criteria change in clinical study protocol] and less than 3.5 mm). Precise longitudinal measurements of CIMT are possible only in individuals with early changes in the thickness of the intimal and medial layers of the artery wall resulting from atherosclerotic disease. If in a participant the imaging circumstances are very poor with limited boundary visualization or the protocol cannot be followed due to anatomical constraints, the participant may be excluded from the study. Participants with extensive carotid disease with large calcifications and acoustic shadowing that will limit appropriate and adequate visualization of sufficient CIMT boundaries should not be enrolled in this study, since this will likely limit the number of CIMT measurements. During the circumferential scan, the minimum visualization requirement for a participant to be eligible for this study is that both the near and far walls of the right and left common carotid arteries be well visualized in addition to at least 4 of the 8 segments in the right and left BIF and ICA.. Either the sonographer or the QC Center(s) may exclude such participants, with details clearly documented on the Ultrasound Requisition Form(s) or eligibility form(s) for that participant.

### 12.7.3 Ultrasound Protocol

Correct participant demographic information is placed on the ultrasound system image screen prior to the beginning of each study. This may include clinical/imaging center ID, subject number, visit code, date of birth (yyyy-mm-dd), and sonographer ID. If needed, digital media labels are completed after completion of the scan. In addition, standard equipment settings provided during the training (e.g., maximum depth, frame rate, dynamic range, edge detection, image persistence, and post processing) must be used in the recording of all images. The sonographer scans from the head of the examination table. The participant is placed in a supine position on the examination table with the head toward the sonographer. A pillow is placed under the participant's knees to support the lower back if requested by the participant. A towel may also be placed under the head of the participant. ECG leads are attached to the participant according to the system specifications. An example of ECG lead attachment for an ultrasound scanner is illustrated in [Figure 4](#).



**Figure 4** Example of ECG placement

#### Points to remember with the ECG:

- The tracing should be positioned at the bottom of the image screen, away from arterial interfaces of interest.
- The amplitude should be sufficient for the R-wave to be clearly identified.
- If artifact is visualized in the tracing, check to be sure that electrodes are not loose or dry. Avoid placing electrodes on bone structures. Limit participant movement during scan.

The participant is required to rest for 5 minutes before proceeding with the examination to establish a stable physiologic state prior to beginning the examination. A plastic arc (Meijer's Carotid Arc) marked with an angle scale is positioned under and against the shoulders of the participant (illustrated in [Figure 5](#)) is used as a reference to read the ultrasound transducer interrogation angles during the examination. The sonographer performs the right carotid scan holding the probe in the right hand and the left carotid scan holding the probe in the left hand. When the sonographer selects each specific image sequence for measurement, an on-screen annotation is provided by the sonographer to indicate the angle and carotid segment.



**Figure 5** Example of the scan position and arc placement

The examination of both right and left sides consists of an initial exploratory transverse/longitudinal scan and a Doppler of the carotid system followed by a detailed longitudinal examination of the specific arterial segments illustrated in [Figure 2](#). For the initial transverse scan the transducer is always positioned for the right side at 135 degrees and for the left side at 225 degrees so that the image presentation is in accordance with the anatomy of the participant. This should result in an image in which the right edge of the image is directed toward the right side of the participant. For the longitudinal scan the transducer is positioned (for both the right and left sides) so that the carotid image is oriented with the participant's head towards the left side of the monitor. The right carotid is scanned first followed by the left side.

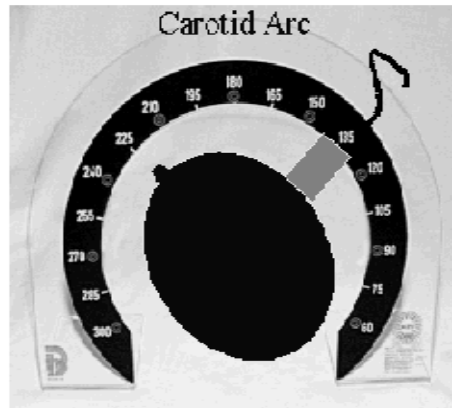
### **12.7.3.1 Exploratory Scout Scan**

Exploratory transverse and longitudinal scans (scout scans) are performed by the sonographer prior to the beginning of clip storage of images. This is to enable the sonographer to become familiar with the participant's anatomy. The image quality of the carotid scan is carefully examined by the sonographer to determine if the 6 arterial wall boundaries can be adequately visualized within the specific arterial segments at the predefined angles. Anatomical features that might preclude the serial acquisition of high quality images are noted on the participant Ultrasound Requisition Form. The minimum visualization requirement for a participant to be eligible for this study is that both the near and far walls of the right and left common carotid arteries be well visualized during the circumferential scan, in addition to at least 4 of the 8 segments in the right and left BIF and ICA.

Precise longitudinal measurements of CIMT are possible in individuals with relatively early changes in the thickness of the intimal and medial layers of the carotid artery wall. Participants that are very difficult to scan or provide images of poor quality because of anatomical constraints or severe and/or extensive atherosclerotic disease may be excluded from the study at this time and the examination will be terminated (see previous section [12.7.2.7](#)).

### **12.7.3.2 Transverse Exploratory Scan**

The transverse scan of the right common carotid artery is performed beginning at the clavicle with the participant's head position 45 degrees to the contra-lateral side (225 degrees) and a transducer (groove pointing to participant's left side) interrogation angle of 45 degrees to the posterior (135 degrees) as shown in [Figure 6](#). The sonographer uses fine transducer angulations to clearly display both the blood-intima boundaries and the media-adventitia boundaries on both the near and far walls of the artery, the transducer is slowly moved toward the mandible until the lumen area increases with the appearance of the carotid bifurcation (also the lumen changes shape from nearly circular to elliptical), and finally the internal and external carotid arteries are visualized. The location of these vessels is denoted in the image by positioning an indicator near the arterial segment. These indicators greatly assist the reader during the reading process. For the transverse scan, a clip at least 6 seconds in duration is saved on the hard drive showing the complete segment of interest, including the orientation of the internal and external carotid arteries. A properly performed transverse scan is demonstrated in the training video. The left initial transverse scan is done at 225 degrees with the head 45 degrees to the other side (135 degrees).

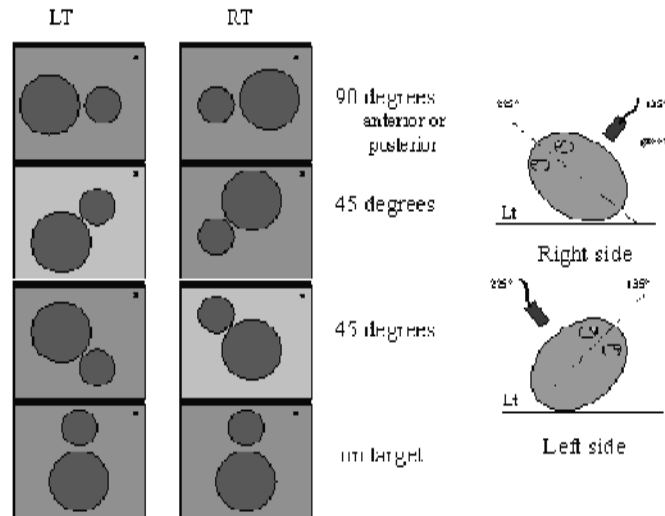


**Figure 6** Position the head of the participant 45 degrees to the contra-lateral side using the Meijer's Carotid Arc; position the transducer 45 degrees to the posterior.

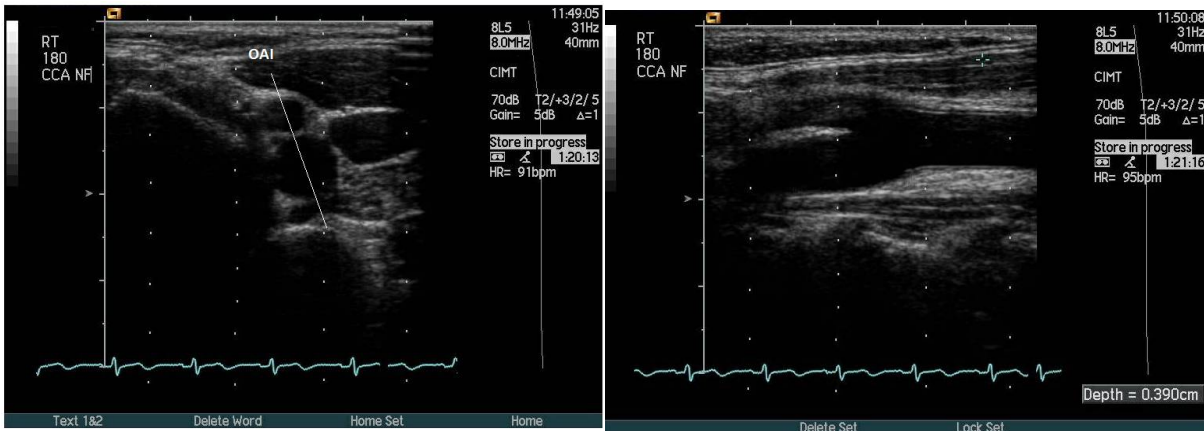
### 12.7.3.3 OAI (Optimal Anatomical Interrogation) Angle

Using the knowledge acquired of the relative anatomical orientation of the internal and external carotid arteries during the transverse scan, the optimal anatomical interrogation (OAI) angle which best displays the tip of the flow divider and the “Y” appearance of the two arteries in a single longitudinal image can be determined (Figure 7 and Figure 8). This angle provides information about the carotid anatomy of this participant. If both extreme anterior and extreme posterior interrogation angles can provide an OAI view, the anterior angle is to be preferred. One way to obtain the OAI is to position one vessel on top of the other in the transverse scan and then turn longitudinal by a 90 degrees rotation of the transducer to demonstrate the “Y” appearance. (Transducer groove points toward participant's head.)





**Figure 7** The different transverse orientations of the artery with the degrees of movement to obtain the OAI. In the lighter shade orientations the movement is towards the anterior.



**Figure 8** The scan approach to obtain the OAI from the transverse plane and the longitudinal image of that particular scan plane

### 12.7.3.4 Longitudinal Exploratory Scan

The sonographer remains at or close to the OAI angle with the tip of the flow divider positioned on the designated gridline. A brief Doppler examination is performed to clearly distinguish the internal carotid artery from the external carotid artery based on the differences in the flow velocity profiles in the two vessels. The entire 30 mm predefined length of the carotid system is now scanned longitudinally starting from the most anterior angle and

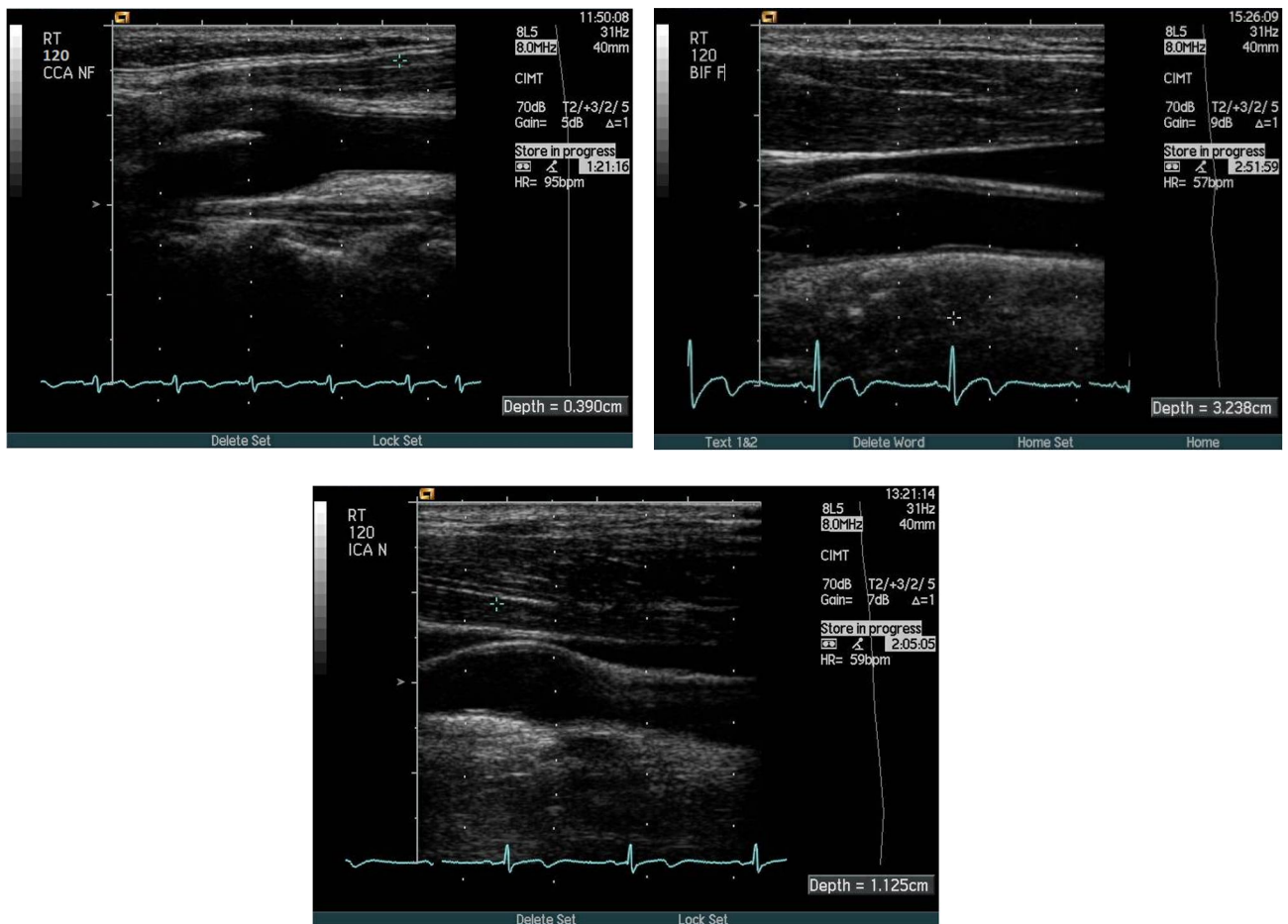
proceeding to the most posterior angle with a brief stop at the predefined angles to explore the anatomy.

#### **12.7.3.5 Preliminary Scan**

On each side, the transverse scan (3.2) is stored in a clip at least 6 seconds in duration. At the longitudinal scan following the collection of the Doppler signals, a still frame "image store" is made of the best image displaying the carotid bifurcation ("Y") with identification of the internal carotid artery and the angle of interrogation. The sonographer should demonstrate with annotation the relative positions of these two vessels when imaged from the OAI angle (shallow or deep). The indicator is placed within the lumen of the internal vessel close to the flow divider wall at the level of the tip of the flow divider. This information will be used at the QC Center(s) to confirm proper artery identification and anatomical relationship.

#### **12.7.3.6 Longitudinal Scan for 12 Selections at Defined Angles**

This scan always starts with the anterior scanning angle of 150 degrees at the RT CCA. The flow divider is positioned approximately 1.5 cm from the left edge of the screen on the designated gridline. To check the position of the tip of the flow divider, the transducer should be rocked backward and forward to visualize the off spring (origin) of the internal and external carotid arteries. On-screen indicators are used to identify the angle and vessel wall segment under interrogation as shown in [Figure 9](#). The right pictogram is placed on the left of the image screen when the right side is being scanned. The left pictogram is placed on the right of the image when the left side is being scanned. The images are acquired from 3 defined interrogation angles on both sides.



**Figure 9** Example of 3 selections: Text and/or on-screen indicators are placed to confirm the segment of interest and the scan angle

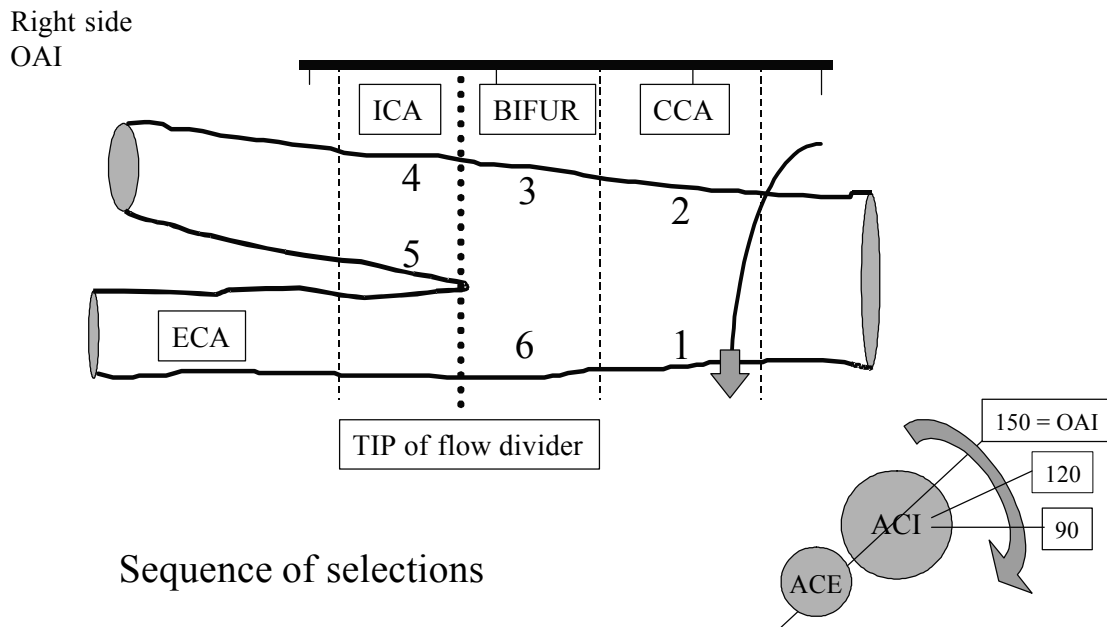
Example:

- A. CCA near and far wall: CCA NF
- B. Bifurcation far wall: BIF F
- C. Internal near wall: ICA N

At the first CCA selection (150 degrees), a video clip containing approximately 5 consecutive cardiac cycles that clearly visualize both the near wall and far wall boundaries in the same image frames are stored on the hard drive of the ultrasound machine. The annotation is placed appropriately before the digital storage is recorded. Following the CCA the sonographer continues with the next segment BIF (near wall) and then the ICA (near wall) at that angle in a similar way. Then the focus of the sonographer is shifted to the ICA (far wall), followed by

the BIF (far wall). The annotation and caliper should be placed correctly for optimization of the image and identification of the segment and angle of interrogation. This sequence of image selections is illustrated in Figure 2 and Figure 10.

The transducer is then positioned on the next angle (120 degrees) and the same sequence of images is acquired. In a similar way images are also selected at the angle of 90 degrees marked on the plastic arc when scanning the right side. For the left side, corresponding angles of interrogation are 210, 240 and 270 degrees.



**Figure 10** Schematic overview of the carotid artery with the sequence of image selections illustrated

### 12.7.3.7 Confirmation of Tip of Flow Divider, Boundary Optimization and Focus Setting

At the beginning of the selection of each segment, the position of the tip is being confirmed by rocking the transducer to visualize the origin of the internal and external carotid arteries, while maintaining the locations of surrounding tissues (drifting from the desired segment location is avoided). Considerable effort is shown to optimize (horizontalize) the boundaries and to maintain the position of the level of the flow divider at the TFD reference gridline on the screen.

## 12.7.4 Comprehensive Protocol Overview/Summary

The carotid artery is divided into three segments (CCA/BIF/ICA) of each 10 mm length with tip of flow divider being the reference point.

The tip of the flow divider will be placed at the designated gridline.

Doppler will be used to differentiate the ICA and ECA. At the 3 consecutive defined angles on the Meijer's Carotid Arc, the image selections of the carotid walls are acquired and stored on hard drive. The carotid arc will help to guide the sonographer through the multi-angle acquisition protocol ensuring that multiple sites are investigated.

On-screen annotations and/or indicators placed by the sonographer will provide the necessary information about the vessel segment, the angle, and the vessel wall under interrogation.

Near and far wall images of 6 carotid segments are acquired at the 3 different defined angles. To have a good understanding of the anatomy of the right and left carotid arteries in each individual, the angle where the tip of the flow divider is clearly imaged (OAI) is documented.

At the training, the sonographer will be instructed on completing data sheets.

### 12.7.4.1 Sonographer Work Protocol

- Start with the transverse scan on the right side at the level of the clavicle and scan at an angle of 45 degrees posterior from the 180 degrees angle (135 degrees). Optimize the boundaries during the scan and locate the orientation of the bifurcation to obtain the "Y" for vessel identification in the longitudinal images later on. Store one image clip at least 6 seconds in duration to illustrate the anatomy.
- Now move the transducer over the neck until the vessels are projected on top of each other. When this is the case rotate the transducer 90 degrees to a longitudinal projection so the vessels are displayed on top of each other and the bifurcation and tip of the flow divider can clearly be seen. The TFD should be placed at the left side of the screen at the designated gridline.

At this longitudinal angle identify the internal vessel with Doppler, place caliper within vessel and store the image.

### 12.7.4.2 Start of the 12 Selections

At the **CCA segment** start the scan at **150 degrees** on the arc; place the text indicating the angle of interrogation on the screen. Position the tip of the flow divider on the designated gridline and keep this position during all selections. Horizontalize the vessel optimizing both boundaries. When both boundaries are clearly seen, store a video clip.

- After the CCA segment, move to the **near wall** of the **bifurcation segment**. Change annotations accordingly, check the tip position, then optimize the boundary, and store the video clip.
- Move to the **near wall** of the **internal segment**. Change annotations accordingly, check the tip position, then optimize the boundary, and store the video clip.
- Move to the **far wall** of the **internal segment**. Change annotations accordingly, check the tip position, then optimize the boundary, and store the video clip.
- Move to the **far wall** of the **bifurcation segment**. Change annotations accordingly, check the tip position, then optimize the boundary, and store the video clip.
- Move the transducer to the next angle on the arc (**120** degrees) and repeat the procedure as described above. Hereafter continue with the **90** degree angle using the same procedure.
- Repeat the same procedure on the left side at angles 210, 240 and 270.

When the scan is completed the stored image clips of the entire scan may be uploaded to the QC Center(s) over the internet.

### **12.7.5 Ultrasound Image Reading**

After the ultrasonic B-mode and Doppler data are recorded, the digital files are transferred to the QC Center(s). The individual image frames selected for measurement are stored in digital format for long term retention.

#### **12.7.5.1 Reading Protocol**

The primary objective of the carotid ultrasound B-mode image reading protocol is to measure the mean CIMT in the common carotid artery and the maximum CIMT in each of the twelve arterial segments as defined in [Figure 2](#) and [Figure 10](#). When present, a plaque can extend over more than one of the defined segments. In this case, more than one maximum thickness measurement may arise from a single extended plaque. The reading process is described briefly below. Additional details are given in the Reading Station Operator's manual.

#### **12.7.5.2 Reading Station Instrumentation**

The B-mode image reading station consists of the following instrumentation: monitor, personal computer, and hardware and software for multiple image frame capture, CIMT measurement and data storage. Measurement software will include semi-automated edge detection algorithms with tracings that can be easily modified by the reader as required.

#### **12.7.5.3 Personnel**

The exact number of readers required will be determined by the reading load, but four to eight readers is typical for moderate to large studies. The time to read a scan is between 1 and 3 hours. Limitations are placed on the number of hours of reading permitted per session to minimize reader fatigue and to help ensure that all studies are read according to the standardized reading protocol. All ultrasound readers are certified after satisfactory completion of a standardized training program described in [Section 1.4](#) of this protocol.

#### **12.7.5.4 Acquisition of B-mode Image Measurement Data**

The data from each of the twelve predefined arterial segments (mean and maximum CIMT) that are required to compute the primary and secondary outcome parameters are obtained using the standardized procedure described below.

#### **12.7.5.5 Image Frame Selection from Digital Files**

From the digital files, the image sequences obtained from several interrogation angles in each segment correctly coded in the image and accompanied by annotations are carefully reviewed frame by frame to select the best quality images for measurement. The reader searches for those end diastolic image frames from each segment which most clearly outline the maximum CIMT within the near wall and/or far wall boundaries within the predefined segments. Following each measurement, the image frame selected is stored on the reading station hard drive or directly to the network of the QC Center(s). The measurement data, the images from which the CIMT measurements were taken, the outlines traced on the images and the digital file contents will be stored and archived for long term retention.

#### **12.7.5.6 Marking of Arterial Boundaries**

On each image frame, the visualized blood-intima and media-adventitia boundaries are marked using the study specific software. These segments are defined relative to the tip of the flow divider, which has been maintained by the sonographer at the TFD reference gridline on the screen as shown in [Figure 2](#). For CIMT measurements, the trailing edges are traced on the near wall boundaries and the leading edges on the far wall boundaries. When measurements of lumen diameter are made in the common carotid artery, the trailing edge of the near wall and the leading edge of the far wall blood-intima boundaries are marked. After all boundaries in a given segment have been traced, the mean of the 10 mm segment and/or maximum CIMT are computed and stored in a data file. Images from all segments are read in an identical manner. The standardized procedure used in making CIMT measurements is illustrated in the training video.

#### **12.7.5.7 Doppler Data Analysis**

The results of the brief Doppler examination performed on the internal and external carotid arteries at the OAI angle following the transverse scan are only used to confirm correct artery identification and anatomical orientation. No quantitative flow measurements are made from the Doppler results.

#### **12.7.5.8 Primary CIMT Outcome**

The primary CIMT outcome for the study is change in the average maximum CIMT over 12 carotid segments defined by the near and far walls of the CCA, BIF and ICA on the right and left sides. We refer to this parameter as the MeanMax CIMT. For each participant visit, the 12 segment specific maximum CIMT values are obtained by combining data across the 3 interrogation angles and selecting the largest CIMT measurement. Participant and visit specific estimates of MeanMax CIMT are computed for descriptive and QA/QC purposes by averaging the observed maximum CIMT values for the 12 carotid segments. For statistical analysis, however, the segment specific maximum CIMT values are treated as dependent variables in a repeated measures analysis of variance and maximum likelihood estimates of the change in MeanMax CIMT are computed within the statistical model.

#### **12.7.5.9 Secondary CIMT Outcomes**

Segment specific estimates of change in MeanMax CIMT will be examined based on subsets of the 4 maximum CIMT formed by the near and far walls on the right and left sides within the CCA, BIF and ICA, respectively.

In addition, change in the MeanMean CCA will be evaluated based on 4 Mean CIMT values for the near and far walls of the right and left CCA formed by averaging mean CIMT values across the 3 angles of interrogation.

#### **12.7.5.10 Transmission of Data**

Outcome parameter data to be incorporated into the study database for analysis are transmitted using a secure upload procedure or bonded courier from the QC Center(s) to the sponsor or their designated vendor at specified intervals.



## **12.7.6 Timing of the Reading Process**

### **12.7.6.1 Screening Scans**

Two screening exams will be performed for all eligible participants approximately 4 and 2 weeks prior to randomization. These will be full examinations consistent with the scanning protocol described in sections 2-4 above and will be read as they are received to determine participant eligibility. Based on the results, the reader will generate and return to the Clinical/Imaging Center an eligibility certificate for each scan, clearly indicating whether the participant meets the eligibility requirements described in section [12.7.2.7](#) or not. The QC Center staff will make every effort to return eligibility certificates to the respective Clinical/Imaging Centers within 2-4 business days of receipt of the scan. Participants must satisfy the criteria described in section [12.7.2.7](#) for both scans to be eligible for the study.

### **12.7.6.2 Initial Follow-up Scans**

CIMT has been used as an endpoint in clinical trials for more than 20 years and a wealth of information is now available regarding the trade-offs between sample size and a number of techniques intended to minimize within-subject variability including the length of follow-up, the number and timing of scans, and the number of measurements collected per scan. Generally, the longer the duration of follow-up, the larger the number of scans and the larger the number of measurements per scan, the smaller the sample size required to detect a clinically significant difference in CIMT change. For example, the METEOR study was designed for 2 years of follow-up, 7 scans per participant and 60 sets of measurements per scan, with a targeted sample size of 840 participants. In this study design, there is a period of months or even years between the completion of recruitment and the beginning of close-out visits. Since this study design will also employ batch reading processes to minimize between reader and temporal reading variability, there will be a period during initial follow-up when scans are being performed and sent to the QC Center(s), but no readings are performed. Special QA activities as described in sections [12.7.7.3](#) and [12.7.7.4](#) may be required to maintain data quality in these cases.

### **12.7.6.3 Batch Readings at Close-out**

Experience suggests that both systematic differences between readers and temporal drift in measurements can influence CIMT reading results. To minimize these influences, all the scans for a given participant can be read together as a batch by a single reader over a relatively short period of time as each participant finishes the study. Details of the batch reading process will be negotiated with the sponsor and described in a batch reading SOP. Unfortunately, it is generally not practical to fully blind the reader to information about scan order during batch reading. Typically, however, scans within a batch will be read in a random order over a period of 2 -4 weeks and may be comingled with readings from other participant batches to minimize any bias resulting from the reader's access to information about the order in which scans were obtained.

### **12.7.7 Quality Control/Quality Assurance Procedures**

Throughout the study, the QC Center(s) continuously monitors the quality of the images submitted from the routine studies and the outcome variable data obtained from the within- and between-sonographer and within- and between-reader QC studies. Should low quality images related to scanning technique be observed, these observations are immediately reported to the sonographers. Reasons for the low quality are identified and remedied in consultation with the sonographer. Should low quality studies related to the reading process be observed, these observations are immediately reported to the reader. Reasons for the low quality are identified and remedied in consultation with the reader. Sonographers and readers that repeatedly produce low quality studies may be decertified and prohibited from scanning or reading scans from study participants.

#### **12.7.7.1 Purpose of QC/QA Programs**

The purpose of the quality control/quality assurance program is to ensure that the ultrasound data collected for this study are of consistently high quality and are collected according to the study protocol. The foundation of the quality control/quality assurance program rests on a well defined protocol, standardization of equipment and procedures, and uniform training and certification of sonographers and B-mode image readers. Training and certification procedures are detailed in Section 12.7.1 of this document, and the standardized ultrasound protocol is detailed in Section 12.7.3. Additional components of the quality assurance program include:

- monitoring the performance of the ultrasound scanning system selected for use in this study
- monitoring sonographer performance to assure consistent acquisition of ultrasound B-mode images
- monitoring reader performance and equipment to assure consistent measurement of arterial dimensions from the B-mode images
- assessment of temporal changes in data collection processes
- preparation of an ultrasound database

A detailed description of the individual quality assurance program components is provided below:

#### **12.7.7.2 Monitoring Ultrasound Equipment Performance**

During the trial, the ultrasound system hardware and software may not be upgraded without prior approval from the QC Center(s) and sponsor. Each Imaging Center should maintain a service log to track the timing, reason, and result of all service visits. Following each service visit, including regularly scheduled preventive maintenance, a service report should be sent to the QC Center(s) detailing the reason for the visit, any problems identified, and all actions taken. Monitors will compare these service reports against each site's service log during

regular site visits to ensure the accuracy and completeness of the service record documentation.

### 12.7.7.3 Monitoring Sonographer Performance

The QC Center(s) will employ a variety of qualitative and quantitative approaches to monitoring sonographer performance, including monthly performance reviews, site visits, and evaluation of study data.

- Monthly and Quarterly Performance Reviews:

One scan per sonographer per month will be reviewed by the sonographer and at the QC Center(s) using a standard review form for the first three months post certification. After three months the sonographer will send in a self review form on a participant or on a volunteer (only during times of low activity) on a quarterly basis. The QC Center(s) will provide a schedule to the sonographers showing the months in which they must submit a quarterly review. The standard review used in the evaluation of the sonographers' scans allows for a detailed review of the preliminary and arterial segment scans on the right and left carotid arteries for sonographer recertification purposes, and provides an overall performance grade of:

- A) **Satisfactory** - the sonographer has followed protocol and used available tools to maximize image quality.
- B) **Marginal** - the sonographer has followed the protocol, or has only minor deviations that have minimal impact on the availability and/or quality of arterial measurements.
- C) **Unsatisfactory** - the sonographer has deviated from the protocol in a manner likely to affect the availability and/or quality of arterial measurements.

Results and critiques from these performance reviews will be provided to sonographers on a regular basis. Sonographer receiving a grade of "C" will automatically have a second study reviewed. If successive "C" grades are received, the QC Center(s) will contact the site to develop a plan for remedial training and reassessment. If no improvement is achieved, the sonographer may be decertified.

The QC Center(s) will also randomly select studies for review to help ensure quality remains high throughout the study. The sonographer's imaging skills will be evaluated using the standard review form. These random evaluations will assure that each sonographer is evaluated on study subjects and remove any prior knowledge on the sonographer's part that a review will take place. Weighted selection processes may be employed to oversample sonographers or sites with indications of quality deficits based on other metrics.

- Low Scan Activity During the Study

If a certified sonographer does not perform a subject scan during one calendar month within the first three months post-certification or does not perform any subject scan during one quarter after the first three months following certification, the sonographer will be required to make a full scan on a volunteer, complete the Sonographer Scan Review Form, log it in the Sonographer Recertification Scan Review Form Log, and send the digital file and a copy of the Sonographer Scan Review Form to the QC Center(s).

- **Quick Scan Reviews**

Each scan will be subject to a quick review upon receipt by the QC Center(s). The purpose of this quick review is to confirm that participant demographics are as expected, the scanning equipment was functioning correctly, instrument settings were appropriate, the scan is complete and visualization of arterial interfaces is sufficient to provide high quality data for analysis. Any deviations noted will be communicated back to the Imaging Center to allow them to attempt to reschedule the participant for a replacement scan or make the necessary corrections for future scans. Note that the quick reviews are especially important if there is a gap between the end of recruitment and the beginning of batch reading, to help prevent problems with equipment or sonographer performance from affecting multiple scans before they can be detected by quarterly reviews.

- **Site Visits and Annual Meetings**

At regular intervals, monitors will visit each Imaging Center to monitor ultrasound records and verify equipment service history. Remedial site visits will be performed by staff from QC Center(s) to review scanning procedures and suggest methods for improvement. The frequency of remedial site visits will be determined by findings from sonographers reviews, repeat scans and study data as well as communications between the QC Center(s) and Imaging Center staff regarding scanning procedures or other issues affecting ultrasound image quality and protocol implementation.

All sonographers should plan to attend group quality control meetings to review study data and to maintain a high degree of standardization of the data collection process throughout the study. The number and timing of these group meetings will depend on the study design, but one will typically be held prior to beginning close-out scans.

#### **12.7.7.4 Monitoring Reader Performance**

Readers for this study will use a standard reading station with hardware and software funded by the sponsor to minimize differences in data acquisition. Upgrades or additions to the reading systems are not permitted unless mutually agreed upon by the QC Center(s) and the sponsor. All readers should also plan to attend group quality control meetings as described above.

QC Center(s) will employ regular performance reviews, inter- and intra- reader repeat readings, and evaluation of study data as necessary to ensure consistent collection of arterial measurements between readers within that Center as outlined below.

During the batch reading process, approximately 1 batch per quarter will be randomly selected for use as a QC batch. For QC batches, the two screening scans and the two close-out scans will be read by all active readers, allowing for a detailed evaluation of within and between reader differences in both cross-sectional and longitudinal estimates of CIMT. Performance thresholds for the batch QC readings will be established, and outliers will be subject to remedial training and possible decertification.

A similar process will be used during recruitment, with QC batches consisting of the two screening scans for a single participant.

#### **12.7.7.5 Use of Study Data**

Study data on mean and maximum arterial dimensions, number of sites selected, average number of visualized interfaces, and average length of visualized interfaces will be evaluated to identify potential differences between sonographers and readers in the application of the study protocol. Caution must be exercised in comparing study data results for sonographers in different Imaging Centers, since these comparisons may be confounded by differences in patient populations (in contrast to repeat scans that automatically control for participant effects). Nevertheless, the study data available for these comparisons offers increased sensitivity to identify issues that merit further investigation, providing a powerful supplement to other approaches for assessing sonographer and reader differences.

#### **12.7.7.6 Safety Monitoring**

Safety monitoring of ultrasound results will be the responsibility of the individual Clinical/Imaging Centers. The research protocol employed in this study is intended to allow precise estimation of average CIMT progression rates at specific arterial sites in groups of participants, and differs substantially from more clinically oriented evaluations. As a result, the QC Center(s) are not able to adequately assess the clinical significance of atherosclerotic disease in individual patients. Subjects with severe and/or extensive carotid artery disease should be reported by the sonographer to the principal investigator and reviewed by medical practitioners at each site and referred for clinical evaluations as appropriate.

#### **12.7.8 Archival of Ultrasound Material**

All digital media will be labeled with the study name, clinical/imaging center ID and a consecutive follow-up number. The digital media will be stored following completion of the study and the sponsor will be consulted prior to destruction of any material.

The B-mode images from which the measurements of carotid intima-media thickness were derived are stored in a digital format. In addition, the lines drawn on the images (outlines) are stored digitally as well as the measurement data. These files are processed on a local PC and subsequently stored on the network of the QC Center(s). Specific file naming conventions and file locations are described in the user requirements specification and data management standard operation procedures on file at each reading center.

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There will be no ultrasound scan paperwork received at the QC Centers. Paperwork generated by the QC Centers will be archived.

## **12.8    Appendix H    Assumptions for Sample Size Calculation**

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