Statistical Analysis Plan

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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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AstraZeneca Study Statistician

PPD

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2

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Global Product Statistician

PPD

5 March 2019

Date

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
Apo	Apolipoprotein
AST	Aspartate aminotransferase
BL2	IMT assessment at Visit 2
BL3	IMT assessment at Visit 3
CAI	Cholesterol - absorption inhibitor
CCA	Common carotid artery
CHD	Coronary heart disease
CIMT	Carotid intima-media thickness
CrCl	Creatinine clearance
CVD	Cardiovascular disease
ECG	Electrocardiogram
eCRF	Electronic case report form
HDL-C	High-density lipoprotein cholesterol
ICA	Internal carotid artery
ICVD	Ischemic cardiovascular disease
IMT	Intima-media thickness
ITT	Intent-to-treat
IxRS	Interactive Voice/Web Response System
LDL-C	Low-density lipoprotein cholesterol
LOCF	Last observation carried forward
MeanMax	Mean of the maximum
MeanMean	Mean of the mean
MedDRA	Medical Dictionary for Regulatory Activities
PP	Per-protocol
PT	Preferred term

Abbreviation or special term	Explanation
SAE	Serious adverse event
Statin	HMG-CoA reductase inhibitor
SOC	System organ class
TG	Triglycerides
ULN	Upper limit of normal

AMENDMENT HISTORY

Date	Brief description of change
26Jun2018	Updated following BDR1 comments and internal review • Clarification added to ensure that if a subject meets inclusion criteria during a re-test between visits 1 and 2, this is not considered a deviation (Appendix A) • Windowing removed • Additional CIMT outputs detailed; summaries by cohort and outputs to show quality control of scanning and reading of results (section 4.3.6).
14Aug2018	Updated after direct LDL measurement transitioned from 2nd generation reagents to 3rd generation reagents (section 4.1)
07Sep2018	Updated following AZ global and upper management team review
23Oct2018	Updated following some additional output requests, an update request from the safety physician, and an update following the review of the CSR prototype (section 4.2.1 and 4.3.5).
01Feb2019	Updated following BDR2 comments: • Minor cosmetic/formatting updates throughout. • Information around disallowed medication and CIMT deviation clarified (section 2.2). • Clarification added around use of CIMT scans from randomized subjects not treated, with no post-randomisation CIMT scans (section 3.1) • Baseline definition for subjects not treated clarified (section 4.1.1). • Definition of a completer clarified (section 4.2.1) • Compliance calculation updated and a definition of dose interruption added (section 4.2.5.3) • Subgroups for on-treatment LDL-C clarified (section 4.3.8) • Definition of AEs to be included as ischaemic cardiovascular AEs updated (section 4.4.2). • Definition of 'consecutive occasions' clarified (section 4.5.2) • Derivation of QTcF added (section 4.5.3) • Clarification added on handling multiple early termination CIMT assessments (section 4.6.2). • Appendix E added

Date	Brief description of change
26Feb2019	Minor cosmetic updates and more detail provided to amendment section
28Feb2019	Minor updates following review of v2.9: • "global METEOR", updated to "global METEOR (D3565C00088)" (Section 1.3) and "US Meteor" updated to "global METEOR" (Section 4.3.3) • Section 4.2.5.3, in sentence "no medication it taken at site at this visit". "it" should be "is". • Section 6, added compliance calculation to the change from protocol analysis table.
05Mar2019	Compliance calculation updated to only calculate overall compliance and not by-visit compliance (section 4.2.5.3) and IPD for compliance updated for consistency (Appendix A)

1. STUDY DETAILS

1.1 Study objectives

1.1.1 Primary objective

The primary objective of this study is 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.

1.1.2 Secondary objective

The secondary objective is 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.

1.1.3 Safety objective

The safety objective is to assess the safety and tolerability of rosuvastatin 20 mg compared to placebo over 104 weeks in Chinese subjects with subclinical atherosclerosis.

1.2 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 CIMT of the common carotid artery (CCA), carotid bulb, and internal carotid artery (ICA) in adult Chinese subjects with subclinical atherosclerosis.

The timing of IMT measurements is detailed in section 3.1. Blood samples for analysis of lipid parameters will be collected at weeks -6, 0, 6, 13, 39, 65, 91 and at the time of discontinuation of study treatment (on or before week 104).

Figure 1   Study flow Chart
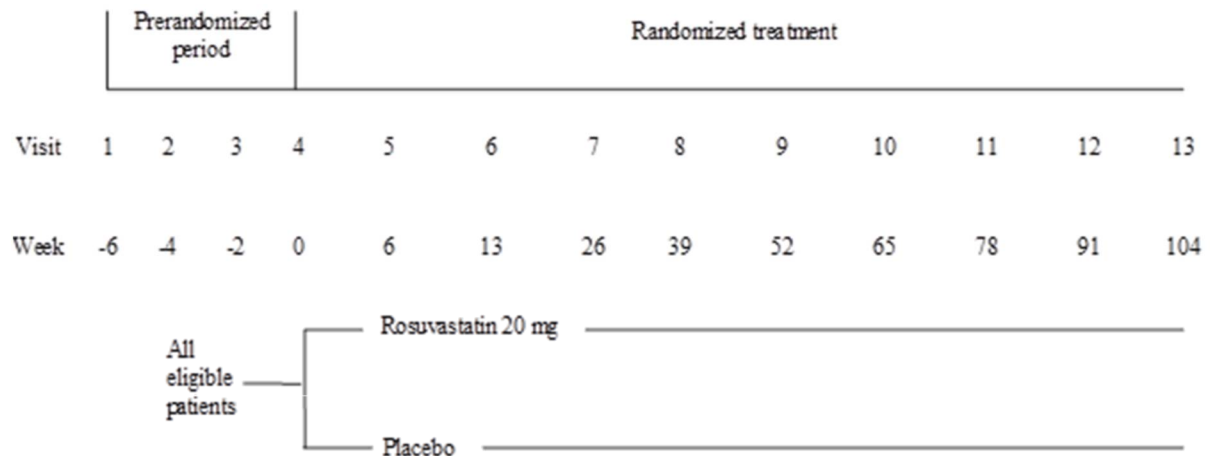
1.3   Number of subjects

CCI

2.   ANALYSIS SETS

2.1   Definition of analysis sets

Two analysis sets will be used for efficacy evaluation:

2.1.1   Intent-To-Treat (ITT) analysis set

The primary and secondary efficacy endpoints will be analyzed using the intent-to-treat (ITT) analysis set. The ITT population consists of all randomized subjects. Subjects will be analyzed according to the treatment randomized.

2.1.2   Per-protocol analysis set

Supportive analyses of CIMT data will be carried out using the per-protocol (PP) analysis set. The PP analysis set is a subset of the ITT population that includes subjects without any important protocol deviations that may affect the study outcome significantly or the interpretability of the study results. The criteria for such important protocol deviations are defined in the section 2.2 and Appendix A. Subjects will be analyzed according to the treatment actually received.

The exclusions from the PP analysis set will include, but will not be limited to, the subjects who took prohibited concomitant medications, who were non-compliant in taking the investigational product (or who's compliance could not be calculated, see section 4.2.5.3), or who had major deviations of study procedures. These exclusions for the PP analysis set are explicitly defined in section 2.2 and Appendix A. The list of prohibited medications is given in section 7.7.1 of the protocol.

2.1.3   Safety analysis set

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, for instance, erroneously treated for a

period of time and then switched back to correct treatment, the subject will be analyzed according to the first dose administered at baseline.

2.2 Violations and deviations

 All protocol deviations need to be appropriately monitored and addressed at the site monitoring/management level.

For reporting purpose, however, only the "important protocol deviations" as assessed by study team will be included in the CSR. All important deviations related to study inclusion or exclusion criteria, conduct of the trial, subject management or subject assessment should be described. The "major/minor" terminology should no longer be used in CSRs. Protocol deviations that the study team considered to be unimportant should not be tabulated or listed, among which might include lack of compliance with visit schedule and subjects who have dose reductions or interruptions.

The following categories are used to describe important protocol deviations, and to be summarized and listed in CSR.

- Eligibility criteria not fulfilled;
- Subjects randomized but subsequently discover they failed the eligibility criteria;
- Disallowed concomitant medication taken during the study (medications with an ATC code of C10AA (HMG COA REDUCTASE INHIBITORS), C10 (LIPID MODIFYING AGENTS), or C10AX (OTHER LIPID MODIFYING AGENTS) or 'Reason for Therapy' is recording on the eCRF as 'Control for dyslipidemia', 'Hyperlipidemia' or 'Hypolipidemic' are only considered disallowed if they are used for more than 3 months across the study period before last dose date.);
- CIMT data taken more than 31 days after the last dose of study medication;
- Received incorrect study drug.

Refer to appendix A for details.

IQVIA will identify any protocol deviators, in conjunction with study team physician and flag all important deviations to AZ study team for exclusion in any relevant populations and output programs

> • Important deviations that may affect the study outcome significantly and the interpretability of the study results will be programmatically derived by the A&R provider where possible.

> • One report will be available to identify the list of all important protocol deviations.

An CCI report will be sent from the AZ study lead in Excel. The MARS lead statistician and AZ study physician will work together to review the list manually and flag which are important and add into the data sets. Of note, the lead statistician from the MARS provider will review this list only to identify the deviations that are programmable and will not classify the deviations as major or minor. Non-programmable deviations will be taken from the CCI report directly for the summary of important protocol deviations.

A subset of important deviations that may affect the study outcome significantly and the interpretability of the study results will be identified and documented prior to unblinding by study team, and defines the per-protocol analysis by excluding data completely or partially as outlined in Appendix A.

3. PRIMARY AND SECONDARY VARIABLES

3.1 Description of CIMT data

CIMT measurements are 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 are made of the near and far walls of the CCA, the carotid bulb, and the ICA sites of the right and left carotid arteries. The standard protocol requires each of these 12 artery sites to be imaged from 3 interrogation angles, each of which differs from the adjacent orientation by 30° of angulation (see Appendix H of the protocol). The images will be recorded and sent to *CCI* or *CCI* for evaluation.

For each of the 12 carotid artery sites at each visit, the 3 images recorded at the various interrogation angles will be measured to determine the minimum, mean and maximum of the CIMT for a specific angle in that site. The maximum CIMT measured from the 3 interrogation angles will be entered as the maxCIMT value for that arterial site. This process is repeated for the 12 carotid arterial sites: the near and far walls of the CCA, the carotid bulb, and the ICA sites of the right and left (near and far walls) carotid arteries.

Additionally, the means of the CIMT measurements of the 4 CCA sites over the 3 interrogation angles will also be recorded as the meanCIMT values for each of the 4 sites (right and left, near and far walls).

We use the following convention to describe the 12 carotid artery sites mentioned above:

- L or R to denote left or right carotid

- B, C or I to denote the bulb, common or ICA segment

- F or N to denote far or near wall

Consequently, the 12 carotid artery sites are

'LBF','LBN','LCF','LCN','LIF','LIN','RBF','RBN','RCF','RCN','RIF' and 'RIN'.

For each subject, IMT assessment from ultrasound scan will be done 7 times: twice before randomization, at weeks 26, 52, 78, and twice at the time of discontinuation of study treatment (on or before week 104). Each scan will yield a set of IMT measurements described above.

The two IMT measurements taken before randomization must meet inclusion criteria of maximum IMT $\geq$ 1.2 mm and < 3.5 mm. The final two IMT procedures should be performed on different days when possible. The second of the final IMT procedures should occur at or before week 104, at the time of discontinuation of study treatment.

Batch reading of all the 7 scans (2 before and 5 after randomization) of a given subject will be done by the same reader over a short period of time for each randomized and treated subject upon completion of (or premature discontinuation from) the 2-year treatment. This will reduce the influence of between reader variability and temporal drift in measurements. Only batch-read CIMT data will be used for statistical analysis of efficacy because of its greater accuracy. However, for randomized subjects who did not receive study medication with no post-randomisation scans, if the two scans before randomization are not be batch read, the eligibility CIMT reading data will be used instead for statistical analysis of efficacy. For randomized subjects who did receive study medication with no post-baseline scans, the same approach will apply.

Since the subjects may miss visits or prematurely withdraw before 2 years, we may have incomplete efficacy observations. Also, IMT measurement from ultrasound scan may occasionally be immeasurable at all 3 angles for some carotid sites.

Following is a summary diagram describing the CIMT measure, data derivation, and data analysis process in terms of dependent variable and summary statistics.

Figure 2   **Summary for CIMT endpoints**

*For CCA only.
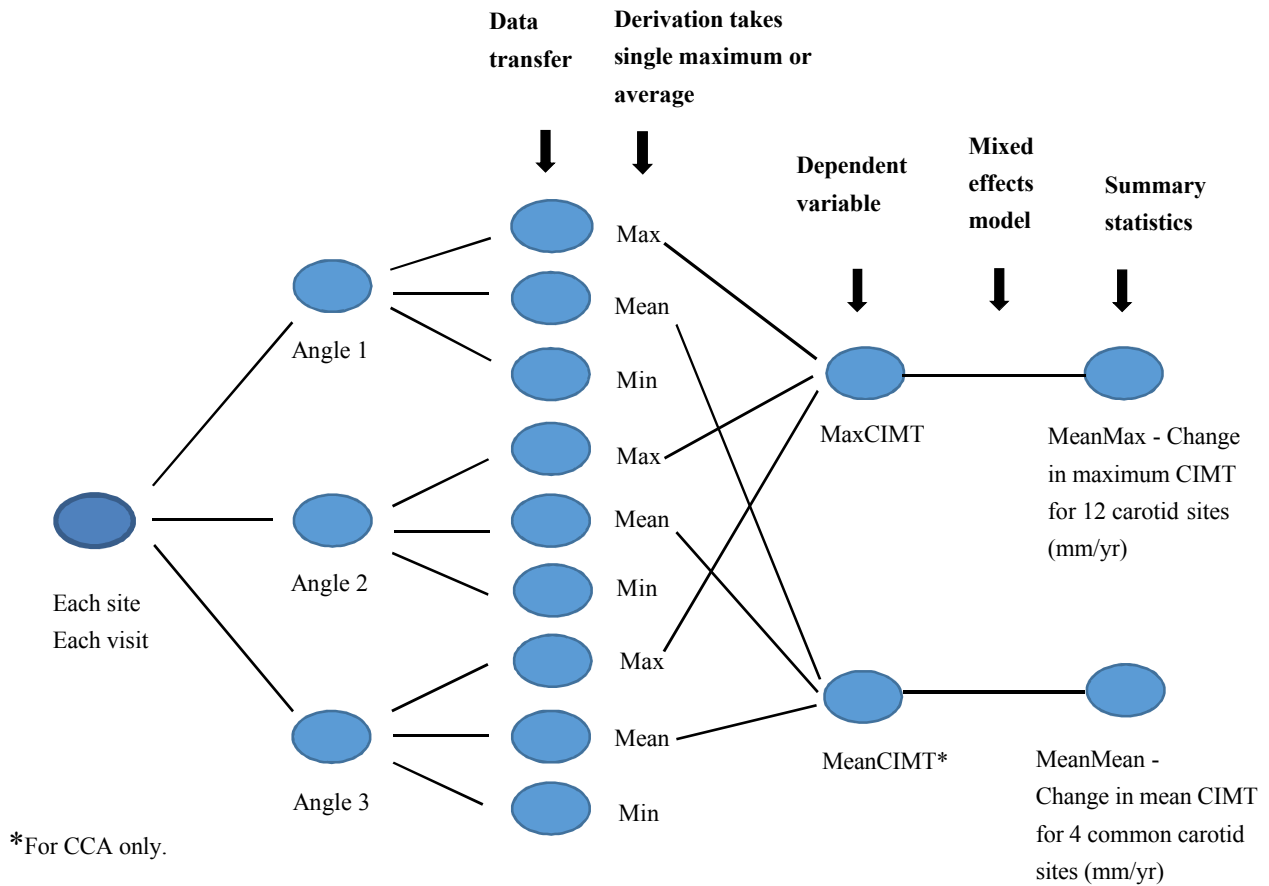
3.1.1   Primary efficacy variable

The primary efficacy variable is the 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. The maxCIMT value for each site will be the
dependent variable in mixed effects model.

3.1.2   Secondary efficacy variables

The secondary outcome variables are

- Annualized rate of change in the MeanMax CIMT of the near and far walls of the
  right and left CCA, using maxCIMT value from CCA as the dependent variable.

- Annualized rate of change in the MeanMax CIMT of the near and far walls of the
  right and left carotid bulb, using maxCIMT value from carotid artery bulb as the
  dependent variable.

- Annualized rate of change in the MeanMax CIMT of the near and far walls of the right and left ICA, using maxCIMT value from ICA as the dependent variable.

- Annualized rate of change in the mean of the mean (MeanMean) CIMT of the near and far walls of the right and left CCA, using meanCIMT value from CCA as the dependent variable.

- Percentage change from baseline to final visit in low-density lipoprotein cholesterol (LDL-C) (using converted results – see section 4.1), total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), non-HDL-C, apolipoprotein (Apo) B, ApoA-I, non-HDL-C/HDL-C, and ApoB/ApoA-I

Please refer to Appendix B for description of efficacy objectives and outcome variables corresponding to each objective.

3.2 Safety and tolerability

No formal statistical testing of the safety and tolerability variables will be carried out. The safety and tolerability variables will be individually summarized using the safety analysis set. The safety and tolerability variables are:

- Adverse events (AEs)

- Serious adverse events (SAEs)

- Changes in clinical laboratory values (hematology, chemistry, and urinalysis)

- 12-lead electrocardiograms (ECGs)

- Vital signs

- Physical examinations

4. ANALYSIS METHODS

4.1 General principles

All statistical evaluation, as well as summaries and tabulations will be done by qualified personnel at IQVIA. Before breaking the treatment codes, following clean file declaration, all decisions made on the evaluability of the data for each individual subject will be documented and each subject will be assigned to the appropriate analysis data set.
The primary analysis for efficacy variables will be based on the ITT analysis set. The CIMT analysis will be performed on the PP population as a robustness check of the analysis on ITT analysis set.

A multilevel, repeated measures, linear mixed effects model will be used for the analysis of the primary and secondary CIMT end points. Rationale for the choice of the model follows Espeland et al (1992 and 1999) and Pitt et al (2000). Details of the model are given in section 4.3.3.

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

Lipid and Apo analyses will be performed on the ITT analysis set only. The definition of baseline for laboratory endpoint variables is given in section 4.1.1.

Secondary lipid and lipoproteins outcome measures are the percentage change from baseline, which will be analyzed by analysis of covariance (ANCOVA) with terms for treatment as a factor and baseline value as a covariate in the model. For lipid measurements (LDL-C, total cholesterol, HDL-C, TG, 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) method. No imputation will be made for missing lipid values for time-weighted average analysis.

During the study, LDL-C measurement was transitioned from 2nd generation reagent to 3rd generation reagent by direct assay. Post-baseline LDL-C values will be affected. To evaluate the consistency of different measurement reagents, all post-baseline LDL-C related analysis will be performed on two sets of data.

- LDL-C values as collected, regardless of the type of reagent.

- LDL-C converted, where values which used 3rd generation reagent (i.e. all values collect on or after the 8th March 2018) are converted to 2nd generation values using the formula $X=0.0626+0.882*Y$, where X is the LDL-C value (in SI units, mmol/L) using 3rd generation reagent, Y is the LDL-C value using 2nd generation reagent. (see Appendix E for details).

For Apo measurements (ApoB, ApoA-I, ApoB/ApoA-I), the analysis of the percent change from baseline to final visit (LOCF) will be performed.

Statistical significance will be set at $\alpha=0.05$

The day of first dose of double-blind study medication (day 1) will be defined as the reference start date for the randomized treatment period and will be displayed in the listings where an assessment date or event date appears when appropriate.

- If the date of the event is on or after the reference date, then: Study Day = (date of event − reference date) + 1.

- If the date of the event is prior to the reference date, then: Study Day = (date of event – reference date).

Duration of an event is calculated as stop date-start date + 1. For example, time on treatment (days) = Date of last dose - date of first dose + 1.

No analysis visit windows will be derived. All by-visit data will be presented by protocol scheduled nominal visits. Listings will include unscheduled visits.

4.1.1   Baseline values

Baseline is the last measurement collected (including measurements taken at unscheduled visits) prior to the date and time of first dose of study medication at randomization visit (visit 4, week 0), or last measurement collected prior to randomization visit, for subjects who are randomized but do not receive any study medication. For in-clinic assessments with assessment date equal to the first dose of study medication and time not available, the assessment will be assigned to the baseline period since all assessments are to be done prior to dispensing study medication according to the protocol. For AEs and concomitant medications with start date equal to the first dose of study medication and time not available, the event will be considered post-baseline.

4.1.2   Change and percent change from baseline

Change in any measurement (CM) from baseline to any randomized treatment period *Week t* is defined as follows:

$$CM_{Week\ t} = M_{Week\ t} - M_{baseline},$$

where:

- $CM_{Week\ t}$ is the change in the measurement from baseline at *Week t*,

- $M_{Week\ t}$ is the measurement at *Week t*,

- $M_{baseline}$ is the baseline measurement.

Percent change in any measurement (PCM) from baseline to any randomized treatment period *Week t* is defined as follows:

$$PCM_{Week\ t} = 100 \times (M_{Week\ t} - M_{baseline}) / M_{baseline}.$$

4.1.3   Creatinine clearance

Creatinine clearance (CrCl) from serum creatinine will be calculated using the following formulae

Male: $\quad \dfrac{(140 - age) * \text{weight in kg}}{72 * \text{creatinine in } \mu mol/L * 0.01131}$

Female: $\quad \dfrac{(140 - age) * \text{weight in kg}}{85 * \text{creatinine in } \mu mol/L * 0.01131}$

4.1.4 Last observation carried forward (LOCF)

In LOCF analyses at Week t, the measurement designated as the Week t measurement will be used. If no Week t measurement is available, the last available earlier post-baseline measurement will be used.

4.1.5 Analysis of covariance (ANCOVA) model for percentage change from baseline

For the secondary efficacy analyses of lipid and lipoprotein outcome measures in the study, the ANCOVA model of percentage change from baseline to Week 104 (or last visit during treatment) efficacy will include treatment as a main effect and baseline value as a covariate. The following model will be used:

$C_{ij} = intercept + \beta \, M_{baseline,ij} + \tau_j + \varepsilon_{ij},$

Where -

- C_{ij} is the percent change from baseline to Week 104 of subject i in treatment group j

- β is the slope of C_{ij} regressing on the baseline measurement

- $M_{baseline,\,ij}$ is the baseline measurement of subject i, in treatment group j

- τ_j is the main effect of treatment group j

- ε_{ij} is random error

The ANCOVA will present least squares (LS) mean estimates and 2-sided 95% confidence intervals (CIs) for mean percent changes from baseline within and (when warranted) between the rosuvastatin and placebo treatments groups. In addition, t-statistics corresponding to the Type III sums of squares for the difference in the LS means will be used to obtain p-values for treatment group comparisons for certain efficacy analyses.

4.1.6 Time weighted average lipid value

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 (this includes observations made at unscheduled visits), 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.

$$TWA = \frac{x_1 t_1 + x_2 t_2 + \dots + x_n t_n}{t_1 + t_2 + \dots + t_n}, \text{ where}$$

x_i s are the lipid values measured at times i=1, 2, …, n, t_i s are the number of days between visit i and visit (i-1).

And $T = t_1 + t_2 + \dots + t_n$ is the total number of days over which the assessments took place. This will be calculated for both sets of LDL-C values (collected and converted) described in section 4.1.

4.1.7 Summaries of continuous variables

Continuous variables will be summarized using number of observations, mean, SD, median, minimum and maximum, and will be presented by visit when applicable. Summaries for continuous endpoints known to have skewed distributions will also include quartiles and the interquartile range.

Minimum and maximum values will be reported to the same degree of precision as the raw data unless otherwise stated. Mean and median will be reported to one further degree of precision. SD will be reported to two further degrees of precision compared to the raw data.

4.1.8 Summaries of categorical variables

Categorical variables will be summarized with number of observations and percentage of subjects in each category.

4.1.9 Summaries of shifts from baseline in categorical variables

Changes from baseline in certain categorical variables will be summarized using shift tables. Frequencies and percentages of subjects within each treatment group will be generated for levels of cross-classifications of baseline and the on-treatment value of the variable. The on-treatment value can be either the value at a certain time point, or the minimum or maximum value in the direction of toxicity that has been observed during a study period (e.g., laboratory tests). Treatment group differences will not be assessed in summaries of shifts.

4.2 Analysis methods

4.2.1 Subject disposition

A summary of subject disposition will display the number of subjects enrolled, i.e., signed informed consent, as well as the number of subjects randomized and who comprised each analysis set by treatment group and overall. In addition, the number and percent of subjects who completed the study (identified on the eCRF as having completed the study – 'Was subject prematurely withdrawn from study' =No), discontinued from the study, and reasons for discontinuation from the study will be summarized by treatment group and overall. An accompanying listing of subjects who prematurely discontinued from the study will be provided.

The exclusions from the PP analysis set will include, but will not be limited to, the subjects who took prohibited concomitant medications, who were non-compliant in taking the investigational product, or who had major deviations of study procedures. These exclusions for the PP analysis set are explicitly defined in Section 2.2 and Appendix A.

A listing will be produced for all enrolled subjects in the ITT analysis set.

4.2.2 Protocol Violations and Deviations

Important protocol deviations will be summarized and listed by treatment group for the ITT analysis set.

4.2.3 Demographic and baseline characteristics

Demographic and other baseline characteristics will be summarized by treatment group and overall, for the ITT analysis set.

Baseline height and weight will be summarized as continuous variables. Sex and race will be summarized as categorical variables. Age at time of informed consent will be summarized as a continuous variable, and by grouping subjects according to age categories (< 65 and ≥ 65 years). Baseline BMI will be summarized as a continuous variable, and by grouping subjects according to BMI categories (< 25 kg/m^2, ≥ 25- < 28 kg/m^2 and ≥ 28 kg/m^2).

Other baseline characteristics to be summarized are listed in the following table:

Table 1   **Summaries of baseline characteristics**

Characteristic	Summarized as	Categories
Smoking status	Categorical	Former, Current, Never
Alcohol use	Categorical	Former, Current, Never
China Adult Dyslipidemia Management Guidelines Risk[1]	Categorical	10-year Ischemic cardiovascular disease (ICVD) risk < 5%
		10-year ICVD risk ≥ 5% - <10%
CrCl	Continuous	

Characteristic	Summarized as	Categories
CrCl	Normal	CrCl > 80 (ml/min)
	Mild impairment	CrCl 50 – 80 (ml/min)
	Moderate impairment	CrCl 30-<50 (ml/min)
	Severe impairment	CrCl <30 (ml/min)
Maximum IMT (Visit 2 and 3)	Continuous	
Major risk factors for ICVD[2]	Categorical	Hypertension
		Smoking
		HDL-C < 40 mg/dL
		Obesity (body mass index $\geqslant$28kg/m^2)
		Family history of premature coronary heart disease (CHD)
		Age Male $\geqslant$45 years, Females $\geqslant$55 years)

[1]Summary will be provided for both interactive voice/web response system (IxRS) data and electronic case report form (eCRF) data.

[2] Total number of risk factors (0 - 6) will also be summarised, with a sub-category under 2 risk factors of with/without hypertension.

All summaries of continuous characteristics will be based on non-missing observations. For categorical characteristics, percentages will be calculated out of the total number of subjects in the data set, overall and by treatment group (i.e., each denominator includes the number of subjects with missing/unknown values for the endpoint).

Demographic and baseline disease characteristics will be presented in listings for all randomized subjects.

4.2.4   Medical and surgical history

Medical history will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) version available at the time of database lock.

Past and current medical history will be summarized together by system organ class (SOC), preferred term (PT), and treatment group for the ITT analysis set. Surgical histories will be summarized in the same way.

The numbers and percentages of subjects with general medical history findings will be provided using the ITT analysis set. Surgical histories will be summarized in the same way.

Medical and surgical histories will be listed for the ITT analysis set.

4.2.5 Duration of exposure

4.2.5.1 Study therapy

Duration of exposure is defined as the number of days between the start and the end dates of study therapy, where the start date of study therapy is the date of the first dose of investigational drug or placebo, and the end date of study therapy is the last known dose of investigational drug or placebo during the double-blind treatment period, i.e., Duration of exposure = Last dosing date - First dosing date + 1. Duration of exposure, excluding interruptions is defined in the same way, but only days where dose taken is greater than 0 are included.

Duration of exposure will be summarized using all subjects treated (safety analysis set), presenting the numbers and percentages of subjects with a duration of exposure within the following week ranges by treatment group: less than 1 week, 1 to less than 7 weeks, 7 to less than 14 weeks, 14 to less than 21 weeks, 21 to less than 28 weeks, 28 to less than 35 weeks, 35 to less than 42 weeks, 42 to less than 49 weeks, 49 to less than 56 weeks, 56 to less than 63 weeks, 63 to less than 70 weeks, 70 to less than 77 weeks, 77 to less than 84 weeks, 84 to less than 91 weeks, 91 to less than 98 weeks, 98 to less than 104 weeks and 104 weeks or more.

The cumulative exposure will be summarized for all subjects in the safety analysis set and separately for subjects who prematurely discontinued. The numbers and percentages of subjects with duration of exposure of at least the following number of weeks will be presented by treatment group:

Up to 1 week, 1 week or more, 7 weeks or more, 14 weeks or more, 21 weeks or more, 28 weeks or more, 35 weeks or more, 42 weeks or more, 49 weeks or more, 56 weeks or more, 63 weeks or more, 70 weeks or more, 77 weeks or more, 84 weeks or more, 91 weeks or more, 98 weeks or more and 104 weeks or more.

Also, the mean, SD, median and range of duration of exposure (days) will be presented by treatment group for all subjects in the safety analysis set and separately for subjects who prematurely discontinued.

Duration of exposure for the investigational product will be listed by subject using the safety analysis set. Additionally, a listing of subjects by batch number of investigational product will be produced.

4.2.5.2 Prior and concomitant medications

All medications will be coded using the latest AstraZeneca Drug Dictionary at the time of database lock.

Prior medication is defined as medication with a stop date before the date of the first dose of study medication.

A medication will be regarded as concomitant if the start date is on or after the date of first dose, or if it started prior to the date of first dose and was ongoing after the date of first dose.

Concomitant rescue medications will be summarized separately. Partial date imputation for medications is described in Section 4.6.7.

Prior and concomitant medications will be summarized by treatment group for the safety analysis set by drug class (anatomic class and therapeutic class), and generic drug name for each treatment group.

Prior and concomitant medications will be listed together.

Vitamin K antagonists including warfarin derivatives and coumadin will be listed by subject. These will be identified using ATC code B01AA.

4.2.5.3 Treatment compliance

Overall treatment compliance percent is calculated during the double-blind treatment period for the blinded study medication (rosuvastatin 20 mg and placebo) as follows:

$$\text{Compliance (\%)} = \frac{Total\ number\ of\ tablets\ dispensed - Total\ number\ of\ tablets\ returned}{Last\ return\ date - First\ dispense\ date}\ x\ 100$$

If no tablets have been returned during the treatment period, the compliance will be set to missing (these subjects will also be excluded from the PP analysis set). If a subject does not return study mediation at the last visit, the last visit date will be used as the last return date for the compliance calculation. If the number of tablets returned is missing, the subject is assumed to have taken the treatment as prescribed by the CSP. If the return date is missing for a dispensed kit during the treatment period, the return date for that kit will be imputed to the next dispensed date, and the subject is assumed to have taken the treatment as prescribed by the CSP (i.e. 1 tablet per day, to a maximum of the dispensed dose).

Treatment compliance will also be displayed in a listing.

4.3 Efficacy analysis

CIMT Data

In this study the CIMT data has a hierarchical (or multilevel) structure. The levels for the data are defined by 1) the study participants and 2) carotid artery sites within the participants. The repeated measure is time.

A multi-level, 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. The model is specified in terms of fixed effects for randomized treatment group, time, time by treatment interaction, ICVD risk stratification (<5%/5%-10%) – based on IxRS data, carotid artery site,

age, sex, centre, and scan reader (In the unlikely event that the model does not converge it may be necessary to drop fixed effects for reader, sex and age in that order). Random effects within the model are the intercept and slope for individual subjects. Time in the model is a continuous measure and is the interval in years from date of randomization to date of CIMT measurement and its effect is linear.

4.3.1 Estimates of effects and tests of statistical significance for trial objectives

Between-group comparisons

In the analysis, let β_1 and β_2 represent respectively the coefficient parameters for time and time by treatment interaction in the mixed effects model. The dependent variable is maximum CIMT.

The annualized rate of change (slope) in MeanMax CIMT in placebo will be estimated by the coefficient parameter β_1, the annualized rate of change (slope) in MeanMax CIMT in the rosuvastatin group will be estimated by $\beta_1 + \beta_2$, and the difference of annualized rate (slope) of change between 2 groups will be estimated by β_2. Then, the null and the alternative primary hypotheses can be expressed as

$H_0 : \beta_2 = 0$ vs. $H_a : \beta_2 \neq 0$ at a significance level of $\alpha = 0.05$.

In other words, the change in MeanMax CIMT from time zero, measured in mm per year, can be estimated from the model as β_1 (Time) for the placebo group and β_1 (Time) + β_2 (Time x Treatment) for the rosuvastatin group. The estimate of the absolute difference in mm in MeanMax CIMT at 2 years between the treatment groups is β_3 (Treatment) + 2 β_2 (Time x Treatment) and change from baseline at 2 years is 2 β_2 (Time x Treatment).

The treatment effect is based on the Time x Treatment term and represents the difference in slopes in mm/year. The between-group test of statistical significance is the p-value associated with this term in the model.

Further details of the analyses and model are given in the following sections.

4.3.2 Justification of the model-based approach

An essential feature of the model is that it fits regression lines to profiles of CIMT values consisting of two pre-randomization values, three values from visits during the treatment period, and two end-of-study visits. In the event that a subject withdraws with an incomplete profile after the pre-randomization ultrasound visits, an advantage of this approach is that regression lines can still be fitted to the data available. This regression approach is appropriate because CIMT values (and therefore primary and secondary endpoints based on them) are expected to change in a linear fashion over time. Analysis of CIMT data and presentation of results as annualized progression or regression rates is conventional, see for example Espeland 2005.

4.3.3   Details of the statistical models

The statistical model (i) reflects the multilevel repeated measures structure of the data, (ii) focuses on the time-profile of CIMT values, (iii) uses all available data by including subjects with incomplete data, and (iv) is consistent with pre-planned statistical analyses described in the protocol. Objectives for analysis are to estimate and test the statistical significance of the treatment effect (rosuvastatin compared with placebo). 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.

The two pre-randomization CIMT scans, denoted by BL2 and BL3, are expected to be highly predictive of CIMT values post-randomization, and the way in which they are included in the statistical model is therefore important (Cnaan et al 1997). A model which has BL2 and BL3 as baseline covariates has greater flexibility in allowing a difference between changes from baseline to the first post-randomization assessment of CIMT (six months) and change from six months on, however the disadvantage is that only change from 6 months to two years is estimated by the model. For this reason, a model which has BL2 and BL3 as part of the response profile is preferred because BL2 and BL3 then contribute to estimation of regression lines at the subject-site level. Furthermore, this model reflects what is believed (and supported by the results in the global Meteor study) to be the behavior of CIMT over time, in other words changes over the 2-year treatment period in both treatment groups are expected to be small and smoothly continuous with time. Further advantages are that terms in the model (Time and
Time x Treatment) estimate changes over the entire treatment period from baseline up to 2 years, and all estimates of effects and p-values for the between-group comparisons can be obtained from a single model by comparing and testing slopes and interactions.

Random effects in the model will consist of subject intercepts and slopes. Thus, random effects in the model allow subjects to have different intercepts and slopes. The model assumes the treatment-time effect will be the same for all carotid sites. This is consistent with the expected effect of rosuvastatin or placebo on carotid artery sites.

An unstructured covariance matrix is used by default to give maximum flexibility in model fitting. If the unstructured covariance matrix results in a lack of convergence, alternative covariance structures, i.e., compound symmetry, will be used.

The adequacy of the basic model will be assessed by including additional terms for time-squared and time-squared by treatment interaction. This is to explore non-linearity in the effect of time. These terms will be assessed using likelihood ratio tests comparing models fitted by maximum likelihood. The additional terms will not be included in the final model if they are not statistically significant at the 0.05 level.

Consistency of the treatment effect in individual carotid artery sites will be demonstrated by means of summary statistics for CIMT values at each visit for each treatment group.

4.3.4 Main and supportive between-group analyses of primary and secondary endpoints

Results from main analyses (based on ITT analysis set) will be considered definitive, and the purpose of supportive analyses (based on PP analysis set) is to demonstrate robustness of results from main analyses with different statistical models and in different subject populations. In the event that results from main and supportive analyses differ substantially further exploratory work will be carried out to explain the differences.

Primary Endpoint

The main analysis which gives a between-group assessment will be carried out using the mixed effects model as previously defined on subjects in the ITT analysis set population using maxCIMT data for all carotid artery sites.

A Supportive analysis will also be carried out in a similar way using only subjects in the PP population.

Secondary Endpoints

- MeanMax CCA CIMT

The main and supportive analyses will be as for the main and supportive analyses of the primary endpoint but using maxCIMT data only for sites in the CCA.

- MeanMax Bulb CIMT

The main and supportive analyses will be as for the main and supportive analyses of the primary endpoint but using maxCIMT data only for sites in the carotid artery bulb.

- MeanMax ICA CIMT

The main and supportive analyses will be as for the main and supportive analyses of the primary endpoint but using maxCIMT data only for sites in the ICA.

- MeanMean CCA CIMT

The main and supportive analyses will be as for the main and supportive analyses of the primary endpoint but using meanCIMT values measured in the CCA.

- Percentage change from baseline to final visit in LDL-C (converted values, see section 4.1), total cholesterol, HDL-C, TG, non-HDL-C, ApoB, ApoA-I, non-HDL-C/HDL-C, and ApoB/ApoA-I.

See section 4.3.5 for details.

4.3.5 Laboratory data

Analyses of percentage change from baseline in lipids and lipoproteins will be carried out for the ITT population using ANCOVA with terms for treatment and baseline value as a covariate in the model. For LDL-C, this will be analysed for both sets of LDL-C values (collected and converted) described in section 4.1. However, the converted values will be considered as the secondary endpoint while the collected values will be used for supportive analysis.

The assumptions of normality and homogeneity of variance will be explored using probability and residual plots. If assumptions are found to be violated, rank ANCOVA approach (Quade 1967) will be used.

4.3.6 Other analyses

For each subject in the ITT analysis set (with at least baseline and one post-baseline scan), the slope of the regression line fitted to the profiles of CIMT values for all 12 carotid artery sites will be estimated in mm/year using a fixed effects model with terms for intercept, site, and time applied to each subject's data. The estimate for slope will be determined from the coefficient of time. A positive slope will indicate progression and a negative slope will indicate regression.

The number and percent of subjects with regression will be summarized for each treatment group.

Summaries of MeanMax CIMT, MeanMax CCA CIMT, MeanMax Bulb CIMT, MeanMax ICA CIMT and MeanMean CCA CIMT (mm) by cohort of assessments completed and visit will be provided. Cohorts of assessments will be Completer - 2 years, non-completer but completed up to 18 months, non-completer but completed up to 12 months, non-completer but completed up to 6 months.

The following outputs will be included to assess quality control of scanning and reading of results.
- Summary of number of carotid artery sites measured per scan by visit
- Distribution of number of carotid artery sites measured per scan at each visit
- Number (%) of subjects read by reader
- Number of measurements obtained at each carotid artery site and percentage out of maximum possible

4.3.7 Subgroup analyses

The effects of rosuvastatin in following subgroups of subjects will be evaluated,

1. Age: < 65 and ≥ 65 years

2. Sex

3. BMI: < 28 vs ≥ 28 kg/m^2

4. China Adult Dyslipidemia Management Guidelines ICVD risk categories (see 4.2.2 for definitions)

5. History of hypertension (Yes/No)

6. Baseline LDL-C: below and above or equal to the mean

7. Baseline TC: below and above or equal to the mean

8. Baseline HDL-C: below and above or equal to the mean

9. Baseline TG: above and below the mean (If TG are not normally distributed, groupings above and below the median value will be considered).

10. Baseline non-HDL-C: below and above or equal to the mean

11. Baseline non-HDL-C/HDL-C: below and above or equal to the mean

12. Baseline ApoB: below and above or equal to the mean

13. Baseline ApoA-I: below and above or equal to the mean

14. Baseline ApoB/ApoA-I: below and above or equal to the mean

15. Smoking: never, current/former

The treatment-by-subgroup interaction will be examined by adding the subgroup variable and the interaction term of treatment-by-subgroup as covariates to multilevel, repeated measures, linear mixed effects model as described for the primary analysis (section 4.3). Similar output will be presented for each subgroup as for the primary analysis. When the subgroups are also stratification factors, the eCRF values will be used rather than the values from IxRS used for randomization.

For smoking subgroup, if there is any category with less than 10% of the population in a review prior to unblinding the study, the subgroup may be re-categorized or eliminated before unblinding.
These analyses will use the ITT analysis set.

4.3.8 Exploratory analyses

Slope of the regression line, as defined in section 4.3.6, will be summarised (means, SD, N) for rosuvastatin treatment group only in each of the following subgroups (for only the converted LDL-C values, as described in section 4.1) to investigate the relevance of a reduction of LDL-C:

1.   % change from baseline to time-weighted average during treatment in LDL-C: below and above or equal to the mean.

2.   On-Treatment LDL-C (time-weighted average value):

   –   below and above or equal to the mean

   –   <100 mg/dL and ≥ 100 mg/dL

   –   <70 mg/dL and ≥ 70 mg/dL

   –   <70, (>=70- <100), and ≥ 100 mg/dL

3.   Loess plot of annualized rate of change in MeanMax CIMT in mm/year by % change in LDL-C and by on-treatment LDL-C (time-weighted average values).

4.4 Safety variables

This section describes safety analyses to be conducted on all subjects who enter the screening phase. All analyses of safety data will present descriptive statistics. Formal statistical comparisons will not be performed.

The baseline value of each safety lab test, ECG, or physical exam endpoint is defined as the last assessment before or including Study Day 1 (i.e., day of first dose of double-blind study drug). AEs occurring on Study Day 1 (the day that the first dose of randomized study medication was taken) will be counted during the double-blind treatment period. For subjects who are randomized but do not receive any double-blind study drug, baseline is defined as the last assessment before randomization. AEs and other safety measures occurring after the last dose of randomized treatment are described in section 4.6.4.

4.4.1 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.
AEs will be categorized according to 2 definitions:

- AEs reported during the screening phase

- Treatment Emergent AEs

Treatment emergent AEs are defined as all AEs which start on or after the first dose of study drug. An AE that was present at treatment initiation but resolved and then reappeared while the subject was on treatment, is a treatment emergent AE (regardless of the intensity of the AE when the treatment was initiated). AEs reported through 10 days after the last dose of study drug will be included in the double-blind treatment period summaries.

AEs will be reported according to the latest MedDRA version available at the time of database lock.

The selection criteria of AEs for counting are as follows:

1.   Where a subject has the same AE, based on PT, reported multiple times in a single analysis period, the subject will only be counted once at the preferred terminology level in AE frequency tables.

2.   When a subject has the same AE, based on PT, reported multiple times in a single analysis period, the following criteria, in order of precedence, will be used to select the event to be included in summary tables:

- **Relationship to study medication**: Related events will take precedence over unrelated events in determining the event to include in summary tables. Missing relationship will be considered a related event.

- **Intensity of event:** More intense events will take precedence over less intense events in determining the event to include in summary tables. Missing intensity will be considered the least intense event.

- **Onset date:** Earlier onset date events will take precedence over later onset date events in determining the event to include in summary tables.

3.   When reporting AEs by intensity, in addition to providing a summary table based on the event selection criteria detailed in item 2 above, summary tables will also be provided based on the most intense event during the analysis period - independent of relationship to study medication. For these tables, the following criteria, in order of precedence, will be used to select the event to be included in summary tables:

    –   Intensity of event

    –   Onset date

In summaries by SOC and PT, AEs will be sorted by decreasing frequency of each PT and SOC, within SOC, according to the "Rosuvastatin 20 mg group" subject incidence. In summaries by PT, AEs will be sorted by decreasing frequency of PT according to the "Rosuvastatin 20 mg" subject incidence.

4.4.2 All adverse events

The subject incidence of AEs reported during the screening phase will be summarised by all AEs, Deaths, SAEs, and withdrawal from study due to AE.

The subject incidence of treatment emergent AEs will be summarized by treatment group in the following ways:

- All AEs, (by severity)
- AEs classified as related to study drug
- Deaths
- SAEs (by severity, and excluding where the outcome was death)
- AEs leading to study discontinuation

The subject incidence of treatment emergent AEs will be summarized separately by SOC, PT and treatment group for the double-blind treatment period.

The subject incidence of the most common (reported in at least 2% of the subjects in any treatment group) treatment emergent AEs will be presented by SOC, PT and treatment group. Also, the subject incidence of treatment emergent AEs will be presented by PT, intensity and treatment group. The subject incidence of ischaemic cardiovascular AEs will also be presented by PT. Ischaemic cardiovascular AEs will be identified using key words of 'myocardial infarction', 'acute coronary syndrome', 'unstable angina'(or angina unstable), 'stroke' (excluding heat stroke), 'cerebrovascular accident', 'cerebral infarction'. A subject listing of all reported AEs during the screening and the double-blind treatment period will be produced.

4.4.3 Deaths

All deaths recorded on the TERM page, the AE page, or SAE page (with a death date, cause of death, outcome or SAE categorization present) of the CRF will be considered a death in the analyses. All deaths will be summarized by SOC and PT for the safety analysis. A listing of all deaths during screening and double-blind treatment period will be produced.

4.4.4 Serious adverse events

The subject incidence of treatment emergent SAEs will be presented by SOC, PT and treatment group. In addition, the subject incidence of related treatment emergent SAEs will be presented by SOC, PT, and treatment group for the safety analysis. A listing of all SAEs during screening and double-blind treatment period will be produced. If we cannot determine whether an AE is serious, it will be considered an SAE.

4.4.5 Related adverse events

The subject incidence of related treatment emergent AEs will be presented by SOC, PT and treatment group for safety analysis.

The subject incidence of most common related treatment emergent AEs (reported in at least 2% of the subjects in any treatment group) during the double-blind treatment period will be presented by PT and treatment group for safety analysis.

4.4.6 Adverse events leading to discontinuation

Number of subjects who discontinue during the screening phase due to an AE will be listed.

Treatment emergent AEs leading to study treatment discontinuation will be summarized by SOC, PT, and treatment group for safety analysis.

In addition, a subject listing of discontinuations due to AEs will be presented for screening and double-blind treatment period.

4.4.7 Other adverse events analyses

Treatment emergent AEs in subjects with any of the following at any time during the treatment phase will be listed:

- CK > 10x upper limit or normal (ULN)

- Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) $\geq$ 3 x ULN and TBL $\geq$ 2 x ULN on one occasion

- Serum creatinine increase > 100% from baseline and > ULN

- Shift in urine protein from none/trace at baseline to ++ or greater

- Shift in urine blood from none/trace at baseline to ++ or greater

- Subjects with proteinuria, hematuria or both at any time

4.5 Clinical laboratory tests evaluation

All scheduled laboratory evaluations are performed by central laboratories. Evaluations done by local laboratories, if any, will not be included in summary tables nor in the listings. All safety measurements will use all available data for analyses, including data from unscheduled visits and repeated measurements. For lab assessment summary by visit, the data will be summarized according to the protocol-scheduled week for that visit. For lab

summaries that are not visit-based, all visits including unscheduled and repeat visits will be included.

Laboratory parameters will be presented both in SI and conventional units where appropriate.

If a laboratory test is reported as above or below the limit of quantification (i.e., result includes operator >, ≥, <, or ≤), the limit of quantification will be used for analysis. The result with the operator will be reported in listings.

4.5.1   Summary of laboratory variables over time

Descriptive statistics (number of observations, mean, SD, minimum, median and maximum values) for collected values, change from baseline, and percentage change from baseline will be summarized for clinical laboratory tests (hematology, chemistry, urinalysis, lipid profile) at each protocol scheduled nominal visit and at the last non-missing post-baseline visit, across treatment groups.

Hepatic biochemistry and CK values as well as their changes from baseline, plus change from baseline and percentage change from baseline in creatinine, will be summarised using descriptive statistics at each visit.

Hematology, hepatic biochemistry (including CK) and clinical chemistry values outside the laboratory reference ranges will be flagged and summarised.

Urinalysis data including pH and specific gravity will be summarised by mean, median, SD, minimum, maximum, and number of subjects for each treatment group at each visit.

4.5.2   Shift tables and summary of subjects with specific laboratory values

The hematology and chemistry data will also be summarized in shift tables comparing results of extreme values over the duration of the double-blind treatment period against the baseline, based on normal range categories.

Urine blood and urine protein will be summarised by

(1) category of most abnormal result and
(2) by category at the final visit, relative to baseline categories (shift tables) for each treatment group.

Numbers and percent of subjects who developed proteinuria (defined as an increase in the dipstick urine protein measurement of at least ++ from baseline to any visit after baseline (e.g. negative/trace to ++, + to +++, ++ to ++++) will be presented by treatment group. Similar summaries will be made of hematuria (defined as an increase in the dipstick urine blood measurement of at least ++ from baseline to any visit after baseline (e.g. negative/trace to ++, + to +++, ++ to ++++) and concurrent proteinuria and hematuria.

Similar tables will summarise shift in urine protein/blood categories from none or trace at baseline to the categories of urine protein/blood at the last visit.

Elevations of ALT [$\geq$ 3 times the ULN on single occasions and two consecutive occasions (defined as any 2 assessments taken on, at either a scheduled or unscheduled visit)] and CK ($\geq$ 5 times and $\geq$ 10 times the ULN) and percentage increases from baseline in creatinine (including >30% and $\leq$ 50%; >50% and $\leq$ 100%; and > 100%, split by $\leq$ ULN and > ULN) at any time point during the treatment phase will be highlighted and summarised by treatment group at time of occurrence.

Elevated ALT and/or AST and Total Bilirubin

The following criteria will be summarized in examination of elevated ALT and/or AST and total bilirubin (TBL):

AST or ALT $\geq$ 3 x ULN together with TBL $\geq$ 2 x ULN at any point during the study following the start of study medication irrespective of an increase in ALP.

4.5.3 ECG

A 12-lead ECG will be recorded at Baseline and Week 104 (or early termination). The overall ECG investigator interpretations will be summarized using a shift table comparing Baseline to endpoint for the safety analysis set. The ECG interpretations will be reported as "Normal", "Abnormal NCS (Not Clinically Significant)", or "Abnormal CS (Clinically Significant)". The denominators for the percentages will be the numbers of subjects with ECG data at both the baseline and at endpoint in each treatment group by parameter.

QTcF will be derived during creation of the reporting database using the reported ECG values (RR and QT) with the following formula:

$$QTcF\ (msec) = (QT\ (msec))/\sqrt[3]{(RR)}$$

where RR=60/heart rate.

Absolute and change from baseline values for heart rate, P and QRS duration, PR and QT intervals and corrected QTc interval (unspecified and QTcF) will be summarized by protocol scheduled nominal visit and the last non-missing post-baseline visit for each treatment group using descriptive statistics.

The number and percentage of subjects presenting in each of the following categories of QTcF will be presented.

- QTcF value above 450ms, 480ms, and 500ms at any time during treatment

- Change from baseline (increase) in QTcF by more than 30ms, 60ms, and 90ms at any time during treatment

- Change from baseline (decrease) in QTcF by more than 30ms, 60ms, and 90ms at any time during treatment

- QTcF value above 450 ms and an increase of more than 30ms at any time during treatment.

- QTcF value above 500 ms and an increase of more than 60ms at any time during treatment.

A subject listing will be presented for those had post-baseline abnormal CS (Clinically Significant).

4.5.4 Vital signs

Vital signs to be analyzed and presented are systolic and diastolic blood pressures and sitting pulse. Vital signs and their changes from baseline values at post-baseline visits will be summarized by protocol scheduled nominal visit and the last non-missing post-baseline visit for each treatment group using descriptive statistics.

Vital sign measurements will be presented by subject, visit and parameter in a data listing.

4.5.5 Weight

Body weight and their changes from baseline values at post-baseline visits will be summarized by protocol scheduled nominal visit and the last non-missing post-baseline visit for each treatment group using descriptive statistics.

Weight will also be presented by subject and visit in a data listing.

4.5.6 Physical examination

The physical examination will be performed at Baseline and Week 104 (or early termination). Frequency tables of the number and percentage of subjects presenting normal/abnormal physical examinations will be presented by protocol scheduled nominal visit. The variables collected are: general appearance, skin, head and neck, lymph nodes, thyroid, musculoskeletal/extremities, cardiovascular, respiratory, abdomen, neurological, and genital/rectal. For subjects reporting abnormalities post-baseline they will be summarized as "the same as baseline" if the abnormality was present, or "new or aggravated abnormality" if it is a new abnormality or has worsened.

4.6 Conventions

4.6.1 Study period start and end dates

Double-blind treatment period

The randomized treatment period is assumed to start at the date of the first randomized double-blind dose, and to end at the last dose of double-blind study drug as recorded in the DOSE CRF module.

4.6.2 Duplicate assessments

When a subject has multiple assessments for the same laboratory, vital signs or the numeric ECG parameter reported as drawn/assessed on the same date, these multiple assessments will be replaced by a single one, the value of which will be the latest assessment prior to first dose of study drug for baseline and the worst observation for post-baseline by-visit and LOCF analysis. The worst observation will be determined by examining the proximity of all multiple observations to the upper/lower reference ranges. In the situation where there is only one observation outside the reference ranges, this value will be considered as the worst.

If there are multiple ECG interpretation or physical exam results on the same date, and any of these interpretations are abnormal, the abnormal interpretation will be used for analyses/summaries.

If a subject has prematurely discontinued and has CIMT data from ultrasound scans for more than one early termination visit, only the earliest assessment will be used in analyses and summaries. Both visits will be listed

4.6.3 Post-dosing efficacy observations

During randomized treatment period, efficacy and safety laboratory observations will be listed regardless of whether the subject was taking blinded study drug. Observations will contribute to summaries only if the subject's last dose of blinded drug was as follows:

- CIMT data from ultrasound scans taken more than 31 days after the last dose of study medication will be excluded from the efficacy analysis based on PP population. All CIMT assessments regardless of collection date relative to last dose of study drug will be included in the analysis of primary and secondary endpoints based on ITT population.

- Lipid and lipoprotein measurements will be summarized only if measured on or before the 10th day after the last randomized, double-blind drug dose date.

4.6.4 Post-dosing Safety Observations

The following conventions are for the safety analysis during the 104-week randomized double-blind treatment period.

Randomized treatment period safety observations will be listed regardless of whether the subject was taking blinded study drug. However, safety observations will not contribute to summaries if the subject's last dose of blinded drug was as follows:

- All AEs, including SAEs, will be summarized only if their onset dates were within 10 days after last dose of study drug.

- Vital signs, physical examination, safety laboratory and ECG results will be summarized only if measured on or before the 14th day after the last blinded drug dosing date.

4.6.5   Missing Start and Stop dates for Adverse Events

Partial start dates and stop dates for AEs are not allowed per eCRF design. If an AE start date is fully missing, the start date will be imputed as the date of first dose of study medication. Imputed dates will not appear on the listings. Fully missing AE stop dates will not be imputed.

4.6.6   Calculation of Body Mass Index

IQVIA will calculate BMI as the ratio of subject's weight (in kilograms) to the square of the subject's height (in meters): BMI (kg/m²) = weight (kg)/height^2 (m²).

4.6.7   Missing Dates Assignment for Concomitant Medications

Start and stop dates for all concomitant medications are collected on the CRF. However, in case of missing or partial information in these dates, the following rules will be used:

If start date is missing or partial:

- if month is missing, use January (01)

- if day is missing, use the 1st (01)

- if year is missing, use year of the entry visit (consent date for those missing entry visit)

- if entire date is missing, use consent date

If stop date is missing, partial or "continuing:"

- if month is missing, use December (12)

- if day is missing, use the last day of the month under consideration

- if year or the entire date is missing or if "continuing", set to missing.

5. INTERIM ANALYSES

No interim analysis is planned for this study.

6. CHANGES OF ANALYSIS FROM PROTOCOL

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Appendix A   Subset of important protocol deviations that will affect study results interpretation and the Per-Protocol population

Number	Important protocol deviations / Criteria	Complete/partial data exclusion
	Inclusion Criteria	
1.	Enrolled, for male, subject < 45 years or ≥ 70 years for female, subject < 55 years or ≥ 70 years	Complete data exclusion.

2.	Enrolled, even though subject did not meet the criteria below:
	
	Subjects with only hypertension (as defined blood pressure ≥ 140/90 mmHg or on antihypertensive treatment) and age as cardiovascular disease (CVD) risk factors and also subjects without hypertension who have 3 or more other risk factors (including age) must have:
	
	   – Fasting LDL C of ≥ 120 mg/dL (3.1 mmol/L) and < 160 mg/dL (4.1 mmol/L) (Note: if a subject meets this criteria during a re-test between visit 1 and 2, this is not considered a deviation)
	
	Subjects without hypertension who have fewer than 3 other risk factors (including age) must have:
	
	   – Fasting LDL-C of ≥ 120 mg/dL (3.1 mmol/L) and < 190 mg/dL (4.9 mmol/L)
	   (Note: if a subject meets this criteria during a re-test between visit 1 and 2, this is not considered a deviation)
	
	Subjects with hypertension and age as CVD risk factors, along with at least one other risk factor, will be considered as having an important protocol deviation, regardless of fasting LDL-C values at screening.
		Complete data exclusion.

Number	Important protocol deviations / Criteria	Complete/partial data exclusion
3	Enrolled, even though subject did not meet the criteria below: TG < 500 mg/dL (5.65 mmol/L) at visit 1 (week -6) (Note: if a subject meets this criteria during a re-test between visit 1 and 2, this is not considered a deviation)	Complete data exclusion.
4	Enrolled, even though subject did not meet the criteria below: HDL cholesterol levels ≤ 60 mg/dL (1.6 mmol/L) at visit 1 (week -6) (Note: if a subject meets this criteria during a re-test between visit 1 and 2, this is not considered a deviation)	Complete data exclusion.
5	Enrolled, even though subject did not meet the criteria below: Maximum IMT ≥ 1.2 mm and < 3.5 mm in the carotid ultrasound studies conducted at both visit 2 (week -4) and visit 3 (week -2).	Complete data exclusion.
	Exclusion criteria	
6	Enrolled, even though subject met the exclusion criteria below: 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)	Complete data exclusion.
	Major deviations:	
8	Overall compliance during the double-blind treatment period <80% of the prescribed drug	Complete data exclusion.

Number	Important protocol deviations / Criteria	Complete/partial data exclusion
9	Use of prohibited/disallowed medication during the double-blind treatment period (medications with an ATC code of C10AA, C10, or C10AX or 'Reason for Therapy' is recording on the eCRF as 'Control for dyslipidemia', 'Hyperlipidemia' or 'Hypolipidemic' are only considered disallowed if they are used for more than 3 months across the study period before last dose date).	Partial data exclusion: Data at the affected visit and subsequent visits will be excluded. These concomitant medications are the lipid lowering agents listed in appendix 7.7.1 of the protocol.
10	CIMT data from ultrasound scans taken more than 31 days after the last dose of study medication.	Partial data exclusion: Data at the affected visit and subsequent visits will be excluded.
11	Subject randomly allocated a treatment out of sequence or inadvertently receives the wrong treatment.	Complete data exclusion.

Appendix B Efficacy objectives and outcome variable relating to each objective

Objectives	Variables	Summary outcome variables for analyses	Analysis sets	Description of planned analysis
Primary				
To assess the efficacy of rosuvastatin 20 mg treatment for 104 weeks on the change in the **mean** of the **maximum** intima media thickness of the 12 carotid artery sites. The subjects randomized to rosuvastatin will be compared to the subjects randomized to placebo.	Annualized rate of change in the MeanMax CIMT measurement for each of the 12 carotid artery sites.	For each subject an annualized rate of change (slope) of Max CIMT will be estimated from the 12 sites using a multilevel mixed effects model. The estimates will be summarized by treatment group.	ITT, PP	Statistical significance of the MeanMax CIMT annualized rate of change (slope) between placebo and rosuvastatin will be evaluated using the time-by-treatment interaction term in the multilevel mixed effects model.
Secondary				
To assess the efficacy of rosuvastatin 20 mg treatment for 104 weeks on the change in the **mean** of the **maximum** intima media thickness of the 4 **CCA** sites. The subjects randomized to rosuvastatin will be compared to the subjects randomized to placebo.	Annualized rate of change in MeanMax CIMT for each of the 4 common carotid sites.	For each subject an annualized rate of change (slope) of MaxCIMT will be estimated from the 4 sites using a multilevel mixed effects model. The estimates will be summarized by treatment group.	ITT, PP	Statistical significance of the MeanMax CIMT annualized rate of change (slope) between placebo and rosuvastatin will be evaluated using the time-by-treatment interaction term in the multilevel mixed effects model.

To assess the efficacy of rosuvastatin 20 mg treatment for 104 weeks on the change in the **mean** of the **maximum** intima media thickness of the 4 carotid **bulb** sites. The subjects randomized to rosuvastatin will be compared to the subjects randomized to placebo.	Annualized rate of change in MeanMax CIMT for each of the 12 carotid bulb sites.	For each subject an annualized rate of change (slope) of MaxCIMT will be estimated from the 4 sites using a multilevel mixed effects model. The estimates will be summarized by treatment group.	ITT, PP	Statistical significance of the MeanMax CIMT annualized rate of change (slope) between placebo and rosuvastatin will be evaluated using the time-by-treatment interaction term in the multilevel mixed effects model.
To assess the efficacy of rosuvastatin 20 mg treatment for 104 weeks on the change in the **mean** of the **maximum** intima media thickness of the 4 **ICA** sites. The subjects randomized to rosuvastatin will be compared to the subjects randomized to placebo.	Annualized rate of Change in MeanMax CIMT for each of the 4 ICA sites.	For each subject an annualized rate of change (slope) of MaxCIMT will be estimated from the 4 sites using a multilevel mixed effects model. The estimates will be summarized by treatment group.	ITT, PP	Statistical significance of the MeanMax CIMT annualized rate of change (slope) between placebo and rosuvastatin will be evaluated using the time-by-treatment interaction term in the multilevel mixed effects model.
To assess the efficacy of rosuvastatin 20 mg treatment for 104 weeks on the change in the **mean** of the **mean** intima media thickness of the 4 **CCA** sites. The subjects randomized to rosuvastatin will be compared to the subjects randomized to placebo.	Annualized rate of change in MeanMean CIMT for each of the 4 CCA sites.	For each subject an annualized rate of change (slope) of Mean CIMT will be estimated from the 4 sites using a multilevel mixed effects model. The estimates will be summarized by treatment group.	ITT, PP	Statistical significance of the MeanMean CIMT annualized rate of change (slope) between placebo and rosuvastatin will be evaluated using the time-by-treatment interaction term in the multilevel mixed effects model.

To evaluate change in lipids and lipoproteins	LDL-C (converted results), HDL-C, TG, Non-HDL-C, Non-HDL-C/HDL-C	Percent change from baseline to week 104 in lipid parameters	ITT (Observed and LOCF data)	ANCOVA with treatment as a factor and baseline value as a covariate
		Percent change from baseline to time-weighted average in lipid parameters	ITT (Observed data)	ANCOVA with treatment as a factor and baseline value as a covariate
To evaluate change in Apo	ApoB, ApoA-I, ApoB/ApoA/I	Percent change from baseline to week 104 in lipoprotein parameters	ITT (Observed and LOCF data)	ANCOVA with treatment as a factor and baseline value as a covariate

Appendix C   SAS codes for statistical models used in the efficacy analysis.

Multi-level linear mixed effects model for primary efficacy analysis:

```
PROC MIXED;
CLASS TRT SITE SUBJID ICVD SEX READER CENTRE;
MODEL RESPONSE = TRT TIME TRT*TIME ICVD SITE CENTRE AGE SEX READER
/ SOLUTION DDFM = KR CL COVB;
RANDOM INTERCEPT TIME /SUB = SUBJID TYPE = UN;
RUN;
```

Note: The maxCIMT value for each site will be the dependent variable (RESPONSE) in the mixed effects model. Time is a continuous variable per the protocol and will be the interval in years from date of randomization to date of the CIMT measurement. The fixed effect Time in the MODEL statement is not declared as a class variable; thus it models a linear trend in time. We want to see the change in slope over time for the difference between rosuvastatin and placebo across all sites.
The TYPE=UN option in the RANDOM statement specifies an unstructured covariance matrix for the random intercept and slope effects at the individual subject level.
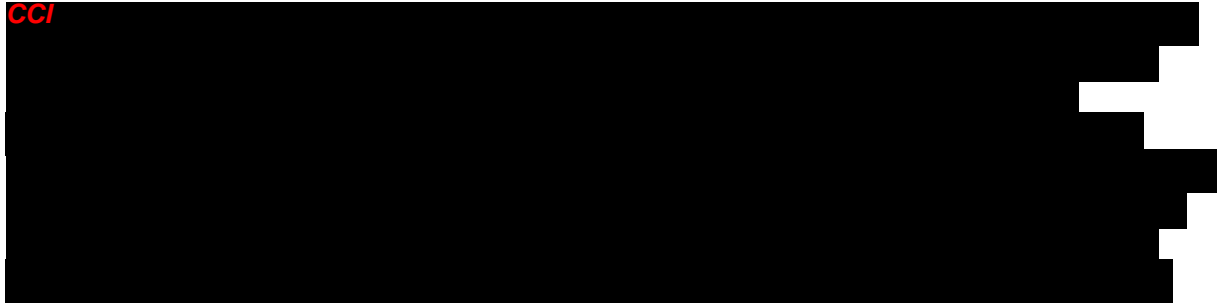
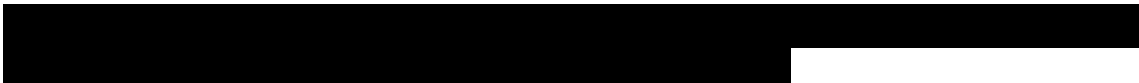ANCOVA analyses for the laboratory efficacy endpoints:

PROC GLM;
CLASS TRT;
MODEL PER_CHG = TRT BASE /CLPARM;
LSMEANS TRT / STDERR PDIFF CL;
ESTIMATE 'ROSUVASTATIN 20 MG VS PLACEBO' TRT 1 –1/CL;
RUN;

PER_CHG = Percentage change from baseline
TRT = Randomized treatment
BASE = Baseline value

Appendix D   Assumptions for sample size calculation.

CCI

CCI

- *CCI*

CCI

Appendix E   **Method Comparison between two generation of reagent for measuring Low Density LDL-C in Serum Samples for Homogeneous Enzymatic Colorimetric Assay using Roche Modular and Cobas series**

LDL-direct-3rdGen_
20171018- Final vers