STATISTICAL ANALYSIS PLAN

A Double-blind, Randomized, Multicenter Study to Evaluate the Safety and Efficacy of Evolocumab, Compared With Ezetimibe, in Hypercholesterolemic Japanese Subjects Unable to Tolerate an Effective Dose of a HMG-CoA Reductase Inhibitor Due to Muscle Related Side Effects

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Authors:	PPD

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Table of Abbreviations

Abbreviation or Term	Definition/Explanation
AE	Adverse event
AHA	American Heart Association
AI	Autoinjector
ALT	Alanine aminotransferase
ApoA1	Apolipoprotein A-1
ApoB	Apolipoprotein B
AST	Aspartate aminotransferase
CAS	Completer analysis set
CEC	Clinical Events Committee
CHD	Coronary Heart Disease
CK	Creatine phosphokinase
CMH	Cochran Mantel-Haenszel
CV	Cardiovascular
CSR	Clinical study report
CTCAE	NCI Common Terminology Treatment Collaboration
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
DQR	Data Quality Review
eCRF	Electronic Case Report Form
EOIP	End of Investigational Product
EOS	End of study (for individual subject)
FAS	Full analysis set
HDL-C	High-density lipoprotein cholesterol
hsCRP	High sensitivity C-reactive protein
IBG	Independent biostatistical group
IEC/IRB	Independent Ethics Committee / Institutional Review Board
IP	Investigational product
IPD	Important protocol deviation
IVRS	Interactive voice response system
LDL-C	Low-density lipoprotein cholesterol
LDLR	LDL receptor
LFT	Liver function test
Lp(a)	Lipoprotein(a)
MedDRA	Medical dictionary for regulatory activities

Abbreviation or Term	Definition/Explanation
OLE	OLE Open Label Extension
OLEAS	OLEAS Open Label Extension Analysis Set
PCSK9	Proprotein convertase subtilisin/kexin type 9
PK	Pharmacokinetic
PKDM	Pharmacokinetics and drug metabolism
PO	Oral administration
POIPD	Dose date of oral investigational product
Q2W	Every 2 weeks
QM	Monthly (Every 4 weeks)
QD	Once a day
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SC	Subcutaneous
SCIPD	Dose date of SC investigational product
SD	Standard deviation
SF-36	Short Form (36) Health Survey
TEAE	Treatment-Emergent Adverse Event
TIA	Transient ischemic attack
UC	Ultracentrifugation
ULN	Upper limit of normal
VLDL-C	Very low-density lipoprotein cholesterol

1. Introduction

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for evolocumab (AMG 145) Study 20140234 Amendment 3 dated 21 March 2017. The scope of this plan includes the primary and final analyses that are planned and will be executed by the Biostatistics department unless otherwise specified.

2. Objectives

2.1 Primary

To evaluate the effect of 12 weeks of subcutaneous evolocumab (AMG 145) compared with ezetimibe, on percent change from baseline in low-density lipoprotein cholesterol (LDL-C) in hypercholesterolemic subjects unable to tolerate an effective dose of a statin.

2.2 Secondary

Secondary objectives are:

- To evaluate the safety and tolerability of subcutaneous (SC) evolocumab, compared with ezetimibe, in hypercholesterolemic subjects unable to tolerate an effective dose of a statin
- To assess the effects of 12 weeks of evolocumab compared with ezetimibe, on change from baseline in LDL-C, and percent change from baseline in non high density lipoprotein cholesterol (non HDL-C), total cholesterol (TC), apolipoprotein B (ApoB), total cholesterol/HDL-C ratio, ApoB/Apolipoprotein A1 (ApoA1) ratio, lipoprotein(a) [Lp(a)], triglycerides, very low-density lipoprotein cholesterol (VLDL-C), and HDL-C in hypercholesterolemic subjects unable to tolerate an effective dose of a statin
- To assess the effects of 12 weeks SC evolocumab, compared with ezetimibe, on percent of subjects attaining LDL-C < 70 mg/dL (1.8 mmol/L) in hypercholesterolemic subjects unable to tolerate an effective dose of a statin

3. Study Overview

3.1 Study Design

This is a phase 3, multicenter, double-blind, randomized, ezetimibe controlled, parallel group study for evolocumab in hypercholesterolemic Japanese subjects unable to tolerate an effective dose of a statin. Subjects who meet all inclusion/exclusion criteria will be randomized with an allocation ratio of 2:2:1:1 into 4 groups: QM 420 mg SC evolocumab + QD PO placebo, Q2W 140 mg SC evolocumab + QD PO placebo, QM SC placebo + QD 10 mg PO ezetimibe, Q2W SC placebo + QD 10 mg PO ezetimibe. Randomization will be stratified by screening LDL-C level and baseline statin use. Randomization should occur within 5-10 days of the screening LDL-C evaluation used to

determine eligibility. Subjects on low or atypical statin therapy must be on a stable dose for at least 4 weeks prior to the screening and throughout the blinded portion of the study; the dose cannot be adjusted during screening and for the duration of the study.

For blinding purposes, every subject will receive investigational product (IP) SC and PO. Patients will be provided with evolocumab or placebo through the use of an autoinjector (AI) or Personal Injector. Depending on availability either a single Personal Injector or 3 autoinjectors will be provided for monthly dosing. A single AI will be used for Q2W dosing. Evolocumab and corresponding placebo will be administered at the study site or at appropriate non-clinic setting per protocol Table 1 (Schedule of Assessment). PO placebo will be available to match PO ezetimibe through over-encapsulation. The SC IP dose frequencies of Q2W and QM will not be blinded.

Following the week 12 visit, all subjects will self-administer IP in the non-clinic setting; subjects will return to the clinical site at W24, W36, W48 and W52 for subsequent visits. There will be an end of study phone call at W54 (Q2W subjects only) for any potential adverse events, serious adverse events, or adverse device effects.

Central laboratory results of the lipid panel, ApoA1, ApoB, lipoprotein(a), and high sensitivity C-reactive protein (hsCRP) will be blinded during double-blind treatment. Investigators will be provided lipid results starting at week 24 until the end of study for each subject. All lipid results from posttreatment to week 24 will remain blinded until the unblinding of the clinical database.

The study includes collection of biomarker samples, where approved by the institutional review board (IEC/IRB). Administration of PO IP (ezetimibe or placebo) will end with the week 12 visit for all subjects. Following the week 12 visit subjects should be treated to standard of care in addition to receiving open label evolocumab.

Subjects will be encouraged to complete all planned visits regardless of their adherence to investigational product (IP) administration. Formal review of the accumulating blinded data by an independent Data Monitoring Committee (DMC) will occur.

3.2 Sample Size

The planned sample size for the comparison between evolocumab and ezetimibe is 40 (20 in Q2W and QM each) and 20 subjects (10 in Q2W and QM each), respectively (60 total). The primary analysis will require the 2-sided tests of each co-primary endpoint to be significant at a level of 0.05. From the global phase 3 study 20110116, the treatment effect of evolocumab compared to ezetimibe for reduction from baseline in

LDL-C at week 12 is at least 37.6% (32.9%, 42.2%) and for the mean of week 10 and 12, 36.9% (31.6%, 42.3%). Assuming 5% of randomized subjects do not receive any IP and with a common standard deviation (SD) of approximately 20%, this study has at least 93% power to detect a treatment effect of 20% or greater reduction for each of the co-primary endpoints in testing the superiority of evolocumab over ezetimibe, based on a two-sided t-test with significance level 0.05.

As the co-primary endpoints are correlated, there is at least 85% (93% x 93%) power to detect significant treatment effects of the co-primary endpoints. The power calculation is derived using nQuery version 7.01.

4. Study Endpoints and Covariates

4.1 Study Endpoints

4.1.1 Co-Primary Endpoints

- Mean percent change from baseline in LDL-C at weeks 10 and 12
- Percent change from baseline in LDL-C at week 12

4.1.2 Co-Secondary Efficacy Endpoints

Co-secondary endpoints of the means at weeks 10 and 12 and at week 12 for:

Tier 1

- Change from baseline in LDL-C
- LDL-C response (LDL-C < 70 mg/dL [1.8 mmol/L])
- Percent change from baseline in total cholesterol
- Percent change from baseline in non-HDL-C
- Percent change from baseline in ApoB
- Percent change from baseline in the total cholesterol/HDL-C ratio
- Percent change from baseline in ApoB/ApoA1 ratio

Tier 2

- Percent change from baseline in Lp(a)
- Percent change from baseline in triglycerides
- Percent change from baseline in HDL-C
- Percent change from baseline in VLDL-C

4.1.3 Tertiary Efficacy Endpoints

- Mean percent change from baseline in ApoA1 at weeks 10 and 12
- Percent change from baseline in ApoA1 at week 12

4.1.4 Exploratory Endpoints

- Subject incidence of non-coronary revascularization
- Observed values, change and percent change from baseline at each scheduled visit in each of the following parameters:
  - LDL-C
  - Total cholesterol
  - non-HDL-C
  - ApoB
  - Total cholesterol/HDL-C ratio
  - ApoB/ApoA1 ratio
  - VLDL-C
  - HDL-C
  - ApoA1
  - Triglycerides
  - Lp(a)
- hsCRP at each scheduled assessment
- PCSK9 change from baseline at each scheduled assessment

4.1.5 Safety Endpoints

- Subject incidence of adverse events
- Safety laboratory values at each scheduled visit
- Incidence of anti-evolocumab antibody (binding and neutralizing) formation

4.1.6 Pharmacokinetics Endpoints

- Serum concentration of evolocumab at selected time points

5. Hypotheses and/or Estimations

The statistical hypothesis of the co-primary endpoints is:

The null hypothesis is that there is no mean difference in the mean percent change from baseline at weeks 10 and 12 or in the percent change from baseline at week 12 in LDL-C between evolocumab and ezetimibe, and the alternative hypothesis is that a mean difference does exist.

6. Definitions

6.1 Study Time Points

Enrollment Date

Enrollment date is the same as randomization date.

Randomization Date

The date a subject is randomized in the interactive voice/web response system (IVRS/IWRS) as recorded on the eCRF.

First Dose Date of SC Investigational Product of Blinded Period (First SCBIPD)

For each subject, the First Dose Date of SC Investigational Product is defined as the first administration date of the SC IP as recorded on the blinded period IP administration eCRF.

First Dose Date of Oral Investigational Product of Blinded Period (First POBIPD)

For each subject, the First Dose Date of Oral Investigational Product is defined as the first start date of the oral IP as recorded on the blinded period oral IP administration eCRF.

First Dose Date of SC Investigational Product of Open Label Extension OLE (First SCOLEIPD)

For each subject who participates in the open label extension (OLE) period of the study, the First Dose Date of SC Investigational Product of OLE is defined as the first administration date of the SC IP of OLE as recorded on the IP administration in OLE eCRF.

Blinded Period Day 1

For each randomized subject, Blinded Period Day 1 is defined as the first day that protocol-specified investigational product of blinded period is administered to the subject, which is the earlier of the first SCBIPD and the first POBIPD.

Open Label Extension OLE Day 1

For each subject who participates in OLE of the study, OLE Day 1 is defined as the first SCOLEIPD.

Study Day 1

Study day 1 is defined as Blinded period day 1.

Blinded Period Day

For each randomized subject, and for a given date of interest, blinded period day is defined as the number of days since Blinded Period Day 1:
Blinded period day = (date of interest (in Blinded Period) – Blinded Period Day 1 date) + 1.
If the date of interest is prior to the Blinded Period Day 1:
Blinded period day = (date of interest (in Blinded Period) – blinded period Day 1 date), so that the day prior to Blinded Period Day 1 is Blinded Period day -1.

OLE Day

For each subject who participates in OLE of the study, and for a given date of interest, OLE Day is defined as the number of days since OLE Day 1:
OLE Day = (date of interest – OLE Day 1 date) + 1.
If the date of interest is prior to the OLE Day 1:
OLE Day = (date of interest – OLE Day 1 date), so that the day prior to OLE Day 1 is OLE Day -1.

Study Day

For each subject, and for a given date of interest, study day is defined as the number of days since Study Day 1:

Study day = (date of interest – Study Day 1 date) +1.

If the date of interest is prior to the Study Day 1:

Study day = (date of interest – Study Day 1 date). So that the day prior to Study Day 1 is Study Day -1.

Last Dose Date of SC Investigational Product of Blinded Period (Last SCBIPD)

For each randomized subject, the Last Dose Date of SC Investigational Product of Blinded Period is defined as the date of the last administration of the SC IP of blinded period as recorded on the blinded period IP administration eCRF.

Last Dose Date of Oral Investigational Product of Blinded Period (Last POBIPD)
For each randomized subject, the Last Dose Date of Oral Investigational Product of Blinded Period is defined as the last stop date of the oral IP.

Last Dose Date of SC Investigational Product of OLE (Last SCOLEIPD)

For each subject who participates in OLE of the study, the Last Dose Date of SC Investigational Product of OLE is defined as the date of the last administration of the SC IP of OLE as recorded on the IP administration in OLE eCRF.

End of Study (EOS) Date

For each subject, the End of Study Date is the date recorded on the End of Study eCRF.

Study End Date

The Study End Date is the last EOS date of all randomized subjects.

6.2 Demographics and Baseline Related Definitions

Age

Age will be calculated as the subject's age in years at enrollment as recorded on the eCRF.

Baseline Lipid and Lipid-related Parameters

Baseline values for fasting lipids (total cholesterol, HDL-C, LDL-C, VLDL-C, non-HDL-C and triglycerides), ApoA1, ApoB, Lp(a), hsCRP and their derived parameters (eg, ratio between them) are defined as the mean of the two most recent non-missing fasting concentrations measured through central lab prior to or on Study Day 1. If for any reason only 1 value is available, then that value will be used as baseline.

Other Baseline Values

For PCSK9, the baseline value is defined as the last non-missing values collected prior to or on Study Day 1, but must before first IP administration.

For all other variables, the baseline value is defined as the last non-missing value collected prior to or on Study Day 1.

Change (absolute change) from Baseline

The arithmetic difference between a post-baseline value and baseline for a given time point:

Change (absolute change) from baseline = (post-baseline value – baseline value)

Percent Change from Baseline

The percent change from baseline for a given variable at a given time point is defined as:

100 x [(value at given time point – baseline value) / baseline value]

Baseline Metabolic Syndrome (JAS, 2017)

Risk Factor	Defining Level
Waist circumference: Men Women	 ≥ 85 cm ≥ 90 cm
For each subject without type 2 diabetes mellitus, metabolic syndrome is identified by the presence of elevated waist circumference and 2 or more of the components listed below. Subjects with type 2 diabetes cannot be categorized as having metabolic syndrome.	
Triglycerides and/or HDL cholesterol	≥ 150 mg/dL < 40 mg/dL
Blood pressure	SBP ≥ 130 mmHg or DBP ≥ 85 mmHg OR Hypertension checked 'yes' on CV Medical History eCRF
Fasting glucose	≥ 110 mg/dL

Baseline CHD Risk Factors

A subject will be categorized as having 2 or more CHD Risk Factors (Y/N) from the list of the modified NCEP ATP III risk factors:

- current cigarette smoking
- hypertension
- type II diabetes mellitus
- family history of premature CHD as recorded on the eCRF
- low HDL-C defined as baseline HDL-C < 40 mg/dL in men and < 50 mg/dL in women.

Baseline National Cholesterol Education Program (NCEP) Risk Categories

Risk Factor	Defining Level
High Risk: CHD or CHD Risk Equivalent	Coronary Artery Disease OR Cerebrovascular or Peripheral Vascular Disease OR Type 2 Diabetes Mellitus OR 2 or more Risk Factors (see below) AND FRS > 20% (see Appendix A for FRS calculation)
Moderately High Risk	NOT High Risk AND 2 or more Risk Factors AND FRS ≥ 10% AND ≤ 20%
Moderate Risk	NOT High Risk AND 2 or more Risk Factors AND FRS < 10%
Lower Risk	NOT High Risk AND 0 to 1 Risk Factor

Risk Factors for NCEP Risk Categories:

Risk factors are: current cigarette smoking, hypertension or (baseline SBP ≥ 140 or DBP ≥ 90 mmHg), family history of premature CHD as recorded in the eCRF form, low HDL-C cholesterol defined as baseline HDL-C < 40 mg/dL, age ≥ 45 years in men or ≥ 55 years in women.

Risk Classification According to ESC/EAS Guidelines

The Systematic Coronary Risk Estimation (SCORE) system estimates the 10 year risk of a first fatal atherosclerotic event, whether heart attack, stroke, or other occlusive arterial disease, including sudden cardiac death (ESC/EAS 2011). The SCORE risk estimates will be computed from the high and low risk region tables based on sex and baseline smoking status, systolic blood pressure, total cholesterol and age. Risk classification of very high, high, moderate and low risk will be according to the ESC/EAS guidelines.

6.3 Other Study Related Definitions

Analytical Study Week Assignments

Analytical windows will be used to assign parameter measurements to study weeks. The algorithm is provided in Appendix B.

Actual Treatment Group

A subject's actual treatment group is the randomized treatment group, unless the subject receives treatment throughout the study that is different than the randomized treatment group assignment, in which case the actual treatment group is the treatment received.

Investigational Product (IP)

Blinded Period:

SC IP includes evolocumab SC 140 mg Q2W, evolocumab SC 420 mg QM and their corresponding SC placebo.

Oral IP includes ezetimibe PO 10 mg QD and placebo PO QD.

OLE: SC IP includes evolocumab SC 140 mg Q2W and evolocumab SC 420mg QM.

SC IP Exposure Period (Months) in Blinded Period

For each Q2W subject:

SC IP Exposure Period in Blinded Period = [min (EOS Date, the day before OLE day 1, Last SCBIPD + 14 days) - First SCBIPD + 1] / 365.25 * 12

For each QM subject:

SC IP Exposure Period in Blinded Period = [min (EOS Date, the day before OLE day 1, Last SCBIPD + 28 days) - First SCBIPD +1] / 365.25 * 12

Oral IP Exposure Period (Months) in Blinded Period

For each subject:

Oral IP Exposure Period = [min (EOS Date, the day before OLE day 1, Last POBIPD + 1 day) – First POBIPD + 1] / 365.25 * 12

SC IP Exposure Period (Months) in OLE

For each Q2W subject:

SC IP Exposure Period in OLE = [min (EOS date, last SCOLEIPD + 14 days) - First SCOLEIPD +1] / 365.25 * 12

For each QM subject:

SC IP Exposure Period in OLE = [min (EOS date, last SCOLEIPD + 28 days) - First SCOLEIPD +1] / 365.25 * 12

Study Exposure Period in Months

For each randomized subject:

Study Exposure Period = (EOS date – Randomization Date + 1) / 365.25 * 12

Treatment Emergent Adverse Event (TEAE)

Events categorized as Adverse Events (AEs) starting on or after first dose of investigational product as determined by the flag indicating if the adverse event started prior to the first dose of IP on the Events eCRF and up to 30 days after the last dose of IP date or EOS, whichever occurs first. Please see below for the definition of TEAE in blinded period and OLE.

TEAE	Summary period
Blinded period	**Blinded period day 1 (the same as study day 1) through min(last dose date + 30 days, EOS date, the day before OLE day 1)**
OLE	**OLE day 1 through min(last dose date + 30 days, EOS date)**

Note that the definition of TEAE has been documented in FORM 000505 prior to the unblinding for the primary analysis.

Reflexive Approach for LDL-C and VLDL-C

For all analyses related to LDL-C and VLDL-C, unless specified otherwise, a reflexive approach will be used. When calculated LDL-C is less than 40 mg/dL or triglycerides are > 400 mg/dL, the UC LDL-C value from the same blood sample will be used instead of calculated LDL-C and the UC VLDL-C value from the same blood sample will be used instead of calculated VLDL-C, if available.

Achievement of LDL-C < 70 mg/dL

A subject has achievement of LDL-C < 70 mg/dL if the post-baseline LDL-C value at week 12 is less than 70 mg/dL. If the value is missing, the subject is considered without the achievement.

Mean achievement of LDL-C < 70 mg/dL at weeks 10 and 12 is defined using the mean of non-missing LDL-C values at those two timepoints (if one is missing, mean equals the available one).

7. Analysis Subsets

7.1 Full Analysis Set

The full analysis set (FAS) includes all randomized subjects who received at least 1 dose of IP in the double blind treatment period. This analysis set will be used in both efficacy and safety analyses for the double blind treatment period.

Generally, in efficacy analyses, subjects will be grouped according to their randomized treatment group assignment and by pooled treatment. In safety analyses, subjects will be grouped according to their randomized treatment group assignment with the exception: if a subject receives treatment throughout the study is different than the randomized treatment group assignment, then the subject will be grouped by the actual treatment group.

7.2 Completer Analysis Set

The completer analysis set (CAS) includes subjects in the FAS who adhered to the scheduled IP (ie, the SC and oral IP completion boxes are checked on the eCRF) in the double blind treatment period and have observed values for the co-primary endpoints.

7.3 Open Label Extension Period Analysis Set

The open label extension period analysis set (OLEAS) includes subjects in the FAS who received at least 1 dose of evolocumab in the open label extension period. This analysis set will be used in both efficacy and safety analyses for the open label extension period.

7.4 Subgroup Analyses

Stratification factors:

- Screening LDL-C level (< 180 mg/dL [4.7 mmol/L] vs. ≥ 180 mg/dL)
- Baseline statin use (yes vs. no)

Subgroup by baseline characteristics:

- Age (< 65 years, ≥ 65 years; < 75 years, ≥ 75 years)
- Sex
- LDL-C (< baseline median, ≥ baseline median)
- PCSK9 level (< baseline median, ≥ baseline median)
- Baseline lipid regulating medications use (yes vs. no)
- Body Mass Index (BMI) (< 25, 25 - < 30, >=30)
- Glucose tolerance status (type 2 diabetes mellitus, metabolic syndrome, neither type 2 diabetes mellitus nor metabolic syndrome)
- Hypertension (yes, no)

- Baseline CHD risk factors >=2 (yes, no)
- Triglycerides (<baseline median, >= baseline median; < 150 mg/dL, >=150 mg/dL; < 200 mg/dL, >=200 mg/dL)
- NCEP (NCEP, 2002) high risk (yes, no)

Subgroup analysis may not be performed if number of subjects in one of the categories is too small for that subgroup variable.

8. Interim Analysis and Early Stopping Guidelines

No interim analysis is planned for this study.

An external independent DMC has been established to formally review the accumulating data from this and other completed and ongoing studies with evolocumab to ensure there is no avoidable increased risk for harm to subjects. The independent DMC is chaired by an external academic cardiologist who is an expert in lipids and clinical trials.

Analyses for the DMC are provided by the Independent Biostatistical Group (IBG), which is external to Amgen. Details are provided in the DMC charter.

9. Data Screening and Acceptance

9.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

9.2 Data Handling and Electronic Transfer of Data

The Amgen Global Study Operations-Data Management (GSO-DM) department will provide all data to be used in the planned analyses. This study will use the RAVE database.

All data collected in the eCRF will be extracted from RAVE. Protocol deviations will be transferred from eClinical. An Analysis Dataset for PK Concentrations (ADPC) will be provided to PKDM from Biostatistics. Unblinded subject and box ID randomization lists will be provided by Amgen's randomization group and the IVRS/IWRS when the study stops. Details on data transfer will be provided in the Data Transfer Plan.

9.3 Handling of Missing and Incomplete Data

9.3.1 Patterns of Missing Data

Subjects may be missing specific data points for various reasons. In general, data may be missing due to a subject's early withdrawal from study, a missed visit, or non-evaluability of a data point or an endpoint at a particular point in time. In the Data Quality Review (DQR) process, queries will be made to the sites to distinguish true

missing values from other unknown values (eg, due to measurement or sample processing error). All attempts will be made to capture missing or partial data for this trial prior to the database lock.

The frequency and pattern of missing data for efficacy endpoints will be assessed through descriptive summaries of the measurements over time.

9.3.2 Missing Lipid Measurements

For efficacy endpoints, where the primary analysis method is repeated measures linear effects model then missing lipid measurements will not be imputed.

The handling of missing LDL-C response (achievement of LDL-C < 70 mg/dL) is provided in Section 6.3.

9.3.3 Handling of Incomplete Dates

Adverse event and concomitant medication with completely or partially missing start dates will be queried. After the issue is queried, the date is still incomplete with year only or year and month only, the start date will be imputed as described in Table 1 below.

Table 1. Imputation Rules for Incomplete Dates

	Missing	Imputation	Exception
Start date (AE and concomitant medication)	Day	1	Default to Study Day 1 if an event starts the same year and month as Study Day 1
	Day / Month	1-Jan	Default to Study Day 1 if an event started the same year as Day 1

9.4 Detection of Bias

This study has been designed to minimize potential bias by the use of randomization of subjects into treatment groups and the use of blinding. It is not expected that any study conduct procedures or statistical analyses will introduce bias in the study results or conclusions. However, potential sources of bias in this study include:

- major protocol deviations likely to impact the analysis and interpretation of the efficacy endpoints
- subject level unblinding before primary database lock and formal unblinding
- DMC related analyses

Important protocol deviations likely to impact the analysis and interpretation of the efficacy endpoints will be tabulated in the Clinical Study Report (CSR).

Any unblinding of individual subjects prior to formal unblinding of the study will be documented in the CSR. The impact of such unblinding on the results observed will be assessed.

For DMC related analyses, details of access to subject level treatment assignments are provided in the protocol, Section 10.3.

Additional sensitivity analyses may be included to assess the impact of potential biases on the primary endpoint. If any sensitivity analyses are required to evaluate potential biases in the study's conclusions, then the sources of the potential biases and results of the sensitivity analyses will be documented in the CSR.

9.5 Outliers

Various methods, including univariate summaries, histograms, scatter plots, box plots, and line graphs, may be used to identify outliers in key safety and efficacy variables. Extreme data points will be identified during the blinded review of the data prior to database lock. Such data points will be reviewed with clinical data management to ensure accuracy. The primary analyses will include outliers in the data. Sensitivity analyses may be undertaken if extreme outliers for a variable are observed.

9.6 Distributional Characteristics

Distributional assumptions for the primary and secondary co-endpoints will be assessed. If the assumptions are not met, then alternative methods will be utilized. The use of alternative methods will be fully justified in the CSR.

9.7 Validation of Statistical Analyses

Programs will be developed and maintained, and output will be verified in accordance with current risk-based quality control procedures.

Tables, figures and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment for statistical analyses consists of Amgen-supported versions of statistical analysis software, for SAS System version 9.2 or later.

10. Statistical Methods of Analysis

10.1 General Principles

The primary analysis will be performed when all randomized subjects in the study have either completed the scheduled study visits up to and including week 24 or have early terminated from the study. At that time, the database of the study will be cleaned,

processed and a snapshot will be taken. The study will be unblinded. Based on the snapshot for the primary analysis, efficacy and safety analyses will be performed on the FAS. Unless otherwise specified, the FAS will be the default analysis set for the primary analysis and data will be summarized by randomized treatment group assignment and by pooled frequency for evolocumab and pooled ezetimibe. The treatment effect of evolocumab compared to ezetimibe will be evaluated for all efficacy endpoints through the Week 12 visit. In addition, descriptive analyses from the open-label extension (weeks 12 to 24) will be performed on OLEAS. **Please note that for the completed primary analysis, data collected for the open-label extension period was expanded beyond weeks 12 to 24. All available data from the open label extension period, as of the data cut-off date 02 November 2017, were included for the open-label extension period analyses in the primary analysis.**

The final analysis will be conducted when all enrolled subjects have either completed the scheduled visits or have early terminated from the study. At that time, the database of the study will be cleaned, processed and **locked**. Based on the **locked database**, long-term efficacy and safety analyses will be performed on OLEAS and the analyses will be descriptive. **The descriptive analyses for the open-label extension period in the primary analysis will be updated using the data from the final database lock. All analyses for blinded period in primary analysis will not be repeated.**

Subject disposition, demographics, baseline characteristics, and exposure to IP will be summarized.

Summary statistics for continuous variables will include the number of subjects, mean, median, Q1, Q3, standard deviation or standard error, minimum, and maximum. For categorical variables, the frequency and percentage will be given.

Missing data will not be imputed for safety endpoints.

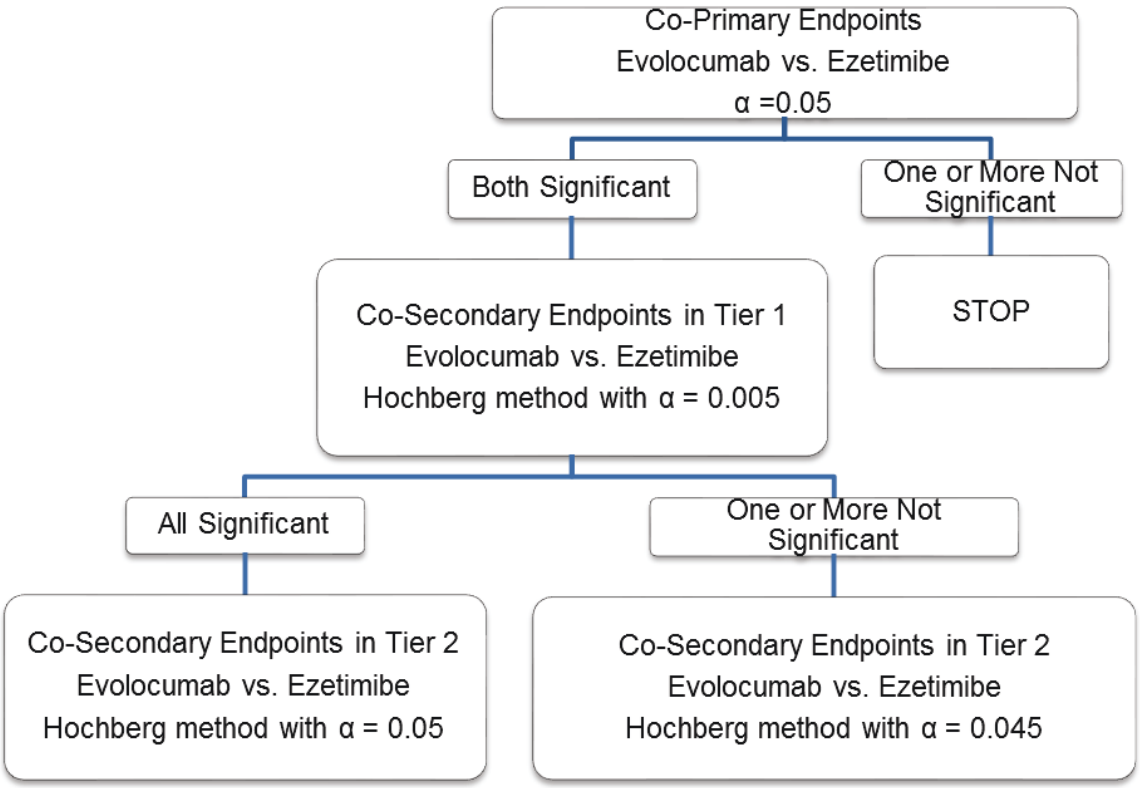
A summary of the analyses for each part of the study can be found in Table 2.

Table 2. Analyses Summary

Analyses	Double-blind Period	OLE Period
Efficacy	• Summary by randomized treatment group in blinded period For co-primary and co-secondary endpoints: • Repeated measures model • Cochran Mantel-Haenszel test for LDL-C achievement • Multiplicity adjustment	• Summary by randomized treatment group in blinded period / evolocumab in OLE period • No statistical inference
AE, Safety lab	• Summary by actual treatment group in blinded period • No statistical inference	• Summary by actual treatment group in blinded period / evolocumab in OLE period • No statistical inference

Multiplicity Adjustment Method

Methods of adjusting for multiplicity due to multiple endpoints (co-primary and co-secondary efficacy endpoints) in order to preserve the familywise error rate at 0.05 are described in the diagram below.



Testing of each co-endpoint pair for the pooled evolocumab vs. pooled ezetimibe analysis will result in a single p-value, and for co-secondary endpoints these p-values

will then be used in the Hochberg procedure. The following test procedure will be used to preserve the familywise error rate for the co-primary and co-secondary endpoints:

1. If the treatment effect from the primary analysis of the co-primary endpoints are both significant at a significance level of 0.05, statistical testing of the tier 1 co-secondary efficacy endpoints will follow the Hochberg procedure at a significance level of 0.005 (Hochberg, 1988).
2. If all tier 1 co-secondary efficacy endpoints are significant, the tier 2 co-secondary efficacy endpoints will be tested using the Hochberg procedure at a significance level of 0.05.
3. If not all tier 1 co-secondary efficacy endpoints are significant, the tier 2 co- secondary efficacy endpoints will be tested using the Hochberg procedure at a significance level of 0.045 (Wiens, 2003).

Unless specified otherwise, all other hypothesis testing will be 2-sided with a significance level of 0.05.

10.2 Subject Accountability

The number of subjects screened, randomized (in blinded period), receiving IP (in blinded period and OLE), completing the double blind treatment period, and completing the study will be summarized. The number and percent of subjects randomized will be tabulated by the stratification factor and study site.

Double blind treatment period discontinuation, the study discontinuation and IP (in blinded period and OLE) discontinuation will be tabulated separately by reasons for discontinuation.

The number of subjects included in and excluded from each analysis set and reason for exclusion will also be summarized.

Key study dates for the first subject enrolled, last subject enrolled, and last subject's end of study will be presented

10.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first subject's visit and updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, sub-category codes, and descriptions will be used during the course of the study. Eligibility deviations are defined in the protocol.

10.4 Demographic and Baseline Characteristics

Demographics (ie, age, sex, race, cardiovascular medical history, laboratory parameters) and baseline disease characteristics will be summarized by randomized treatment group and overall using descriptive statistics. If multiple races have been reported for a subject, the subject will be categorized as multiple races. Difference in stratum assignment between IVRS/IWRS stratum and data-derived stratum will be tabulated.

10.5 Efficacy Analyses

The following table summarizes the key efficacy analyses that will be conducted.

Table 3. Key Efficacy Analyses Summary

Endpoint	Statistical Analysis Method	P-values from the Statistical Tests	Hierarchical Testing Procedure as Specified in the Multiplicity Adjustment Method Diagram Testing of Pooled EvomabTreatment Effect vs. Ezetimibe
Co-Primary Endpoints			
• Mean percent change from baseline at weeks 10 and 12 in LDL-C • Percent change from baseline at week 12 in LDL-C	Repeated measures model	P1 = Maximum of the two p-values for the co-endpoint pair from the primary analysis in FAS	P1 compare to $\alpha = 0.05$
Co-Secondary Endpoints (Tier 1)			
• Mean LDL response (achievement of LDL-C < 70 mg/dL) at weeks 10 and 12 • LDL response at week 12	Cochran Mantel-Haenszel (CMH) test	P2a = Maximum of the two p-values for the co-endpoint pair in FAS	If P1 < 0.05, ➔ P2a and all P2b's will be tested through Hochberg method with $\alpha = 0.005$ Else (ie, co-primary endpoint in FAS is not significant) ➔ No further testing.
• Mean change from baseline at weeks 10 and 12 in LDL-C • Change from baseline at week 12 in LDL-C and • Mean percent change from baseline at weeks 10 and 12 • Percent change from baseline at week 12 in each of the following lipid parameter: total cholesterol, non-HDL-C, ApoB, total cholesterol/HDL-C ratio, ApoB/ApoA1 ratio	Repeated measures model	For each lipid parameter, P2b = Maximum of the two p-values for each co-endpoint pair in FAS	
Co-Secondary Endpoints (Tier 2)			
• Mean percent change from baseline at weeks 10 and 12 • Percent change from baseline at week 12 in each of the following lipid parameters: Lp(a), triglycerides, HDL-C, and VLDL-C	Repeated measures model	For each lipid parameter, P2c = Union-intersection test p-value from the two contrasts of each co-endpoint pair in FAS	If P2a and all P2b's are significant through Hochberg method, ➔ P2c will be tested through Hochberg method with $\alpha = 0.05$. Else (ie, not all tier 1 co- endpoints in FAS are significant), ➔ P2c will be tested through Hochberg method with $\alpha = 0.045$.

10.5.1 Analyses of Co-Primary Endpoints

10.5.1.1 Primary Analysis of Co-Primary Endpoints

To assess the co-primary endpoints of the mean percent change from baseline at weeks 10 and 12 and the percent change from baseline at week 12 in LDL-C, a repeated measures linear effects model will be used to compare the efficacy of evolocumab (pooled Q2W and QM) with pooled ezetimibe. The repeated measures model will include terms of treatment group, stratification factor of screening LDL-C level, scheduled visit, and the interaction of treatment group with scheduled visit. Missing values will not be imputed when the repeated measures linear effects model is used.

10.5.1.2 Sensitivity Analyses of Co-Primary Endpoints

To evaluate the robustness of the primary analysis results, sensitivity analyses will be performed as follows:

- The primary analysis will be repeated on the CAS.
- Non-parametric analyses (Quade test) will be performed on the FAS and CAS.

10.5.1.3 Subgroup Analyses of Co-Primary Endpoints

Subgroup analyses on the co-primary efficacy endpoints will be conducted using the subgroups specified in Section 7.4. Treatment effect differences among subgroups, which represent subgroup by treatment interactions, will be estimated and tested based on statistics from the subgroup repeated measures models.

For subgroup analyses, the data-derived stratification factor (ie, screening LDL-C level and baseline statin use) will be used.

10.5.1.4 Additional Analyses of Co-Primary Endpoints

The co-primary endpoints will also be assessed within each dose frequency using dose frequency matched control (ie, evolocumab Q2W SC plus placebo PO QD vs ezetimibe QD plus placebo Q2W SC; evolocumab QM SC plus placebo PO QD vs. ezetimibe QD plus placebo QM SC) and pooled ezetimibe (ie, evolocumab Q2W vs. pooled ezetimibe; evolocumab QM vs. pooled ezetimibe).

In addition, the difference between the evolocumab Q2W and evolocumab QM groups will be estimated.

10.5.2 Analyses of Secondary Efficacy Endpoints

The statistical model and testing of the tier 1 co-secondary efficacy endpoints will be similar to the primary analysis of the co-primary endpoints. The co-secondary efficacy

endpoints of LDL-C response will be analyzed using the Cochran-Mantel Haenszel (CMH) test adjusted by the stratification factor.

Analyses of the tier 2 co-secondary efficacy endpoints will use the same analysis model as the tier 1 endpoints, and the testing will use a union-intersection test.

Multiplicity adjustment procedures are defined in Section 10.1.

10.5.3 Analyses of Tertiary Efficacy Endpoints

Analysis of the tertiary efficacy endpoints will be similar to the primary analysis of the co-primary endpoints. No multiplicity adjustment will be applied

10.5.4 Analyses of Exploratory Endpoints

Exploratory endpoints related to lipid parameters, and hsCRP will be summarized by treatment group and by scheduled visit using descriptive statistics.

Non-coronary revascularizations will be collected on the eCRF. Subject incidence of exploratory endpoint events will be summarized for each treatment group.

10.6 Safety Analyses

10.6.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 or later will be used to code all events categorized as adverse events (AEs) to a system organ class and a preferred term. Severity of AEs will be graded using the CTCAE (Appendix C) and recorded on the eCRF. All adverse event tables will be summarized by actual treatment group. Treatment-emergent adverse events are events with an onset after the administration of the first dose of IP.

The subject incidence of AEs will be summarized for all TEAEs, serious TEAEs, TEAEs leading to withdrawal of investigational product, treatment-related TEAE and fatal TEAEs.

Subject incidence of all TEAEs, serious TEAEs, TEAEs leading to withdrawal of investigational product, and fatal TEAEs will be tabulated by system organ class and preferred term in descending order of frequency.

All TEAEs, serious TEAEs and TEAEs leading to withdrawal of investigational product will also be summarized by subgroups of age (< 65 years, ≥ 65 years; < 75 years, ≥ 75 years) and baseline statin use (Yes, No).

Subject incidence of TEAEs related to a device will be tabulated by preferred term in descending order of frequency.

Subject incidence of adverse events associated with injectable protein therapies:

- Injection site reactions
- Hypersensitivity or allergic reactions

will be summarized by category and preferred term. Neurocognitive events will also be summarized.

10.6.2 Laboratory Test Results

Descriptive statistics will be provided for actual values and changes from baseline in select laboratory parameters at each protocol-specified scheduled visit. Laboratory analytes are provided in the protocol section 7.2. Lab shift tables using the CTCAE v4.03 or later grading will be used for the select analytes of interest, when applicable.

In addition, CK and liver function test (LFT) abnormalities will be assessed by the incidence overall and by visits of the following categories:

- CK > 5 x ULN
- CK > 10 x ULN
- ALT or AST > 3 x ULN
- ALT or AST > 5 x ULN
- Total bilirubin > 2 x ULN
- (ALT or AST > 3 x ULN) and Total bilirubin >2 x ULN and Alkaline Phosphatase < 2 x ULN

10.6.3 Vital Signs

Systolic and diastolic blood pressure and heart rate will be summarized by treatment group using descriptive statistics at each scheduled visit.

10.6.4 Antibody Formation

The incidence and percentages of subjects who develop anti-evolocumab antibodies (binding and if positive, neutralizing) at anytime will be tabulated.

10.6.5 Exposure to Investigational Product

Descriptive statistics will be produced to describe the patient-month exposure to SC IP, the categorical representation of dose received, and the total quantity of oral IP used (for the double-blind treatment period only) by randomized treatment group. Exposure definitions are provided in Section 6.3.

10.6.6 Exposure to Concomitant Medication

For each part of the study, the number and proportion of subjects receiving selected lipid regulating medications captured on the Concomitant Medications eCRF will be

summarized by category and preferred term for each treatment group as coded by the World Health Organization Drug (WHODRUG) dictionary. Summaries will be provided for baseline use and use during each part of the study. The subject incidence of changes in lipid regulating medications during the double-blind treatment period and open-label extension period will also be provided.

11. Changes From Protocol-specified Analyses

Analysis of physical measurements will not be performed, because post-baseline measurements only occur at week 52.

12. Literature Citations / References

Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. *Biometrika* 1988;75:800-802.

Wiens BL. A fixed sequence Bonferroni procedure for testing multiple endpoints. *Pharmaceut. Statist.* 2003; 2:211-215

Japan Atherosclerosis Society (JAS) Guidelines for Prevention of Atherosclerotic Cardiovacular Diseases 2017

13. Appendices

Appendix A. Framingham Risk Score (FRS)

Method to calculate the Framingham Risk Score (FRS):

The β coefficients given in the two tables below are used to compute a linear function. The latter is corrected for the averages of the participants' risk factors (mean) from the Framingham study, and the subsequent result is exponentiated and used to calculate a 10-year probability of HCHD after insertion into a survival function (Wilson et al).

The calculation is different for men and women and use the following coefficients β_i, where *i* represents each of the independent variables. The values below are from the Framingham heart study (http://www.framinghamheartstudy.org/risk-functions/coronary-heart-disease/hard-10-year-risk.php).

t_chol = total cholesterol, hdl = HDL-C, sbp = systolic blood pressure, trt_htn = treatment for hypertension (if sbp > 120), smoker = current smoker

Men		
Independent variable	Coefficient βi	mean
ln(age)	52.00961	3.8926095
ln(t_chol)	20.014077	5.3441475
ln(hdl)	-0.905964	3.7731132
ln(sbp)	1.305784	4.8618212
trt_htn (spb>120)	0.241549	0.1180474
smoker	12.096316	0.335602
ln(age)* ln(t_chol)	-4.605038	20.8111562
ln(age)*smoker[1]	-2.84367	1.2890301
ln(age)*ln(age)	-2.93323	15.2144965
[1] if age>70 then ln(70)*smoker		

Women		
Independent variable	Coefficient βi	mean
ln(age)	31.764001	3.9213204
ln(t_chol)	22.465206	5.3628984
ln(hdl)	-1.187731	4.0146369
ln(sbp)	2.552905	4.8376494
trt_htn (spb>120)	0.420251	0.142802
smoker	13.07543	0.3236202
ln(age)* ln(t_chol)	-5.060998	21.0557746
ln(age)*smoker[2]	-2.996945	1.2519882
[2] if age>78 then ln(78)*smoker		

The steps to determine the FRS is the same for men and women.

<u>Men</u>

For each subject:

1. Calculate $L_{men} = \beta_{ln(age)}*ln(age) + \beta_{ln(t\_chol)}*ln(t\_chol) + \beta_{ln(hdl)}*ln(hdl) + \beta_{ln(sbp)}*ln(sbp) + \beta_{trt\_htn}*(if\ trt\_htn) + \beta_{smoker}*(if\ smoker) + \beta_{ln(age)*ln(t\_chol)}*ln(age)*ln(t\_chol) + \beta_{ln(age)*smoker}*ln(age)*(if\ smoker) + \beta_{ln(age)*ln(age)}*ln(age)*ln(age)$
2. Calculate $A_{men} = L_{men} - 172.300168$ (note: the value of 172.300168 was derived based on the mean columns in above table)
3. Calculate $B_{men} = exp\ (A_{men})$

4. Calculate $P_{men} = 1 - 0.9402^{B_{men}}$
5. $FRS_{men} = P_{men}*100$ (rounded to nearest integer)

Women

For each subject:

1. Calculate $L_{women} = \beta_{ln(age)}*ln(age) + \beta_{ln(t\_chol)}*ln(t\_chol) + \beta_{ln(hdl)}*ln(hdl) + \beta_{ln(sbp)}*ln(sbp) + \beta_{trt\_htn}*(if\ trt\_htn) + \beta_{smoker}*(if\ smoker) + \beta_{ln(age)*ln(t\_chol)}*ln(age)*ln(t\_chol) + \beta_{ln(age)*smoker}*ln(age)*(if\ smoker)$
2. Calculate $A_{women} = L_{women} - 146.5933061$ (note: the value of 146.5933061 was derived based on the mean columns in above table)
3. Calculate $B_{women} = exp\ (A_{women})$
4. Calculate $P_{women} = 1 - 0.98767^{B_{women}}$
5. $FRS_{women} = P_{women}*100$ (rounded to nearest integer)

Notes

- For men, if subject is > age 70, then use ln(70)*smoker
- For women, if subject is > age 78, then use ln(78)*smoker
- For dichotomous variables trt_htn and smoker use 1/0 to represent yes/no respectively
    - If a subject has sbp ≤ 120 mmHg, then trt_htn is no

Calculated scores should match the interactive calculator

http://cvdrisk.nhlbi.nih.gov/calculator.asp

Appendix B. Analytical Study Week Assignments

Selected endpoints will be summarized by scheduled study visits in descriptive analyses.

Since the actual visits may not exactly coincide with their scheduled visit day, the actual visit day is mapped to the study visit generally by non-overlapping consecutive intervals covering the entire time continuum. The mapping intervals for all distinct schedules are summarized in the following tables.

Scheduled Visit Week	Week 2	Week 8	Week 10	Week 12	Week 24	Week 36	Week 48	Week 52	Week 54 EOS Phone Call
Scheduled Visit Day	15	57	71	85	169	253	337	365	379
Vital Signs		(1, 63]	(63, 77]	(77, min(91, first dose date of OLE)]	(min(91, first dose date of OLE), 210]	(210,294]	(294,350]	>350	
Fasting Lipids	(1, 35]	(35, 63]	(63, 77]	(77, min(91, first dose date of OLE)]	(min(91, first dose date of OLE), 210]	(210,294]	(294,350]	(350,378]	
Lp(a), ApoA1, ApoB			(1, 77]	(77, min(91, first dose date of OLE)]	(min(91, first dose date of OLE), 210]	(210,294]	(294,350]	(350,378]	
PK, PCSK9	(1, 42]		(42, 77]	(77, min(91, first dose date of OLE)]				(min(91, first dose date of OLE), 378]	
Hematology and Chemistry		(1, 70]		(70, min(91, first dose date of OLE)]				> min(91, first dose date of OLE)	
Physical Exam, hsCRP, Urinalysis, HbA1c, Biomarkers, anti-evolocumab antibodies				(1, min(91, first dose date of OLE)]				> min(91, first dose date of OLE)	
Weight, waist circumference								> 1	

Handling multiple records assigned to an analytical study week:

If there is more than one record in a study week interval, the analytical record for that specific study week will be defined as the record closest to the scheduled visit day of that specific study week (7 x study week + 1). If two records are equidistant from the scheduled day, then the earlier record will be chosen. If there are multiple records on the same day, the last record will be used.

Appendix C. Common Terminology Criteria for AEs (CTCAE)

Refer to the NCI Common Terminology Criteria for AEs (CTCAE) for AEs and lab shift grading and information. The CTCAE is available at the following link:

http://evs.nci.nih.gov/ftp1/CTCAE/About.html