Statistical Analysis Plan

Protocol Title:	High-Resolution Assessment of Coronary Plaques in a Global Evolocumab Randomized Study (HUYGENS)
Short Protocol Title:	Imaging of Coronary Plaques in Subjects Treated With Evolocumab
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Version Number	Date (DDMMMYYYY)	Summary of Changes, including rationale for changes
Original (v1.0)	28MAR2019	N/A
Amendment 1 (v2.0)	15 January 2021	• Editorial changes were made throughout the document to improve the overall clarity. • Updated section 1 to reflect the planned analysis. • Updated section 5.1.1 regarding the definition of Maximum Lipid Arc and Lipid Core Length, and added definition for Lipid Rich Plaque as per clinical team discussion. • Updated section 5.1.2 regarding the definition of Number of Microchannels and Macrophage Composition, and added definition for Lipid Content as per clinical team discussion. • Updated section 5.3 to differentiate the baseline for Lipid and Lipid-related Parameters, Concomitant Medication Usage and Medical History, and other Baseline Values to reflect true baseline for the endpoints. • Updated section 6.2 to reflect FCT instead of OCT for clarification. • Updated section 6.3 to change “Completer” to “Completers”. • Updated section 6.4 to delete Per-Protocol Analysis Set (PPAS) as per stats team discussion. • Updated section 8.3 to clarify imputation method for secondary endpoints. • Updated section 9.2 and section 9.3 to include COVID-19 Impact related descriptive analysis to measure COVID impact. • Updated section 9.5 to add COVID-19 impact analysis into Sensitivity Analysis for Primary Endpoint for mitigating COVID impact. • Updated method to be used for PROC MI from section 9.5.1 as per stats team discussion.

		• Updated section 9.5.3 to describe the analyses for exploratory endpoints for clarification. • Updated section 9.6.5 to clarify analysis method for statin intensity. • Updated Appendix A to allow for additional window for week 50 assessments impacted due to COVID-19 Impact. • Added Appendix B. • Updated Appendix C to reflect the changes in statin therapy intensity with respect to the latest ACC/AHA guideline (2018).

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List of Abbreviations and Definition of Terms

Abbreviation or Term	Definition/Explanation
ACC	American College of Cardiology
AHA	American Heart Association
ANCOVA	analysis of covariance
ApoA1	apolipoprotein A1
ApoB	apolipoprotein B
CI	confidence interval
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
FAS	full analysis set
FCT	fibrous cap thickness
HDL-C	high-density lipoprotein cholesterol
IVUS	intravascular ultrasound
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
Lp(a)	lipoprotein(a)
MI	myocardial infarction
NSTE-ACS	non-ST-segment elevation acute coronary syndrome
OCT	optical coherence tomography
PCSK9	proprotein convertase subtilisin/kexin type 9
QM	monthly (every 4 weeks with a window of ± 3 days for each visit or dose)
SAT	Safety Assessment Team
SEC	Self-Evident Corrections
SC	subcutaneous
SD	standard deviation
UC	Ultra Centrifugation
VLDL-C	very low-density lipoprotein cholesterol
WHODRUG	World Health Organization Drug

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 study 20160184, Evolocumab dated 19 April 2018. The scope of this plan includes the final analysis that is planned and will be executed by the Amgen Global Biostatistical Science department unless otherwise specified.

2. Objectives, Endpoints and Hypotheses

2.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the effect of evolocumab on fibrous cap thickness (FCT) in subjects with non-ST-elevation acute coronary syndrome (NSTE-ACS) who are taking maximally tolerated statin therapy.	• Absolute change in minimum FCT in a matched segment of artery as determined by optical coherence tomography (OCT) from baseline to week 50.
Secondary	
• To evaluate the effects of evolocumab on coronary plaque morphology in subjects with NSTE-ACS who are taking maximally tolerated statin therapy.	• Coronary artery segment-based: • Percent change in minimum FCT in a matched segment of artery as determined by OCT from baseline to week 50. • Absolute change in mean minimum FCT for all images assessed in an individual subject as determined by OCT from baseline to week 50. • Absolute change in the maximum lipid arc in a matched segment of artery as determined by OCT from baseline to week 50. • Plaque-based: • Absolute change in minimum FCT in lipid rich plaques defined as minimum FCT < 120 µm and lipid arc > 90° in at least 3 consecutive images as determined by OCT from baseline to week 50. • Absolute change in maximum lipid arc in lipid rich plaques defined as minimum FCT < 120 µm and lipid arc > 90° in at least 3 consecutive images as determined by OCT from baseline to week 50. • Absolute change in lipid core length in

Objectives	Endpoints
Secondary(Continued)	
	• lipid rich plaques defined as minimum FCT < 120 µm and lipid arc > 90° in at least 3 consecutive images as determined by OCT from baseline to week 50.
Safety	
• To evaluate the safety and tolerability of evolocumab treatment in subjects with NSTE-ACS who are taking maximally tolerated statin therapy.	• Subject incidence of treatment-emergent adverse events and serious adverse events.
Exploratory	
• To evaluate the effects of evolocumab on lipid parameters in subjects with NSTE-ACS who are taking maximally tolerated statin therapy • To evaluate the effects of evolocumab on features of coronary plaques in subjects with NSTE-ACS who are taking maximally tolerated statin therapy using different imaging techniques.	• Absolute and percent changes in lipid parameters by visit from baseline. • Absolute change in number of microchannels in matched segments of all lesions assessed in an individual subject as determined by OCT from baseline to week 50. • Absolute change in macrophage composition in matched segments of all lesions assessed in an individual subject as determined by OCT from baseline to week 50. • Absolute changes in lipid content in matched segments of all lesions assessed in an individual subject as determined by IVUS from baseline to week 50.

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The primary estimand consists of:

- The target population, which is the adult subjects with NSTE-ACS who are taking maximally tolerated statin therapy with or without additional lipid-modifying medication.
- The primary variable, which is the absolute change in minimum FCT in a matched segment of artery as determined by OCT from baseline to week 50.
- The summary measure, which is the mean treatment difference of the primary variable means between evolocumab and placebo.
- The intercurrent events, all randomized subjects who receive at least 1 dose of investigational product regardless of adherence to treatment or commencing commercial proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors.

2.2 Hypotheses and/or Estimations

The primary hypothesis is that low-density lipoprotein cholesterol (LDL-C) lowering with evolocumab 420 mg monthly (QM) will result in a greater increase from baseline in

minimum FCT at week 50 than placebo in subjects taking maximally tolerated statin therapy.

3. Study Overview

3.1 Study Design

This is a phase 3, double-blind, placebo-controlled, randomized study evaluating the effect of evolocumab on coronary atherosclerotic plaques as assessed by OCT at baseline and at week 50 in subjects with an NSTE-ACS. The trial duration of 1 year was chosen based on the results of several historical trials. Subjects will be randomized 1:1 into 2 treatment groups no more than 7 days after the signing of the informed consent: evolocumab 420 mg subcutaneously (SC) QM or placebo SC QM. The randomization will be stratified by current statin use (> 4 weeks or ≤ 4 weeks duration) at screening. Investigators will up-titrate statin therapy to the maximally tolerated dose, in accordance with local guidelines, for subjects prior to randomization.

3.2 Sample Size

The planned total sample size is 150 subjects (75 randomized to evolocumab 420 mg SC QM and 75 randomized to placebo SC QM). This sample size will provide sufficient power (90%) to determine whether there is a treatment effect of evolocumab relative to placebo in the primary endpoint.

The assumptions in the sample size calculation are based on a linear regression meta-analysis of 7 historical trials (Dai et al, 2017; Hou et al, 2016; Kataoka et al, 2014; Komukai et al, 2014; Nishio et al, 2014; Hattori et al, 2012; Takarada et al, 2009) weighted by sample sizes.

The analysis result indicates that every 1 mg/dL reduction in LDL-C is estimated to be associated with 1.4785 μm increase in FCT in 12-month follow-up. Assuming a 50 mg/dL reduction in LDL-C, the predicted mean increase (95% CI) in FCT from the meta-analysis was 73.92 (50.97, 96.88) μm. For this study, the assumed treatment effect is at least 50.97 μm increase in FCT, which is approximated from the lower bound 95% CI of the expected change in FCT from the regression model, based on a conservative assumption of 50 mg/dL reduction in LDL-C from baseline to week 50.

The SD of FCT measurement at baseline or at the end of various length of follow-up was reported in a wide range (10.6 to 124 μm) based on 15 to 134 subjects per arm in the historical trials. The SD of change in FCT was only reported in 2 of the 7 trials, ranging from 22 to 86 μm. The assumed common SD for this study is 86 μm to be conservative.

Assuming 1 out of 6 subjects will not complete both baseline and week 50 OCT assessments, and therefore be excluded in the primary analysis, the sample size of 150 subjects will provide approximately 125 subjects in the primary analysis to ensure 90% power to test the study hypothesis.

The sample size calculation was performed using a 2-sided t-test with a 0.05 significance level. The sample size calculation was derived using East® software (version 6.4).

4. Covariates and Subgroups

4.1 Planned Covariates

The following covariates will be used in covariate analyses of the primary endpoint.

Stratification factor:

- current statin use (> 4 weeks or ≤ 4 weeks duration at the time of screening)

Baseline covariates:

- Age
- Sex
- Baseline LDL-C
- Type 2 diabetes mellitus (yes, no)
- Current tobacco use (yes, no)

4.2 Subgroups

Subgroup analysis of the primary endpoint will be conducted for the following subgroups:

Subgroup by stratification factor:

- Current statin use (> 4 weeks or ≤ 4 weeks at the time of screening)

Subgroup by baseline covariates:

- Age (< median, ≥ median; < 65 years of age, ≥ 65 years of age)
- Sex
- Baseline LDL-C (< median, ≥ median)
- Current tobacco use (yes, no)

5. Definitions

5.1 Endpoint Related Definitions

5.1.1 Primary and Secondary Endpoints

Minimum FCT

Minimum FCT in μm for a subject is defined as the minimum of all minimum FCT measurements within each individual frame across all frames of that subject.

Mean Minimum FCT

Mean minimum FCT in μm for a subject is defined as the mean of the minimum FCT measurements performed within all individual frames for that subject.

Maximum Lipid Arc

Maximum Lipid arc in degree for a subject is defined as the maximum of **total** lipid arc measurements within each individual frame across all frames of that subject.

Lipid Core Length

Lipid core length in mm is defined as the longitudinal extent of plaque within the vessel wall that continuously meets the criteria defined in the study protocol. The lipid core length will be **calculated as the number of frames with lipid existence*0.2mm. Normalization is also required for lipid core length.**

Lipid Rich Plaque

Lipid rich plaque serves as identifier for plaque-based secondary endpoints. There are three steps to follow to identify frames with lipid rich plaque:

1. **Identify plaque existence using lipid existence or fibrous existence or calcium existence at baseline. The gap between two independent plaques has to be larger than 5mm (ie, 25 frames)**
2. **Among plaques detected in step 1 at baseline, verify if they are lipid rich plaque using lipid existence and lipid arc is analyzable and total lipid arc > 90° and FCT existence and FCT < 120 μm in at least 3 consecutive frames**
3. **Obtain frame numbers for each lipid rich plaque detected in step 1 and 2**

5.1.2 Exploratory Endpoints

Number of Microchannels

Number of microchannels per mm is defined as the sum of microchannels measured from all frames for one subject with a maximal count of 10 per frame. It will be normalized by dividing by the number of frames for each subject **and multiplying by 5.**

Macrophage Composition

Macrophage composition per mm is defined as the sum of macrophage scores from all frames for one subject. It will be normalized by dividing by the number of frames for each subject **and multiplying by 5.**

Lipid Content

For IVUS datasets perform the following across all IVUS frames from both timepoints for a given subject:

1. **Calculate the plaque area as external elastic membrane cross sectional area (EEM) minus lumen cross sectional area**
2. **Select frame with maximum plaque area and frame with minimum plaque area in the 10 mm (20 frames) proximal to frame with maximum plaque area**
3. **Use the EEM value of frame with the maximum plaque area divided by the EEM value of frame with the minimum plaque area to derive remodeling index**
4. **Use > 1.05 as cut-off to determine if "positive remodeling" is 'yes' or 'no'**
5. **If "positive remodeling" is 'yes' for BL dataset, go to step 6; otherwise this subject data will be excluded for IVUS endpoints**
6. **Count all frames with plaque area > 63% of EEM and calculate normalized count of frames as 10*(the number of frames with plaque area > 63% of EEM)/(total number of frames) at BL and FU, for each subject. Please note the unit would be 'mm/cm artery'.**
7. **Calculate absolute change in mm/cm artery and percent change of normalized frame count between the two timepoints (BL and FU) as the IVUS endpoints.**

5.2 Study Time Points

Enrollment Date

Enrollment date is defined as the randomization date.

Randomization Date

Randomization Date is defined as the date subject was allocated to a treatment group.

First Dose Date of Investigational Product (First IP Date)

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

Study Day 1

Study Day 1 is defined as the date of first investigational product (IP) administration or the date of randomization for subjects who are not administered any dose of IP.

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 Investigational Product (Last IP Date)

For each subject, the Last Dose Date of Investigational Product is defined as the date of the last administration of the IP.

Subject-level End of Study (EOS) Date

End of study for each subject is defined as the date the subject last completed a protocol-specified procedure. The date will be recorded on the End of Study CRF page.

Study End Date

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

5.3 Demographics and Baseline Related Definitions

Age

Age is the subject's age in years at enrollment as recorded on the eCRF.

Baseline Lipid and Lipid-related Parameters

Baseline values for LDL-C, triglycerides and troponin are defined as the concentrations measured through **local** lab **at screening. Baseline values for other lipids (eg, total cholesterol, HDL-C and VLDL-C), ApoA1, ApoB, Lp(a) and their derived parameters (eg, ratio between them) are defined as the concentrations measured through central lab on Study Day 1.**

Baseline Laboratory Variables

Baseline values for laboratory variables are defined as the assessment measured at screening.

Baseline Concomitant Medication Usage and Medical History

Baseline values for background statin therapy, lipid-modifying concomitant medication usage and medical history are defined as the assessment measured at screening. For concomitant medication that is not lipid-modifying baseline is defined as measurement at study day 1.

Baseline Image Data

Baseline values for OCT, IVUS image data are defined as the assessment measured at screening.

Baseline Vital Signs

Baseline values for vital signs are 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].

5.4 Other Study Related Definitions

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)

IP includes AMG 145 SC 420 mg QM and its SC placebo.

IP Exposure Period in Months

For each QM subject: IP Exposure Period = [min (Last IP Date + 28 days, EOS Date) - First IP Date +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 date, whichever is earlier.

Reflexive Approach for LDL-C and VLDL-C

Reflexive approach for LDL-C and VLDL-C is only applicable for the central lab data. When calculated LDL-C is less than 40 mg/dL or triglycerides are > 400 mg/dL, LDL-C and VLDL-C will be measured per ultracentrifugation (UC) instead of calculated LDL-C and calculated VLDL-C, if available.

6. Analysis Sets

6.1 Full Analysis Set

The full analysis set (FAS) includes all randomized subjects who received at least 1 dose of IP. In efficacy analyses, subjects will be grouped according to their randomized treatment group assignment, regardless of the treatment received

6.2 OCT Analysis Set (OAS)

The OCT analysis set includes subjects in the FAS with a baseline **FCT** and an **FCT** measurement conducted on or after week 40.

6.3 Completers Analysis Set (CAS)

The Completers Analysis Set (CAS) includes subjects in the OAS who adhered to the scheduled IP (ie, EOIP reason is completed IP on eCRF) and had an observed value for the primary endpoint.

6.4 Safety Analysis Set

The safety analysis set includes all randomized subjects who have taken at least 1 dose of investigational product. For safety analyses, the subjects will be grouped according to actual treatment group.

7. Planned Analyses

7.1 Interim Analysis and Early Stopping Guidelines

No interim analysis is planned for this study.

7.2 Final Analysis

The final analysis will be conducted after all subjects have either completed all the scheduled study visits or have early terminated from the study. At that time, the database will be cleaned, processed, locked, and a snapshot will be taken; the study will also be unblinded for analyses. Based on the snapshot, efficacy and safety analyses will be performed.

8. Data Screening and Acceptance

8.1 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.

8.2 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 **including data from RAVE database, imaging data and central lab data (outside of RAVE database). The database will be subjected to edit checks outlined in the Data Management Plan (DMP). Additional details will be provided in DMP and Data Acquisition Requirements Specifications (DARS).**

8.3 Handling of Missing and Incomplete 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 endpoint at a time. All attempts will be made to capture missing or partial data for this trial prior to the database lock. The frequency of missing data for efficacy endpoints will be assessed through descriptive summaries of the measurements over time. For subjects with missing post-baseline FCT, the missing primary **and secondary** endpoint**s** will be imputed using multiple imputation.

Adverse event and concomitant medication with completely or partial 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 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

For historical events (eg, date first taken in the prior statin therapy form) that will be used to summarize data derived stratum, the imputation rules are as follows: if the day is missing, default to 1; if both month and day are missing, default to Jan 1. If the imputed date is on or after the randomization date, default to randomization date minus 1. Missing years will not be imputed under any condition.

8.4 Detection of Bias

This study has been designed to minimize potential bias using randomization of subjects into treatment groups and the use of blinding. Other factors that may bias the results of the study include:

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

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.

8.5 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. The primary analyses will include outliers in the data. Sensitivity analyses may be undertaken if extreme outliers for a variable are observed.

8.6 Distributional Characteristics

If the distributional assumptions are not met, then alternative methods will be utilized. The use of alternative methods will be fully justified in the CSR.

8.7 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 example, the SAS System version 9.4 or later.

9. Statistical Methods of Analysis

9.1 General Considerations

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

Statistical inferences will be provided for analyses of primary and secondary efficacy endpoints. Unless specified otherwise, all statistical tests are 2-sided with a significance level of 0.05; no statistical inference and imputation will be conducted for analyses of safety endpoints. No imputation will be conducted for analyses of exploratory endpoints. Even though the p-values will be generated for exploratory endpoints, they are descriptive in nature.

Multiplicity Adjustment Method

To preserve the family wise type 1 error rate at 0.05 for testing the primary and secondary endpoints, the primary analysis of primary endpoint will be tested first. If the treatment effect from the primary analysis of the primary endpoint is significant at a significance level of 0.05, the secondary endpoints will be tested with significance level of 0.05 using the Hochberg method.

9.2 Subject Accountability

The number of subjects screened, randomized to IP, receiving IP, and completing the study will be summarized. Study discontinuation and IP discontinuation will be tabulated separately by reasons for discontinuation, **including due to COVID-19 Impact if applicable**. 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, last subject's end of IP and last subject's end of study will be presented.

The number and percentage of subjects randomized will be tabulated by study site.

9.3 Important Protocol Deviations

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

The number of subjects reporting Protocol Deviations due to COVID-19 Impact will be summarized in a table. A Protocol Deviation listing of subjects impacted due to COVID-19 Impact will also be provided.

9.4 Demographic and Baseline Characteristics

All baseline tables will be summarized by randomized treatment group and for all subjects in the FAS. Baseline tables will summarize the following (but not limited to): baseline characteristics, demographics, cardiovascular medical history, and **lipid** parameters. Difference in stratum assignment between randomized stratum and data-derived stratum will be tabulated.

9.5 Efficacy Analyses

Endpoint	Primary Analysis	Sensitivity Analysis	Multiplicity Adjustment
Primary Endpoint			To preserve the family wise type 1 error rate at 0.05 for testing the primary and secondary endpoints, the primary analysis of primary endpoint will be tested first. If the treatment effect from the primary analysis of the primary endpoint is significant at a two-sided significance level of 0.05, the secondary endpoints will be tested with two-sided significance level of 0.05 using the Hochberg method.
Absolute change in minimum FCT from baseline to week 50	Multiple Imputation + ANCOVA (FAS)	Quade Test (FAS) **COVID-19 Impact Analysis**	
Secondary Endpoints			
Coronary artery based: • Percent change in minimum FCT in a matched segment of the artery as determined by OCT from baseline to week 50. • Absolute change in mean minimum FCT for all images accessed in an individual subject as determined by OCT from baseline to week 50. • Absolute change in the maximum lipid arc in a matched segment of artery as determined by OCT from baseline to week 50. Plaque-based: • Absolute change in minimum FCT, maximum lipid arc, and lipid core length in lipid rich plaques defined as minimum FCT < 120μm	Multiple imputation + ANCOVA (FAS)	NA	

9.5.1 Analyses of Primary Efficacy Endpoint(s)

Primary Analysis:

To assess the primary endpoint of absolute change in minimum FCT from baseline to week 50, an ANCOVA (Analysis of Covariance) model on the FAS will be used, including terms for treatment group, stratification factor (current statin use [> 4 weeks or ≤ 4 weeks] at screening), baseline minimum FCT as covariates. Least square means and corresponding 95% confidence intervals (CI) will be calculated for each treatment group and for the difference between treatment groups. For subjects with missing post-baseline **minimum** FCT, the **post-baseline minimum FCT value** will be imputed

using multiple imputation. The imputation model will include treatment group, stratification factor, baseline LDL-C, baseline minimum FCT, age as covariates. **At least** five imputations will be conducted, and each complete dataset after imputation will be analyzed using the ANCOVA model. SAS PROC MIANALYZE will be used to combine the results from individual ANCOVA models.

Sensitivity Analysis

1) Non-parametric analysis (Quade test) will be performed on FAS as sensitivity analysis. The missing data will be imputed using multiple imputation. **The imputation model and the analysis approach of combining results from multiple imputed datasets will be same as the primary analysis.**
2) **COVID-19 Impact sensitivity analysis:**

   To determine the impact of COVID-19, a sensitivity analyses will be conducted. All the available post-baseline FCT values will be considered in the analysis, irrespective of the analysis visit window (ie, the post-baseline FCT values after week 56 will also be considered for the analysis). The ANCOVA model for COVID-19 Impact analysis will include the covariates of treatment group, stratification factor (current statin use [> 4 weeks or ≤ 4 weeks] at screening), baseline minimum FCT as covariates. The imputation method, model and analysis approach will be same as the primary analysis.

Covariate and Subgroup Analysis

In addition to the primary analysis, covariate adjusted analysis of the primary efficacy endpoint will be performed as supportive analyses using the baseline covariates in Section 4.1, in their original format, one at a time, in the ANCOVA model used in the primary analysis.

Subgroup analyses on the primary efficacy endpoint will be conducted using the subgroups specified in Section 4.2, in the ANCOVA model used in the primary analysis. Subgroup by treatment interactions will be tested and the p-value of the interaction term will be reported.

For covariate and subgroup analyses, the data-derived stratification factor from the CRF will be used.

Supplementary Analysis:

The following additional analyses will also be performed to evaluate the robustness of the primary analysis result:

- The primary analysis will be repeated using OAS
- The primary analysis will be repeated using CAS

9.5.2 Analyses of Secondary Efficacy Endpoint(s)

The secondary efficacy endpoints will be analyzed using the similar method as used in primary analysis of the primary efficacy endpoint but adjusting for corresponding baseline variable. The Hochberg method for multiplicity adjustment will be used to maintain the overall error rate at 0.05.

9.5.3 Analyses of Exploratory Efficacy Endpoint(s)

The exploratory endpoints will be analyzed using ANCOVA. The model will include change or percent change from baseline for each exploratory endpoint as dependent variable, and terms for treatment group, stratification factor (current statin use [> 4 weeks or ≤ 4 weeks] at screening) and corresponding baseline values as covariates. The p-values displayed will be considered as descriptive. The analysis will be carried out on observed data and missing data will not be imputed.

9.6 Safety Analyses

9.6.1 Adverse Events

Subject incidence of all treatment-emergent adverse events will be tabulated by system organ class**, high level term** and preferred term. Tables of fatal adverse events, serious adverse events **and** adverse events leading to withdrawal from investigational product will also be provided. Subject incidence of TEAEs related to a device, if applicable, will be tabulated by system organ class and preferred term.

The latest version of Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all events categorized as adverse events to a system organ class and a preferred term.

The subject incidence of adverse events will be summarized for all treatment-emergent adverse events, serious adverse events, and adverse events leading to withdrawal of investigational product.

Subject incidence of all treatment-emergent adverse events, serious adverse events, adverse events leading to withdrawal of investigational product, and fatal adverse events will be tabulated by system organ class and preferred term in alphabetical order.

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.

9.6.2 Laboratory Test Results

Descriptive statistics will be provided for actual values and changes from baseline in selected laboratory parameters at each protocol-specified scheduled visit. Laboratory analytes are provided in the protocol (Appendix 2).

9.6.3 Vital Signs

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

9.6.4 Exposure to Investigational Product

The exposure to investigational product will be summarized by treatment group using descriptive statistics.

9.6.5 Exposure to Concomitant Medication

The number and proportion of subjects receiving medications of interest (MOI) will be summarized by preferred term or category for each treatment group as coded by the World Health Organization Drug (WHODRUG) dictionary. **Statin intensity will be summarized by treatment group at each targeted scheduled visit date.**

10. Changes From Protocol-specified Analyses

There are no changes to the protocol-specified analyses.

11. Literature Citations / References

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12. Appendices

Appendix A. 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 table:

Analytical Study Week	Screening	Day 1	Week 4	Week 24	Week 50
Scheduled Visit Day		1	29	169	351
Physical Examination	[-7, 1)	1			> 176
Vital Signs	[-7, 1)	1			> 176
Fasting Lipid Testing		1		(1, 259]	> 259
OCT	[-7, 1)				(280, **393**]
IVUS	[-7, 1)				(280, **393**]
Biomarker collection (blood/plasma)					> 176
Statin Therapy	[-7, 1)	1	29	169	351

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.

Concomitant medication records will be selected when the start day or end day euqal to the scheduled visit day, or the concomitant medication usage time period includes the scheduled visit day.

Appendix B. Common Terminology Criteria for AEs (CTCAE)

Refer to the NCI Common Terminology Criteria for Adverse Events (CTCAE) for adverse event grading and information. The CTCAE is available at the following link: http://evs.nci.nih.gov/ftp1/CTCAE/About.html

Appendix C. Lipid Modifying Background Therapy Intensity

Based on ACC/AHA guidelines **(2018)**

	HIGH-INTENSITY STATIN THERAPY	MODERATE-INTENSITY STATIN THERAPY	LOW-INTENSITY STATIN THERAPY
Atorvastatin	**≥ 40 mg QD**	**10 – < 40 mg QD**	**< 10 mg QD**
Rosuvastatin	**≥ 20 mg QD**	**5 – < 20 mg QD**	**< 5 mg QD**
Simvastatin	**≥ 80 mg QD**	**20 – < 80 mg QD**	**< 20 mg QD**
Pravastatin		**≥ 40 mg QD**	**< 40 mg QD**
Lovastatin		**≥ 40 mg QD**	**< 40 mg QD**
Fluvastatin XL		**80 mg QD**	**< 80 mg QD**
Fluvastatin		**40 mg BID**	**< 40 mg BID**
Pitavastatin		**1 – 4 mg QD**	**< 1 mg QD**

UNKNOWN-INTENSITY STATIN THERAPY if dose frequency is other or dose unit is other and therefore total daily dose in mg cannot be derived; NO STATIN THERAPY if subject does not use any statin at baseline.

High-intensity lipid lowering regimen is defined as:

- **Atorvastatin ≥ 40 mg QD**
- **Rosuvastatin ≥ 20 mg QD**
- **Simvastatin ≥ 80 mg QD**
- **Combination of any statin therapy and Ezetimibe 10 mg QD**

Note protocol cited an older categorization of statin intensity based on ACC/AHA's official guidance at the time of study initiation