Protocol B1481038

PHASE 3 MULTI-CENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL GROUP EVALUATION OF THE EFFICACY, SAFETY, AND TOLERABILITY OF BOCOCIZUMAB (PF-04950615), IN REDUCING THE OCCURRENCE OF MAJOR CARDIOVASCULAR EVENTS IN HIGH RISK SUBJECTS

SPIRE: Studies of Proprotein convertase subtilisin kexin type 9 (PCSK9) Inhibition and the Reduction of vascular Events – SPIRE-2

Statistical Analysis Plan (SAP)

Version: 2.0

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

1.1. Changes from Version 1.1 to Version 2.0

This amendment to the SAP is the second amendment to the original approved SAP (version 1 dated 24October2013). This amendment was initiated after the finalization of Amendment 2 to Protocol B1481038 (dated 12February2016), and further revised due to the discontinuation of the bococizumab clinical development program on 01November2016, and finalized prior to sponsor unblinding. Six unblinded DMC reviews have been conducted, all with recommendations to continue the study without modification.

Summary of changes of this amendment versus the previously amended SAP (Version 1.1 on 12November2014) include:

Changes to the SAP driven by changes to the protocol:

- Visit dates in months were replaced by visit dates in weeks throughout the SAP.
- Italicized text from the Protocol Amendment 1 was replaced with italicized text from Protocol Amendment 2 in Sections 2 - 6, Appendix 1.2 and Appendix 2. Italicized text from Protocol Amendment 1 in Sections 7 - 8 was replaced with normal text from Protocol Amendment 2.
- The sample size of the study was increased from 9,000 subjects to 11,000 subjects (Section 2.1).
- The number of primary endpoint events required for stopping the trial in certain subgroups, including diabetic subjects with no prior CVD event, was corrected to 35 (Section 2.1), the probability of a point estimate of the hazard ratio being less than 1 within these subgroups was corrected to 80% (Sections 2.1 and 3).
- An interim analysis for clinical benefit was added (Sections 2.1 and 3). Note that as a result of the discontinuation of the bococizumab clinical development program, the interim analysis for clinical benefit specified in Protocol Amendment 2 will not be done.
    - The two-sided α level for the primary analysis and the key secondary analyses was reduced to 0.04898 to maintain the experimentwise Type 1 error rate (Section 4.2). Even though the interim analysis will not be performed, the reduced alpha level will be used.
- In response to changes in the objectives and endpoints:
    - The composite endpoint of all-cause death, non-fatal MI and non-fatal stroke was upgraded to a key secondary objective from other secondary objective (Section 2.2), the corresponding endpoint was elevated to a key secondary endpoint (Section 6.1.2) and the corresponding analysis was elevated to a key secondary analysis (Section 4.2).

    - The analyses specifically for key secondary endpoints were added (Section 8.2.2).

  - The objective for hs-CRP was changed from the nominal change from baseline to the percent change from baseline (Section 2.2). The corresponding analysis was changed from MMRM on the percent changes from baseline to MMRM on the changes in the log-transformed observations, followed by a transformation of the results to the percent change scale (8.1.1.2, and 8.2.2).

- The method for controlling Type I error for the key secondary analyses was changed from the Hochberg procedure to a fixed sequence testing procedure to increase power for more important endpoints (Section 4.2).

- The reporting of adverse events and severe adverse events was modified to incorporate the role of the Pfizer SAE Triage Group (Section 6.2).

- Arjas plots were added to assess the goodness of fit of the Cox proportional hazards regression model for the time to the first event for the primary endpoint and the key secondary composite endpoint of cardiovascular death, non-fatal MI, or non-fatal stroke (Sections 8.1.1.1, 8.2.1, and 8.2.2).

- Stent stenosis [Type 4c] was added to the types for myocardial infarction (Appendix 1.2).

- The definition of arterial revascularizations was changed from peripheral artery revascularizations of the lower extremity and carotid arteries (percutaneous and surgical interventions) to any peripheral artery revascularization of any type (Appendix 1.2).

- The Schedule of Activities was updated (Appendix 2).

<u>Changes to the SAP driven by discontinuation of the bococizumab clinical development program</u>

- The interim analysis for clinical benefit will not be done (Section 3).

- The interim analyses to support the regulatory submission for the treatment of hyperlipidemia will not be done (Section 3).

- The efficacy cutoff date was eliminated. All available data will be used (Section 5.1).

    - References to the efficacy cutoff date were eliminated from Sections 5.1, 7, 8.1.1.1, and 8.2.1.

    - Analyses through the efficacy cutoff date were modified to include all events (Sections 8.2.1 and 8.2.2).

- After discontinuation of the bococizumab clinical development program, sites were instructed to only forward those clinical events occurring on or before 01November2016 for adjudication. Consequently, subjects without and event will be censored no later than 01November2016 (Sections 7 and 8.2.1).

- All recurrent event analyses, including Wei-Lin-Weissfeld analyses and cumulative hazards plots, were removed (Sections 8.1.1.1, 8.2.1, and 8.2.2).

    - References to Wei-Lin-Weissfeld regression models were deleted from Sections 6.4 and 8.2.5.

    - The summaries of number of events for secondary endpoints were deleted (Section 8.2.2).

    - The paper cited for the Wei-Lin-Weissfeld methodology was removed from the References (Section 9).

- The multiple imputation model for subjects who discontinued due to an adverse event was deleted (Section 8.2.1).

- All treatment-adherent analyses were removed (Sections 8.2.1, 8.2.2, and 8.2.3).

- The adverse event subgroups by number of dose adjustments were removed (Section 5.4.2.2).

- The Kaplan-Meier plot for time to discontinuation from the study was removed (Section 8.2.1).

- The Kaplan-Meier plots for time to secondary clinical endpoints were removed, except for the plots for the key composite secondary endpoint of cardiovascular death, non-fatal MI or non-fatal stroke and for all-cause death (Section 8.2.2).

- The tabulations of procedure types for hospitalizations for unstable angina needing urgent revascularization were removed (Section 8.2.2).

- The tabulations of type of ECG changes for MIs were removed (Section 8.2.2).

- The tabulations of stroke type and modified Rankin score for subjects with strokes were removed (Section 8.2.2).

- Longitudinal plots of least-squares means and 95% confidence intervals were removed for certain parameters (Section 8.2.2).

- Summaries and plots of Friedewald LDL-C were removed (Section 8.2.2).

- Safety summaries using only observations through 40 days after the last dose of study medication were deleted (Section 8.2.3).

- Summaries of AEs leading to temporary discontinuation of study medication were deleted (Section 8.2.3).
- Summaries of adverse events during the screening period were deleted (Section 8.2.3).
- Summaries of adverse events by the relationship to study medication were removed, except for the summaries for AEs and SAEs (Section 8.2.3).
- The plots for Tier 1 and Tier 2 AEs were removed (Section 8.2.3).
- Longitudinal plots and summaries of observations of potential clinical concern were removed for vital signs (Section 8.2.3).
- Boxplots for CK, hemoglobin and HbA1c were removed (Section 8.2.3).
- All summaries of ECG data were removed (Section 8.2.3).
- The listing of physical examination data was removed (Section 8.2.3).
- The summaries of neurological exams were removed (Section 8.2.3).
- The summaries of causes of death and primary organ system for cancer deaths in the Safety Analysis Set were removed as all subjects in the Safety Analysis Set are also in the Full Analysis Set (Section 8.2.3).
- The summaries of pretreatment and concomitant non-lipid lowering medications and pretreatment and concomitant non-drug treatments were removed (Section 8.2.4).
- Summaries of shifts in background lipid lowering therapy were removed (Section 8.2.4).
- The Kaplan-Meier plot of time to discontinuation from study medication was removed (Section 8.2.4).
- Listings for eligibility criteria, contraception detail, dietary and lifestyle counseling, drug allergies, previous participation on a bococizumab trail, primary diagnosis and time since primary diagnosis were removed (Section 8.2.4).
- The summaries and analyses of EQ-5D endpoints were removed (Section 8.2.4.2).
    - The handling of missing values on the EQ-5D was removed (Section 7).
- All summaries and analyses of Health Care Resource Utilization endpoints were removed (Section 8.2.4.7).
    - References to HRCU endpoints were deleted from Sections 7 and 8.1.1.1.

Changes to the SAP not driven by changes to the protocol or discontinuation of the bococizumab clinical development program:

- The methodology for the blinded assessments of modifying the sample size or study duration was clarified (Section 3).
- The definition of the Full Analysis Set was modified to exclude subjects who attempted to be randomized more than once into a bococizumab cardiovascular outcomes trial (Section 5.1).
- The definition of the Safety Analysis Set was clarified to indicate that only subjects in the Full Analysis Set are included (Section 5.3).
- The definition of All Screened Subjects was modified to exclude subjects who attempted to be randomized more than once into a bococizumab cardiovascular outcomes trial (Section 5.4.1).
- The subgroups for the primary endpoint, the corresponding forest plot and the methodology for subgroups were removed (Sections 5.4.2.1, 8.1.1.1, and 8.2.1).
- Subgroups based on age (2 categories) for adverse event were removed (Section 5.4.2.2). The three-category subgroups for age were retained.
- The definition of the subgroup of subjects having a post-baseline LDL-C $\leq$ 25 mg/dL at the end of a dosing interval was modified to remove the requirement that the measurement is at the end of a dosing interval (Sections 5.4.2.2 and 5.4.2.3).
- Subgroups defined by having a post-baseline LDL-C $\leq$ 25 mg/dL were redefined to subset placebo-treated subjects as well (Sections 5.4.2.2 and 5.4.2.3).
- Subgroups for adverse events based on ADAs were modified to only include bococizumab-treated subjects as samples from placebo-treated subjects were not assayed for ADA (Section 5.4.2.2).
- Subgroups for adverse events based on nAb status were added (Section 5.4.2.2).
- The subgroup of treated subjects without a baseline history of diabetes was added for summarizing new diagnoses of diabetes and for summarizing HbA1c (Sections 5.4.2.2 and 5.4.2.3).
- Subgroups for labs based on nAb status were added (Section 5.4.2.3).
- The subgroups for PK/PD were modified (Section 5.4.2.4).
- Subgroups for ADA and nAb titers were added (Section 5.4.2.5).
- The handling of treatment misallocation was modified for safety analysis of the subjects randomized but took at least one dose of the incorrect treatment to reflect what is feasible (Section 5.5).

- The handling of circulating biomarkers measurements below the limit of quantification was added (Section 6.1.3).
- Derived lipid values (RLP-C and non-HDL-C) below zero will be set to zero (Section 6.1.3).
- The collection of primary diagnosis and time since primary diagnosis was discontinued following a change to the CRF (Section 6.3).
- The definition of treatment duration was added (Section 6.3).
- The algorithm for calculating the number of actual dose administrations was modified to use the dosing data (Section 6.3).
- The algorithm for calculating the dose administrations planned was modified (Section 6.3):
    - The injection at the randomization visit was added.
    - It was clarified that only doses through when the site instructs the subjects to stop taking IP would be counted.
    - It was clarified that the doses the site instructs the subjects to skip would not be counted.
- Ireland was added to the appropriate geographic regions (Section 6.4).
- Lithuania and the Philippines were deleted from the appropriate geographic regions and the study was not conducted in those countries (Section 6.4).
- The definition of the date of last contact was modified to include the date of last visit and the date of last telephone contact. The former change was for the sake of completeness; the latter in response to a change in the Case Report Form (Section 7).
- The definition of missing values for the Digit Span Forward and Digit Span Backward was added (Section 7).
- Guidance for handling of missing values for the PHQ-2 and PHQ-9 was added (Section 7).
- Strategies for attaining convergence of MMRM model fitting were expanded (Sections 8.1.1.2, 8.2.2, and 8.2.3).
- It was clarified that estimation in MMRM models would use observed margins (Sections 8.1.1.2, 8.2.2, and 8.2.3).

- Summaries of the first component of the composite endpoint events were added for the primary endpoint and the composite secondary endpoint of cardiovascular death, non-fatal MI and non-fatal stroke. (Sections 8.2.1 and 8.2.2). The definition of the first component was added (Section 8.1.1.1).

- Multiple imputations for the primary endpoint were modified to impute for all subjects who discontinued from study prior to the date of program discontinuation and did not have a primary endpoint event from subjects who withdrew consent to be followed (Section 8.2.1).

- As a result of recent feedback on other trials, the sensitivity analyses were modified to remove the imputation based on the MAR assumption (Section 8.2.1).

- The sensitivity analysis involving multiple imputation for subject who report a targeted medical event associated with the mechanism of action of bococizumab was deleted, as it does not add value of the existing multiple imputation for subjects who discontinue the study due to an adverse event (Section 8.2.1).

- The tabulation of Adjudication Committee confirmation of suspected primary and secondary endpoint events by investigator evaluation and treatment group according to sponsor standards was removed and was replaced by a listing (Sections 8.2.1 and 8.2.2).

- The summaries of the component that occurs first for the primary endpoint and composite endpoint of cardiovascular death, non-fatal MI or non-fatal stroke were added (Sections 8.2.1 and 8.2.2).

- Summaries of injection site adverse events with onset after the first dose of study medication for the bococizumab subjects according to ADA status and according to nAb status was added (Section 8.2.3).

- A tabulation of investigator-reported new diagnosis of diabetes in subjects without a baseline history of diabetes was added (Section 8.2.3).

- As the only post-baseline measurement is the End of Study visit, the longitudinal summary of mean change from baseline for waist circumference was removed and was replaced with a listing (Section 8.2.3).

- The ADA and nAb summaries and plots were modified (Section 8.2.3).

- Laboratory parameters for longitudinal summarization and plotting were added (Section 8.2.3).

- It was clarified that the summary of exposure to study medication will include treatment duration, total number of injections, and total dose (Section 8.2.4).

- The PK/PD/Immunogenicity summaries were modified (Section 8.2.4.1).

- The tabular summary of efficacy analyses was updated to reflect the above changes (Section 8.2.5).

1.2. Changes from Version 1.0 to Version 1.1

This amendment to the SAP was initiated while the study was ongoing, after finalization of Amendment 1 to Protocol B1481038 (dated 01OCT2014), and finalized prior to sponsor unblinding. Two unblinded DMC reviews have been conducted, both with recommendations to continue the study without modification.

Changes to the SAP driven by changes to the protocol:

- Italicized text from the original protocol was replaced with italicized text from Protocol Amendment 1 throughout the document.

- In response to changes in the objectives and endpoints,

    - Objectives (Section 2.2), endpoints and corresponding analyses were deleted.

    - For all lipids other than LDL-C, nominal changes from baseline (Endpoints: Section 6.1.3; Analyses: Section 8.1.1.2, Section 8.2.2).

    - For hs-CRP, percent changes from baseline (Endpoints: Section 6.1.3; Analyses: Section 8.1.1.2, Section 8.2.2).

    - For all circulating biomarkers other than LDL-C, percent change from baseline to last non-missing post-baseline observation (Endpoints: Section 6.1.3; Analyses: Section 8.1.1.2, Section 8.2.2).

    - For all circulating biomarkers, nominal change from baseline to last non-missing post-baseline observation (Endpoints: Section 6.1.3; Analyses: Section 8.1.1.2, Section 8.2.2).

- Objectives, endpoints and corresponding summaries and analyses were added:

    - Any stroke (fatal and non-fatal) of any etiology (Endpoints: Section 6.1.3; Analyses: Section 8.2.2).

    - Remnant lipoprotein cholesterol (RLP-C) (Endpoints: Section 6.1.3; Analyses: Section 8.1.1.2, Section 8.2.2).

    - Health care resource utilization: all-cause hospitalizations, CV hospitalizations, emergency room visits, physician office visits, hospitalizations within 30 days of a previous hospitalization, CV hospitalizations within 30 days of a previous hospitalization (Endpoints: Section 6.3.2; Analysis Section 8.2.4.2).

- In response to the addition of assessments not captured in the objectives and endpoints sections of the protocol, endpoints, summaries and analyses were added to the SAP for
    - An additional cognitive assessment: the Hopkins Verbal Learning Test (Endpoints: Section 6.2; Analyses: Section 8.2.3).
    - A depression assessment: the Patient Health Questionnaire (Endpoints: Section 6.2; Summary: Section 8.2.3).
- Potential adaptations to shorten the duration of the trial and to improve the likelihood that the estimated hazard ratios in certain subgroups will be less than one were added. If the latter adaptation were triggered, the criterion for stopping the study would be modified. In addition, it was clarified that the extant potential modification to improve the likelihood of attaining 70% power for the composite endpoint of CV death, non-fatal myocardial infarction and non-fatal stroke, if triggered, would also modify the criterion for stopping the study (Section 2.1). Detail on the estimations was updated (Section 3).
- Details concerning the alpha adjustment for DMC reviews of all-cause death were added (Section 3).
- The pooled analyses to support a hyperlipidemia indication were changed from pooling all Phase 3 studies to only pooling the cardiovascular outcomes studies (Section 3).
- In response to changes in the subgroups,
    - Subgroups for the primary endpoint were added (Section 5.4.2.1).
        - Based on a baseline history of qualifying atherosclerotic/cardiovascular event.
        - Based on a baseline history of diabetes and qualifying atherosclerotic/cardiovascular event.
        - Based on a baseline history of coronary revascularization.
        - Based on a baseline history of peripheral artery revascularization.
        - Based on baseline history of microalbuminuria.
        - Based on a baseline history of any renal impairment and a qualifying atherosclerotic/cardiovascular event.
        - Based on baseline Lp(a).

- Subgroups for the primary endpoint were removed (Section 5.4.2.1).
  - Based on a baseline history of arterial revascularization.
  - Based on baseline HDL-C.
- Subgroups for the primary endpoint were modified (Section 5.4.2.1).
  - Subgroups for a baseline history of Type 1 diabetes and Type 2 diabetes were combined into a single subgroup.
  - Renal impairment subgroups are based on eGFR instead of creatinine clearance.
  - Subgroups for familial hypercholesterolemia were modified to include LDL-C≥190 mg/dL at pre-screening.

- The formulae for calculating non-HDL-C, VLDL-C and RLP-C were added (Section 6.1.3).
- The collection timepoints for circulating biomarkers were updated (Section 6.1.3).
- Additional detail was added with respect to the number of subjects for cognitive testing (Section 6.2).
- The definition of compliance with study drug was updated (Section 6.3).
- The expected times required to complete the cognitive tests (Section 6.2) and EQ-5D (Section 6.3.2) were deleted.
- Time-to-event analyses including events after the efficacy cutoff date were added for the primary endpoint (Section 8.2.1) as supplement analyses.
- For time to recurrences, the presentation of a p-value from the Wei-Lin-Weissfeld was added (Sections 8.1.1.1 and 8.2.2).
- It was clarified that Cox models with an interaction term for subgroups would only be fit if more than one subgroup had at least 40 events and that only those subgroups with at least 40 events would be included (Sections 8.1.1.1 and 8.2.1).
- Details around the analysis of the log transformation for selected endpoints were added (Sections 8.1.1.2 and 8.2.2).

- Treatment adherence analyses and summaries were added:
    - Cox proportional hazards regression for the primary endpoint (Section 8.2.1);
    - Summaries of adverse events, Tier 1 AEs and SAEs with onset after the first dose of study medication (Section 8.2.3); and
    - For laboratory parameters, longitudinal summaries and plots of selected parameters and a summary of observations of potential clinical concern without regard to baseline abnormality (Section 8.2.3),
- The rationale for separate reporting of adverse events during the screening period and adverse events with onset after the first dose of study medication without any requirement of an increase in intensity was presented (Section 8.2.3).
- Longitudinal plots were added for vital signs and clinical laboratory measurements (Section 8.2.3).
- The summaries of cognitive test results were replaced with MMRM analyses (Section 8.2.3).
- An analysis of time to all-cause death in the Safety Analysis Set was added (Section 8.2.3).
- It was clarified that observed values of individual EQ-5D items would be summarized (Section 8.2.4.2).
- The appendix on further definitions of the clinical endpoints was updated (Appendix 1.2).
- The Schedule of Activities was updated (Appendix 2).

Changes to the SAP not driven by changes to the protocol:

- As the generic name for the product has now been approved, PF-04950615 was changed to bococizumab throughout the document.
- Subgroups based on age (2 categories) were deleted (Section 5.4.2.1).
- In order to conform more closely to the guidelines issued by the American Heart Association, it was clarified that qualifying atherosclerotic/cardiovascular event included all events/procedures, no matter when the event/procedure occurred (Section 5.4.2.1).
- The formation of subgroups based on post-randomization data was clarified (Section 5.4.2.1).

- Subgroups based on ADA results were added for selected AE summaries (Section 5.4.2.1).
- Subgroups for LDL-C summaries to assess the effect of ADAs on LDL-C response were modified (Sections 5.4.2.1 and 8.2.4.1).
- Subgroups for box plots of LDL-C to assess the effect of ADAs on LDL-C response were added (Section 5.4.2.1 and 8.2.4.1).
- Subgroups for summaries of ADA titers and neutralizing ADA titers were added (Sections 5.4.2.1 and 8.2.3).
- The percent coefficient of variation was added to summaries of ADA titers and neutralizing ADA titers (Section 8.2.3).
- A listing of ADAs, a figure for the prevalence of positive ADA titers over time, and a comprehensive listing of ADA titers, neutralizing ADA titers, LDL-C, bococizumab concentration and PCSK9 concentration were added (Section 8.2.3).
- Spaghetti plots for bococizumab and PCSK9 concentrations were deleted (Section 8.2.4.1).
- Laboratory shift tables in the SAS (Section 8.2.3) and in the laboratory shift subgroup (Section 5.4.2.1) were added.
- The definition of baseline values for pulse rate and blood pressure were altered to include the times of the measurements (Section 6.2).
- The definition of post-baseline values for pulse rate and blood pressure were refined to include all observations recorded on the CRF for that date (Section 6.2).
- The definition of persistent and transient positive ADA results was added (Section 6.2).
- For cognitive testing endpoints, whether higher or lower scores indicate better cognitive function was added (Section 6.2).
- It was clarified that AE reporting would start at informed consent (Section 6.2).
- Statin and non-statin lipid lowering treatments were added as other endpoints (Section 6.3).
- The information collected with respect to study medication was clarified (Section 6.3).

- Puerto Rico, Lithuania, Turkey, Philippines, Thailand, Denmark, New Zealand, Sweden, and Switzerland were added to the appropriate geographic regions (Section 6.4).

- For composite time-to-event endpoints, a summary of the component that occurred first for each subject was added (Section 8.1.1.1).

- For the primary and key secondary endpoints, a summary of the reasons for censoring was added (Section 8.1.1.1).

- A log-rank test was added to the analysis of time to premature discontinuation from the study (Section 8.2.1).

- Baseline smoking status was added as a covariate in the imputation model for multiple imputations of the primary endpoint (Section 8.2.1).

- Time-to-event analyses including events after the efficacy cutoff date were added for the key secondary endpoints (Section 8.2.2) as supplement analyses.

- For time to recurrent major cardiovascular events, the presentation of a p-value from the Wei-Lin-Weissfeld was added (Section 8.2.1).

- To avoid performing subgroup analyses on too few events to be statistically valid and/or of scientific interest, a requirement of at least 40 events was added (Sections 8.1.1.1 and 8.2.1).

- Treatment adherence analyses for time to all-cause death and for time to the composite endpoint of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke (Section 8.2.2);

- A summary of the Adjudication Committee confirmation of suspected clinical endpoints by investigator evaluation and treatment group was added (Sections 8.2.1 and 8.2.2).

- Summaries of stroke type and modified Rankin scores were added (Section 8.2.2).

- Longitudinal box plots for CK, hemoglobin and HbA1c were added (Section 8.2.3).

- A summary of subjects meeting one or more of the criteria for Hy's law was added (Section 8.2.3).

- The summaries of quantitative ECG parameters were removed and were replaced with listing following a CRF change to discontinue collecting quantitative ECG parameters (Section 8.2.3).

- Shifts from baseline in neurological exams were added (Section 8.2.3).

- It was clarified that statin medications, non-statin lipid lowering medications and other medications would be summarized separately (Section 8.2.4).
- The summary of drug allergies was changed to a listing (Section 8.2.4).
- A log rank test, Cox proportional hazards regression model, and Kaplan-Meier plot were added for time to premature discontinuation of study medication (Section 8.2.4).
- Listings of medication errors, previous participation in a bococizumab trial and subcutaneous injection site reaction assessments were added (Section 8.2.4).
- The windows to be used for cognitive assessments and depression assessments were added (Appendix 1.1).

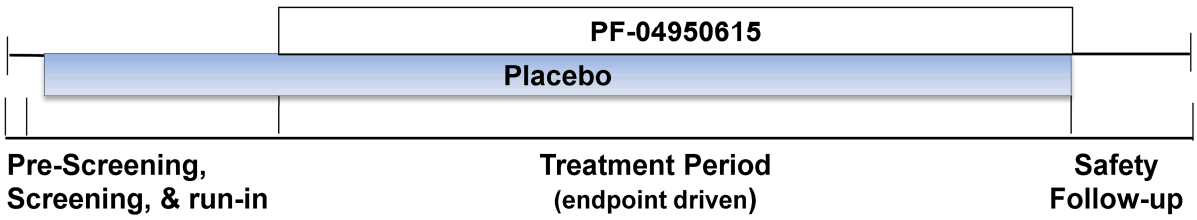
2. INTRODUCTION

Note: in this document, any text taken directly from the Amendment 2 to the Protocol in Sections 2-6, Appendix 1.2 and Appendix 2 is ***italicized***.

2.1. Study Design

This is an event driven, Phase 3 multi-center, double-blind, randomized parallel group evaluation of the efficacy, safety, and tolerability of bococizumab compared with placebo, in reducing the occurrence of major cardiovascular (*CV) events in subjects at risk, who are on background lipid lowering treatment and have an LDL-C ≥100 mg/dL (2.59 mmol/L) or non-HDL-C ≥130 mg/dL (3.36 mmol/L). After obtaining informed consent, there will be a pre-screening visit. At this visit subjects will have consented to have had lipid levels assessed and to provide medical records for review, only, so as to determine if the subject qualified for this study.* If qualified, [t]*he interactive response technologies (IRT) system will determine if the subject is eligible for this study or if the subject should be screen failed. This will be followed by a screening visit, within 30 days, and a run-in period of up to 6 weeks, during which subjects will be fully assessed with respect to the trial enrollment criteria and compliance with the self-administration of subcutaneous injections. The run-in period will be followed by the treatment period, the duration of which will be determined by the number of subjects with primary endpoint events, and concluded by a safety follow-up period, as illustrated in the schematic below (Figure 1).*

Figure 1. B1481038 Study Diagram



The End of Study (EOS) will be announced to study sites, when the Sponsor estimates that criteria for stopping the study in Section 3 of the protocol *have been satisfied. EOS visits should be scheduled as soon as possible, after that announcement. The end of study visit should occur no sooner than 14 days after the last dose of* investigational product (*IP*) *was administered for subjects taking IP. If the EOS visit has taken place earlier than 40 days after the last dose of IP administration, subjects will receive a telephone call to determine if any serious adverse events have taken place. All EOS procedures should be done for all randomized subjects when the study is completed, whether or not the subject is taking double-blind IP.*

Approximately 55,000 subjects may be screened and approximately 11,000 will be randomized. Subjects will be randomized to bococizumab 150 mg or placebo Q2wks in a 1:1 ratio. Subjects will self-inject, or if unable to self-inject, have investigational product administered by a caregiver (e.g., a family member or health care assistant). Randomization will be stratified by geographic region and complete statin intolerance.

The trial is intended to complete when approximately 508 subjects have accrued adjudicated and confirmed primary endpoint events, or 12 months following the randomization date of the last subject, whichever occurs later.

The sample size may be modified to shorten the expected duration of the trial or to improve the likelihood of attaining 70% power, for the key secondary composite endpoint of CV death, non-fatal MI and non-fatal stroke. Prior to the end of enrollment, blinded assessments will be made of the expected duration of the trial and of the power for this endpoint, assuming a hazard ratio (HR) of 0.75 at a two-sided alpha of 0.05. The decision to make either or both modifications will be documented in the Trial Master File. If the modification for the key secondary endpoint is made, the trial would be intended to complete when approximately 508 subjects have accrued adjudicated and confirmed primary endpoint events, 299 subjects have accrued adjudicated and confirmed events of the above key secondary endpoint, or 12 months following the randomization date of the last subject, whichever is last.

In addition, the sample size in certain subgroups, including diabetic subjects with no prior CVD event, may be modified or the trial duration may be extended to improve the likelihood that the estimated hazard ratios in the subgroups are less than one. Prior to the end of enrollment, the sponsor will perform a blinded assessment of the probabilities, assuming a hazard ratio of 0.75. If one or more of the probabilities are too small, the number of subjects in the corresponding subgroups may be modified, possibly increasing the total enrollment to do so. Prior to the end of the study, the sponsor will include a second blinded assessment of the probabilities. If one or more of these probabilities are too small, the duration of the trial may be extended. If the latter modification is made, the criterion for stopping the trial will include accruing 35 primary endpoint events in the corresponding subgroups. These decisions will be documented in the Trial Master File.

The study may be terminated early following an interim analysis (IA) for clinical benefit. This IA will be performed by a group external to the sponsor and reviewed by the DMC when both an adjudicated and confirmed primary endpoint event has occurred in 75% of the

required number of subjects, and an adjudicated and confirmed composite key secondary endpoint of cardiovascular death, non-fatal MI, or non-fatal stroke has occurred in 75% of the expected number of subjects (288). This IA may occur before 12 months after the last randomization. The non-binding decision rule is to stop the trial if the two-sided p-values for the primary endpoint and the above composite key secondary endpoint are at most 0.001. The decision to stop or continue the trial will be made by the DMC without any input from the Sponsor; the Sponsor will remain blinded and will not be exposed to any of these analyses. The Heybittle-Peto method with alpha=0.001 will be used to control the experimentwise Type 1 error rate, resulting in an adjustment to the final alpha of 0.00002.

Randomized subjects who withdraw from the study will have consented, at the onset of the study, to provide vital status information to the study site at the completion of the study.

Because the trial is designed to assess the effect of PCSK9 inhibition on recurrent as well as first clinical events, it is expected that subjects who sustain a clinical event, will remain on their assigned treatment, and continue in the study, unless the investigator chooses to withdraw the subject or the subject declines continued participation in the study.

All potential disease-related efficacy endpoints occurring on the day of or *after randomization, through study completion/end of study visit, should be … submitted for adjudication, whether or not the subject is on double-blind investigational product.*

The schedule of activities appears in Appendix 2.

2.2. Study Objectives

Primary Objective

The primary objective of this clinical trial is to demonstrate the superior efficacy of bococizumab compared with placebo in reducing the risk of major CV events, a composite endpoint which includes adjudicated and confirmed CV death, non-fatal MI, non-fatal stroke, and hospitalization for unstable angina with urgent revascularization (as defined in Appendix 1.2), in subjects at high or very high risk of major CV events who are on background lipid lowering treatment and have an LDL-C ≥100 mg/dL (2.59 mmol/L) or non-HDL-C ≥130 mg/dL (3.36 mmol/L).

Key Secondary Objectives

The key secondary objectives of this clinical trial are to demonstrate in subjects with high or very high risk of major CV events, who are on background lipid lowering treatment and have an LDL-C ≥100 mg/dL (2.59 mmol/L) or non-HDL-C ≥130 mg/dL (3.36 mmol/L), the superior efficacy of bococizumab compared with placebo in reducing the risk of adjudicated and confirmed key secondary endpoints (as defined in Appendix 1.2) of:

- *A composite endpoint of CV death, non-fatal MI, and non-fatal stroke;*
- *A composite endpoint of all-cause death, non-fatal MI, non-fatal stroke, and hospitalization for unstable angina needing urgent revascularization;*

- *A composite endpoint of all-cause death, non-fatal MI and non-fatal stroke.*
- *Hospitalization for unstable angina needing urgent revascularization.*

Other Secondary Objectives

Additional clinical secondary objectives are to evaluate in subjects with high or very high risk of major CV events, who are on background lipid lowering treatment and have an LDL-C ≥100 mg/dL (2.59 mmol/L) or non-HDL-C ≥130 mg/dL (3.36 mmol/L), the efficacy of bococizumab compared with placebo in reducing the risk of other adjudicated and confirmed secondary endpoints (as defined in Appendix 1.2) of:

- *A composite endpoint of CV death, non-fatal MI, non-fatal stroke, and hospitalization for unstable angina;*
- *CV death;*
- *Any MI (fatal and non-fatal);*
- *Fatal MI;*
- *Non-fatal MI;*
- *Any stroke (fatal and non-fatal);*
- *Any stroke (fatal and non-fatal) of any etiology;*
- *Fatal stroke;*
- *Non-fatal stroke;*
- *Hospitalization for unstable angina;*
- *Hospitalization for congestive heart failure (CHF);*
- *Any coronary revascularization procedure;*
- *Coronary artery bypass graft surgery (CABG);*
- *Percutaneous coronary intervention (PCI);*
- *Any arterial revascularizations;*
- *All-cause death.*

The LDL-C objective is *[t]o evaluate, in subjects at high or very high risk of major CV events, who are on background lipid lowering treatment and have an LDL-C ≥100 mg/dL (2.59 mmol/L) or non-HDL-C ≥130 mg/dL (3.36 mmol/L), bococizumab compared with*

placebo, with respect to the circulating lipid biomarker LDL-C (direct measure): its percent change and nominal change from baseline at Week 14, and its percent change from baseline to the last available post randomization measure.

Other circulating lipid biomarker objectives are *[t]o evaluate in subjects at high or very high risk of major CV events, who are on background lipid lowering treatment, and have an LDL-C ≥100 mg/dL (2.59 mmol/L) or non-HDL-C ≥130 mg/dL (3.36 mmol/L), bococizumab compared with placebo, with respect to the following circulating lipid biomarkers, and their percent change from baseline at Week 14:*

- *Non-HDL-C;*
- *Total cholesterol;*
- *Very low density lipoprotein cholesterol (VLDL-C);*
- *Remnant lipoprotein cholesterol (RLP-C);*
- *Apolipoprotein B (apo B);*
- *Lipoprotein(a) (Lp(a));*
- *Triglycerides;*
- *HDL-C;*
- *Apolipoprotein A-I (apo A-I).*

The inflammatory circulating biomarker objective is *[t]o evaluate in subjects at high or very high risk of major CV events, who are on background lipid lowering treatment, and have an LDL-C ≥100 mg/dL (2.59 mmol/L) or non-HDL-C ≥130 mg/dL (3.36 mmol/L), bococizumab compared with placebo, with respect to high sensitivity C-reactive protein (hs-CRP), and its percent change from baseline at Week 14.*

Health care resource utilization objectives are *[t]o evaluate in subjects at high or very high risk of major CV events, who are on background lipid lowering treatment, and have an LDL-C ≥100 mg/dL (2.59 mmol/L) or non-HDL-C ≥130 mg/dL (3.36 mmol/L), the comparison of health care resource utilization (HCRU) associated with bococizumab versus placebo,* for *the following:*

- *Incidence, primary and secondary discharge diagnoses, overall length of stay, duration of stay in different medical care units, and discharge disposition, for all-cause hospitalizations;*
- *Incidence, primary and secondary discharge diagnoses, overall length of stay, duration of stay in different medical care units, and discharge disposition, for CV hospitalizations;*

- *Incidence of emergency room visits;*
- *Incidence of physician office visits;*
- *Incidence of outpatient rehabilitation visits;*
- *Incidence of all-cause hospitalizations within 30 days of a previous hospitalization, primary and secondary discharge diagnoses, length of stay, and discharge disposition;*
- *Incidence of CV hospitalizations within 30 days of a previous hospitalization, primary and secondary discharge diagnoses, length of stay, and discharge disposition.*

Safety objectives

Safety objectives are *[t]o describe in subjects at high or very high risk of major CV events, who are on background lipid lowering treatment, and have an LDL-C ≥100 mg/dL (2.59 mmol/L) or non-HDL-C ≥130 mg/dL (3.36 mmol/L), the safety, tolerability and immunogenicity of bococizumab or placebo, including the assessment of adverse events (including Type 1 and 3 hypersensitivity reactions and injection site reactions), serious adverse events, vital signs, examination observations (physical and neurological examinations and cognitive testing), 12-lead ECG recordings, and safety laboratory tests, including hematology, blood chemistry studies (including liver function tests and creatine kinase tests), and urinalysis studies, and* anti-drug antibody (*ADA*) *assessments.*

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

DMC Analyses

This study will use an external Data Monitoring Committee (*DMC*)*. The DMC will be responsible for ongoing monitoring of the safety of subjects in the study and will meet periodically to review the safety data according to the DMC Charter. As part of the periodic safety reviews, the DMC will review analyses of the primary endpoint and all-cause death. These analyses will be conducted by a group external to the sponsor; no individual with the sponsor will be unblinded or exposed to the results of these analyses. The DMC Charter contains pre-defined rules for stopping the trial. Those rules are described in Appendix 5 of* this *protocol* and appear below. *The trial will not be stopped to declare success or futility on the primary endpoint as a result of these analyses; however, the DMC may recommend terminating the trial early due to a benefit on all-cause death, based on a pre-defined stopping rule which appears* below. *The recommendations made by the DMC to continue the study as planned or alter the conduct of the study will be forwarded to Pfizer and the Executive Committee leadership for final decision. Pfizer will make the final decision and will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data which are not endpoints, to regulatory authorities, as appropriate.*

The trial may be stopped early for success on all-cause death. As cardiovascular death counts towards both the primary endpoint and all-cause death, an alpha of 0.001 will be set aside for the DMC reviews of all-cause death. The alpha spending function for these analyses is described below.

The minutes of the End of Phase 2 Meeting with the United States Food and Drug Administration (FDA) include the following regarding DMC analyses of the primary endpoint and all-cause death:

> The sponsor stated that the DMC will periodically look at the comparison between treatment arms on the primary endpoint. These looks are intended for safety… FDA advised allowing for a small alpha to test for a mortality advantage at the interim analysis... The sponsor may want to consider having formal interim analyses on all-cause mortality.

When considering evidence to support a recommendation to stop early for overwhelming benefit for all-cause death, each CV outcomes study will be evaluated separately starting only when at least 33% of the study's targeted adjudicated and confirmed primary endpoint events have occurred and subject to a minimum of 8000 patient-years of follow-up (total in both arms in the trial) for B1481022 and 2750 patient-years of follow-up for B1481038 (total in both arms in the trial). The following procedure will be used to control overall Type 1 error.

In each CV outcomes study, the total (two-sided) Type 1 error of 0.050 will be partitioned, allocating 0.049 to the primary endpoint and 0.001 to all-cause death. The primary endpoint will not be subject to interim monitoring for benefit, and the final analysis will use a critical value of 0.049. Once the conditions above are met (33% of adjudicated and confirmed primary events and 8000 or 2750 patient-years of follow-up for B1481022 and B1481038, respectively), all-cause death will be subject to interim monitoring for benefit using a linear alpha spending function $\alpha(t) = 0.001 \times t$ where t is the information fraction, with final alpha $\alpha(1) = 0.001$. Depending on the number of looks, this choice of alpha-spending function corresponds to an approximately constant monitoring boundary of Z=3.4 to 3.6 (nominal p=0.0003 to 0.0006). Because the total alpha spent in interim monitoring of all-cause death will be bounded above by the final alpha value 0.001, the experimentwise Type 1 error will be bounded above by 0.049 + 0.001 = 0.05, preserving overall Type 1 error.

Because the trial is designed around a target number of primary endpoint events and the corresponding final number of all-cause death events is difficult to estimate with precision, at each interim analysis, the current cumulative alpha, $\alpha(t)$, will be calculated based on an information fraction t equal to the aggregate number of observed *adjudicated and confirmed primary endpoint events* divided by the target event count, and critical values will be calculated based on correlations determined from observed aggregate counts of all-cause death at the current and previous interim analyses (as in the WIZARD study; Cook, Benner, and Fisher, 2006).

Once the conditions above are met to begin interim monitoring for benefit for a particular trial, a formal interim monitoring calculation will be performed for that trial for every DMC report, including safety reports not associated with DMC meetings. The analysis will be based on a log-rank test of all-cause death from all data sources. Missing death dates will be imputed based on date of last contact.

When the test for all-cause death meets the above guideline for stopping a particular study early for overwhelming efficacy, the DMC will consider the all-cause death evidence within the context of all available efficacy and safety information in making their recommendation. In addition, the DMC may wish to give consideration to continuing the study, even where the all-cause death analysis meets the above criteria for benefit at an interim analysis, if the study is nearing completion (e.g., where 90% of targeted primary endpoint events have occurred).

The table below indicates the percent risk reduction associated with nominal p-values of 0.0003 and 0.0006 for various numbers of events, along with the probability of observing the reduction if the true risk reduction is 10%. Note that if the true risk reduction is 0% (no treatment effect) the probability of stopping is equal to the nominal p-value.

Table 1. Risk Reductions for Various Numbers of Events with Corresponding Probabilities

	$\alpha = 0.0003$		$\alpha = 0.0006$	
Number of Deaths	Percent Risk Reduction	Probability if 10% Risk Reduction	Percent Risk Reduction	Probability if 10% Risk Reduction
50	68.4%	0.07%	64.9%	0.16%
100	52.9%	0.11%	50.7%	0.20%
150	45.4%	0.14%	43.8%	0.24%
200	40.0%	0.22%	38.7%	0.34%
250	36.6%	0.27%	34.4%	0.57%
300	33.3%	0.42%	32.4%	0.59%
350	31.7%	0.43%	30.1%	0.78%
400	29.8%	0.55%	28.3%	0.95%

In addition, the DMC will review the interim analysis (IA) for clinical benefit and provide the recommendation for stopping or continuing the study for B1481038. *This IA will be performed by a group external to the sponsor and reviewed by the DMC when both an adjudicated and confirmed primary endpoint event has occurred in 75% of the required number of subjects, and an adjudicated and confirmed composite key secondary endpoint of cardiovascular death, non-fatal MI, or non-fatal stroke has occurred in 75% of the expected number of subjects (288). This IA may occur before 12 months after the last randomization. The non-binding decision rule is to stop the trial if the two-sided p-values for the primary endpoint and the above composite key secondary endpoint are at most 0.001. The* recommendation *to stop or continue the trial will be made by the DMC without any input from the Sponsor; the Sponsor will remain blinded and will not be exposed to any of these analyses. The Heybittle-Peto method with alpha=0.001 will be used to control the experimentwise Type 1 error rate, resulting in an adjustment to the final alpha of 0.00002.*

The interim analyses will be described in a separate Interim Analysis Statistical Analysis Plan.

As a result of the discontinuation of the bococizumab clinical development program, these analyses will not be done.

Analyses to Support the Regulatory Submission for the Treatment of Hyperlipidemia

Prior to the completion of this study, additional analyses of time to the first occurrence of *the primary endpoint and time to all-cause death, which includes data pooled from the two Phase 3 CV outcomes studies (B1481022 and B1481038), will be done to support an overall safety assessment, prior to a regulatory submission for the treatment of hyperlipidemia*, if this is a stand-alone submission. *These analyses will also be conducted by a group external to the sponsor and sent to the DMC for review. Regulators will not receive the results of the analyses, but instead the DMC recommended actions with respect to the ongoing trials, which are blinded; again, no individual at the sponsor will be unblinded or exposed to the results of these pooled safety analyses. Access to the unblinded data will be described in the DMC Charter. As there is no possibility of the study stopping early for clinical benefit as a result of this interim safety analysis of the pooled CV outcomes studies and no individual at the sponsor will be unblinded or exposed to the results of this analysis, no adjustment to the experimentwise Type 1 error will be made.*

As a result of the discontinuation of the bococizumab clinical development program, these analyses will not be done.

Analyses for Adaptive Design

The sample size may be modified to shorten the expected duration of the trial or to improve the likelihood of attaining 70% power for the key secondary composite endpoint of CV death, non-fatal MI and non-fatal stroke. Prior to the end of enrollment, blinded assessments will be made of the expected duration of the trial and of the power for this endpoint, assuming a hazard ratio (HR) of 0.75 at a two-sided alpha of 0.05. Under these assumptions, 299 confirmed and adjudicated events will provide approximately 70% power.

In addition, the sample size in certain subgroups, including diabetic subjects with no prior CVD event, may be modified or the trial duration may be extended to improve the likelihood that the estimated hazard ratios in the subgroups are less than one. Prior to the end of enrollment, the sponsor will perform a blinded assessment of the probabilities, assuming a hazard ratio of 0.75. Under this assumption, 35 events will provide approximately 80% probability that a point estimate is less than one.

The assessment of the trial duration will be based on prediction intervals obtained by simulations. The simulations will incorporate the observed randomization dates and projected accrual rates, observed adjudicated and confirmed first occurrences of a primary endpoint event, the observed pooled event rate, the observed discontinuations from the study due to withdrawn consent and loss to follow-up, and the corresponding rate from the protocol.

The assessments of power for the above key secondary endpoint and the probabilities that the estimated hazard ratios in the subgroups will be less than one will be based on Thatcher exact prediction intervals (Krishnamoorthy and Ping [2011]). The observed proportions of the first adjudicated and confirmed primary endpoint events that are also the key secondary endpoint event, and that are in the subgroup of diabetic subjects with no prior CVD event, respectively, will be used in the calculations.

As any adjustment to the sample size or duration of follow-up will be based on blinded data, the distribution of the test statistic for the primary analysis under the null hypothesis will not be affected and no alpha adjustment will be made.

Analyses to support scientific presentation

After completion of the two CVO studies and prior to final database release, unblinded efficacy, safety and immunogenicity data from both studies will be analyzed to support a presentation at the 2017 American College of Cardiology 66th Annual Scientific Session.

The analyses will be described in a separate SAP.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

Primary Analysis

The statistical hypothesis to be tested in the primary analysis in support of the primary objective of the study is

$$H_{0:P}: S_{P:Bococizumab}(t) = S_{P:Placebo}(t) \text{ for all } t > 0,$$

where

- $S_{P:Bococizumab}(t)$ is the survivor distribution of time to first adjudicated and confirmed major CV event in the bococizumab group and
- $S_{P:Placebo}(t)$ is the corresponding survivor distribution in the placebo group.

The alternative hypothesis is

$$H_{A:P}: S_{P:Bococizumab}(t) \neq S_{P:Placebo}(t), \text{ for some } t > 0.$$

Key Secondary Analyses

The statistical hypotheses to be tested in the key secondary analyses in support of the key secondary objectives are

$$H_{0:K1}: S_{K1:Bococizumab}(t) = S_{K1:Placebo}(t) \text{ for all } t > 0,$$

$$H_{0:K2}: S_{K2:Bococizumab}(t) = S_{K2:Placebo}(t) \text{ for all } t > 0,$$

$$H_{0:K3}: S_{K3:Bococizumab}(t) = S_{K3:Placebo}(t) \text{ for all } t > 0,$$

$$H_{0:K4}: S_{K4:Bococizumab}(t) = S_{K4:Placebo}(t) \text{ for all } t > 0,$$

where

- $S_{K1:Bococizumab}(t)$ is the survivor distribution of time to first occurrence of a composite endpoint of CV death, non-fatal MI and non-fatal stroke in the bococizumab group, and
- $S_{K1:Placebo}(t)$ is the corresponding survivor distribution in the placebo group;
- $S_{K2:Bococizumab}(t)$ is the survivor distribution of time to first occurrence of a composite endpoint of all-cause death, non-fatal MI, non-fatal stroke, and hospitalization for unstable angina needing urgent revascularization in the bococizumab group, and
- $S_{K2:Placebo}(t)$ is the corresponding survivor distribution in the placebo group.
- $S_{K3:Bococizumab}(t)$ is the survivor distribution of time to first occurrence of a composite endpoint of all-cause death, non-fatal MI, and non-fatal stroke in the bococizumab group, and
- $S_{K3:Placebo}(t)$ is the corresponding survivor distribution in the placebo group.
- $S_{K4:Bococizumab}(t)$ is the survivor distribution of time to first hospitalization for unstable angina needing urgent revascularization in the bococizumab group, and
- $S_{K4:Placebo}(t)$ is the corresponding survivor distribution in the placebo group.

The alternative hypotheses for $H_{0:K1}$, $H_{0:K2}$, $H_{0:K3}$, and $H_{0:K4}$ are

$$H_{A:K1}: S_{K1:Bococizumab}(t) \neq S_{K1:Placebo}(t), \text{ for some } t > 0,$$

$$H_{A:K2}: S_{K2:Bococizumab}(t) \neq S_{K2:Placebo}(t), \text{ for some } t > 0,$$

$$H_{A:K3}: S_{K3:Bococizumab}(t) \neq S_{K3:Placebo}(t), \text{ for some } t > 0,$$

$$H_{A:K4}: S_{K4:Bococizumab}(t) \neq S_{K4:Placebo}(t), \text{ for some } t > 0,$$

respectively.

4.2. Statistical Decision Rules

Primary Analysis

The null hypothesis for the primary analysis, $H_{0:P}$, will be rejected if the two-sided p-value from the log rank test is less than or equal to 0.04898. The primary objective will be considered met if, in addition, the estimated hazard ratio bococizumab:placebo in the corresponding Cox proportional hazards model is strictly less than 1. Otherwise, the primary objective will be considered unmet.

Key Secondary Analyses

The experimentwise Type 1 error rate, after a single Bonferroni adjustment for DMC reviews of all-cause death (see Section 3), will be controlled by using a gatekeeping procedure followed by a fixed sequence testing procedure. That is, if the primary objective is considered unmet, each of the key secondary objectives will be considered unmet. If the primary objective is considered met, the fixed sequence testing procedure with a two-sided α equal to that used for the primary analysis will be used to evaluate the key secondary objectives as described below.

1. The p-value from the log rank test of $H_{0:K1}$, which addresses the composite endpoint of CV death, non-fatal MI, and non-fatal stroke, will be compared to the alpha for the primary analysis. If this p-value is less than or equal to the primary endpoint alpha and the estimated hazard ratio bococizumab:placebo in the corresponding Cox proportional hazards model is strictly less than one, this key secondary objective will be considered met and the testing procedure will continue; otherwise the procedure will terminate and all key secondary objectives will be considered unmet.

2. If the above key secondary objective is met, the p-value from the log rank test of $H_{0:K2}$, which addresses the composite endpoint of all-cause death, non-fatal MI, non-fatal stroke, and hospitalization for unstable angina needing urgent revascularization, will be compared to the alpha for the primary analysis. If this p-value is less than or equal to the primary endpoint alpha and the estimated hazard ratio bococizumab:placebo in the corresponding Cox proportional hazards model is strictly less than one, this key secondary objective will also be considered met and the testing procedure will continue; otherwise the procedure will terminate and all key secondary objectives other than the above key secondary endpoint will be considered unmet.

3. If the above two key secondary objectives are met, the p-value from the log rank test of $H_{0:K3}$, which addresses the composite endpoint of all-cause death, non-fatal MI, and non-fatal stroke, will be compared to the alpha for the primary analysis. If this p-value is less than or equal to the primary endpoint alpha and the estimated hazard ratio bococizumab:placebo in the corresponding Cox proportional hazards model is strictly less than one, this key secondary objective will also be considered met and the testing procedure will continue; otherwise the procedure will terminate and both key secondary objectives other than the above two key secondary endpoints will be considered unmet.

4. If the above three key secondary objectives are met, the p-value from the log rank test of $H_{0:K4}$, which addresses the endpoint of hospitalization for unstable angina needing urgent revascularization, will be compared to the alpha for the primary analysis. If the p-value is less than or equal to the primary analysis alpha and the estimated hazard ratio bococizumab:placebo in the corresponding Cox proportional hazards mode is strictly less than one, this key secondary objective will also be considered met; otherwise this key secondary objectives will be considered unmet.

5. ANALYSIS SETS

5.1. Full Analysis Set

The Full Analysis Set (FAS) *includes all subjects who were randomized*, excluding fraudulent subjects who attempted to be randomized more than once into a bococizumab cardiovascular outcomes trial (B1481022 or B1481038). *Subjects will be analyzed according to their randomized dose regardless of any change in dose. Data will not be excluded from the FAS due to changes in dose or adherence to, or discontinuation of, study medication.* With the discontinuation of the bococizumab development program, the efficacy cutoff date will not be used. All data will be included.

5.2. 'Per Protocol' Analysis Set

Not applicable.

5.3. Safety Analysis Set

The Safety Analysis Set (SAS) *includes all subjects* in the FAS *who have received at least one dose of randomized study medication.*

5.4. Other Analysis Sets

5.4.1. All Screened Subjects

All Screened Subjects will include all subjects who have signed at least one informed consent document, regardless if the subjects have entered the screening phase or have been randomized, excluding those fraudulent subjects who attempted to be randomized more than once into a bococizumab cardiovascular outcomes trial (B1481022 or B1481038).

5.4.2. Subgroups

5.4.2.1. Subgroups for the Primary Endpoint

None.

5.4.2.2. Subgroups for Adverse Events

AEs with onset after the first dose of study medication will be tabulated for subjects in subgroups of the SAS *defined by:*

- *Age (<65, 66-74, ≥75);*
    - Treated Subjects < 65 Years of Age; Treated Subjects 66-74 Years of Age; Treated Subjects ≥ 75 Years of Age.
        - Assignment to subgroups will be based on age at screening and the Dosing Record CRF.
- *Gender;*
    - Treated Male Subjects; Treated Female Subjects.

- *Having* any *post-baseline LDL-C ≤ 25 mg/dL* **;
    - Treated Subjects With any Post-Baseline LDL-C ≤ 25 mg/dL; Treated Subjects With No Post- Baseline LDL-C ≤ 25 mg/dL.
- ADA status**;
    - Treated Bococizumab Subjects With Positive ADA Status; Treated Bococizumab Subjects With Negative ADA Status.
- nAb status**;
    - Treated Bococizumab Subjects With Positive nAb Status; Treated Bococizumab Subjects With Negative nAb Status.

** Note that subgroups based on having a post-baseline LDL-C ≤ 25 mg/dL, ADA status and nAb status are based on post-randomization data. The interpretation of results in the subgroups must be approached with caution.

In addition, the number of subjects with an investigator-reported new diagnosis of diabetes will be summarized in Treated Subjects With No Baseline History of Diabetes. Assignment to this subgroup is based on the Cardiovascular Stratification CRF page and on the AE CRF page. The high level term 'Diabetes mellitus (incl subtypes)' will be used for AEs with onset prior to randomization.

5.4.2.3. Subgroups for Clinical Laboratory Measurements

Selected laboratory summaries will be done in subgroups defined by having any post-baseline LDL-C ≤ 25 mg/dL, ADA status and nAb status (defined in Section 5.4.2.2 above). As these subgroups are based on post-randomization data, interpretation of the results must be approached with caution.

Observed value and change from baseline in HbA1c will be tabulated by visit as continuous endpoints in Treated Subjects With No Baseline History of Diabetes. Assignment to this subgroup is based on the Cardiovascular Stratification CRF page, the Dosing Record CRF and on the AE CRF page. The high level term 'Diabetes mellitus (incl subtypes)' will be used.

5.4.2.4. Subgroups for Pharmacokinetics/Pharmacodynamics

Summaries and plots of bococizumab concentration and LDL-C response will be done in subgroups defined by the following variables, except as noted below. The definitions of anti-drug antibody (ADA) and neutralizing antibody (nAb) status, ADA and nAb duration response type and ADA and nAb titer response type are provided in Section 8.2.4.1.1.

1. Treatment with bococizumab and ADA status;
    - Treated Bococizumab Subjects With Positive ADA Status; Treated Bococizumab Subjects With Negative ADA Status.

2. Treatment with bococizumab and pre-treatment ADA result;

    - Treated Bococizumab Subjects With Pre-Existing Antibodies; Treated Bococizumab Subjects Without Pre-Existing Antibodies.

3. Treatment with bococizumab and nAb status;

    - Treated Bococizumab Subjects With Positive nAb Status; Treated Bococizumab Subjects With Negative nAb status.

4. Treatment with bococizumab and duration of ADA response type;

    - Treated Bococizumab Subjects with Indeterminate Duration of ADA Response; Treated Bococizumab Subjects with Persistent Duration of ADA Response; Treated Bococizumab Subjects with Transient Duration of ADA Response.

5. Treatment with bococizumab and duration of nAb response type;

    - Treated Bococizumab Subjects with Indeterminate Duration of nAb Response; Treated Bococizumab Subjects with Persistent Duration of nAb Response; Treated Bococizumab Subjects with Transient Duration of nAb Response.

6. Treatment with bococizumab and ADA titer response type;

    - Treated Bococizumab Subjects with Negative ADA status; Treated Bococizumab Subjects with Positive ADA Status and Maximum ADA Titer in the 1st Tertile; Treated Bococizumab Subjects with Positive ADA Status and Maximum ADA Titer in the 2nd Tertile; Treated Bococizumab Subjects with Positive ADA Status and Maximum ADA Titer in the 3rd Tertile.

7. Treatment with bococizumab and nAb titer response type;

    - Treated Bococizumab Subjects with Negative nAb status; Treated Bococizumab Subjects with Maximum nAb Titer in the 1st Tertile; Treated Bococizumab Subjects with Maximum nAb Titer in the 2nd Tertile; Treated Bococizumab Subjects with Maximum nAb Titer in the 3rd Tertile.

5.4.2.5. Subgroups for Anti-drug Antibody Titers and Neutralizing Antibody Titers

Time to first positive ADA result will be summarized in Treated Bococizumab Subjects With Positive ADA Status, which is defined in Section 5.4.2.4 above. Time to first positive nAb result will be summarized in Treated Bococizumab Subjects with Positive nAb Status.

5.5. Treatment Misallocations

If a subject was:

- randomized but not treated, the subject will be reported under the randomized treatment group for efficacy analyses. However, such a subject must be excluded from the safety analyses as the actual treatment is missing.
- treated but not randomized, the subject must be excluded from the efficacy analyses since the randomized treatment is missing. The subject will also be excluded from the Safety Analysis Set.
- randomized but took at least one dose of the incorrect treatment, the subject will be reported under the randomized treatment group for all efficacy and safety analyses.

5.6. Protocol Deviations

Protocol deviations will not impact inclusion in data sets or analysis methodology.

5.6.1. Deviations Assessed Prior to Randomization

Not applicable.

5.6.2. Deviations Assessed Post-Randomization

Not applicable.

6. ENDPOINTS AND COVARIATES

6.1. Efficacy Endpoint(s)

This protocol will use an independent blinded Adjudication Committee wherein, to maintain scientific integrity, adjudication of disease-related efficacy endpoints will be performed. The Adjudication Committee will adjudicate potential disease-related efficacy endpoints, including CV deaths, all-cause death, MI, stroke, hospitalization for unstable angina needing urgent revascularization, hospitalization for unstable angina, hospitalization for CHF, and arterial revascularization procedures including percutaneous coronary interventions, CABG, and all other arterial revascularization procedures as described in Appendix 1.2. The Adjudication Committee will confirm whether potential disease-related efficacy events meet the pre-specified clinical criteria defined in the Adjudication Committee charter. The definition of MI, for the purposes of adjudication will conform to the Third Universal Definition of Myocardial Infarction. Other endpoint definitions will be based upon the Standardized Definitions for Cardiovascular and Stroke End Point Events in Clinical Trials.

Clinical endpoints defined as primary or secondary efficacy parameters will be assessed beginning with the day of randomization. All potential disease-related efficacy endpoints occurring after randomization, through study completion/end of study visit, should be reported as adverse events and submitted for adjudication, whether or not the subject is on double-blind investigational product (*IP*).

After discontinuation of the bococizumab clinical development program, the sites were instructed to only forward those events occurring on or before 01Novemeber2016 for adjudication.

Only data from central laboratories will be used to assess the secondary circulating biomarker endpoints.

Changes from baseline will be calculated as the post-baseline value minus the baseline value.

6.1.1. Primary Efficacy Endpoint

The primary endpoint is the time from randomization to the first adjudicated and confirmed occurrence of a major CV event, a composite endpoint which includes CV death, non-fatal MI, non-fatal stroke, and hospitalization for unstable angina needing urgent revascularization (as defined in Appendix 1.2).

6.1.2. Key Secondary Endpoints

The key secondary endpoints are *[t]he times from randomization to the first adjudicated and confirmed occurrence of the endpoints below (as defined in Appendix 1.2):*

- *A composite endpoint of CV death, non-fatal MI, and non-fatal stroke;*
- *A composite endpoint of all-cause death, non-fatal MI, and non-fatal stroke, and hospitalization for unstable angina needing urgent revascularization;*
- *A composite endpoint of all cause death, non-fatal MI, and non-fatal stroke;*
- *Hospitalization for unstable angina needing urgent revascularization.*

6.1.3. Other Secondary Endpoints

Other clinical secondary endpoints are *[t]he times from randomization to the first adjudicated and confirmed occurrence of the endpoints below (as defined in Appendix 1.2):*

- *A composite endpoint of CV death, non-fatal MI, non-fatal stroke, and hospitalization for unstable angina;*
- *CV death;*
- *Any MI (fatal and non-fatal);*
- *Fatal MI;*
- *Non-fatal MI;*
- *Any stroke (fatal and non-fatal);*
- *Any stroke (fatal and non-fatal), of any etiology;*

- *Fatal stroke;*
- *Non-fatal stroke;*
- *Hospitalization for unstable angina;*
- *Hospitalization for congestive heart failure (CHF);*
- *Any coronary revascularization procedure;*
- *CABG;*
- *PCI;*
- *Any arterial revascularizations;*
- *All-cause death.*

Circulating biomarker endpoints are secondary efficacy endpoints and include the lipid and inflammatory parameters listed below. Lipid parameters will be evaluated as percent change from baseline. In addition, LDL-C (direct and Friedewald) *will be evaluated as nominal change from baseline. The inflammatory parameter, hs-CRP, will be evaluated as the percent change from baseline.*

The sponsor, investigators and clinical staff and the subject will remain blinded to all circulating efficacy biomarker laboratory findings. Once all subjects have completed participation and the study is unblinded, results of the fasting lipid tests for each study participant will be sent to the investigator.

Investigators should inform the study subject's primary care physician (PCP) of the study design and the importance of maintaining the blind for lipid laboratory results. If possible, PCPs should refrain from measuring lipids while the subject is a participant in the study, if possible, but if measurement is necessary, they should refrain from informing the subject of the results. Subjects will be provided an information card to give to a health provider, when being seen for medical care or when undergoing phlebotomy that is not study related. The information card will explain the nature of the subject's participation in the study and that lipid and other biomarker data is being reviewed, to maintain the safety of the subject during the conduct of the trial.

Baseline will be calculated as the mean of the last two non-missing values prior to and including the randomization date.

Non-fasted as well as fasted measurements will be used in all summaries, analyses, and plots.

Values below the limit of quantification will be set to one-half of the limit of quantification.

The circulating biomarker secondary endpoints are:

- *LDL-C;*
- *Total cholesterol;*
- *HDL-C;*
- *Triglycerides*;
- *Non-HDL-C (calculated as total cholesterol – HDL-C);*
- *Friedewald LDL-C (calculated as total cholesterol – HDL-C – [triglyceride x 0.2] when using mg/dL or as total cholesterol – HDL-C – [triglyceride x 0.458)] when using mmol/L);*
- *VLDL-C (calculated as triglycerides x 0.2, when using mg/dL or triglycerides x 0.458, when using mmol/L);*
- *RLP-C (calculated as total cholesterol – [HDL-C + LDL-C])*;
- *Apo-A-I;*
- *Apo-B;*
- *Lp(a);*
- *hs-CRP.*

LDL-C, total cholesterol, HDL-C, triglycerides, non-HDL-C, Friedewald LDL-C, VLDL-C and RLP-C will be collected at pre-screening, during the run-in period, at Baseline, and at Weeks 4, 8, 14, 26, 40, 52, 70, 86, 104, 122, 140, 156, 174, 192, and 208. If the trial runs longer than 48 months, these parameters will be collected in the 16 or 18 week intervals after Week 208, as they were collected after Week 156. Apo-A-I, Apo-B, Lp(a) and hs-CRP will be collected at Baseline, Week 14, and Week 52. In addition, Lp(a) and hs-CRP will be collected during the screening period.

For calculations of non-HDL-C, Friedewald LDL-C and RLP-C, the measurements used in the calculations must be from samples drawn on the same date.

Analyses of LDL-C will be based on the direct measurements.

For those analyses that use RLP-C or non-HDL-C, a measurement less than zero will be set to zero.

6.2. Safety Endpoints

Safety endpoints include investigator reported adverse events, (including Type 1 and 3 hypersensitivity reactions and injection site reactions), serious adverse events, vital signs, examination observations (physical and neurological examinations and cognitive testing), 12-lead ECG recordings, and safety laboratory tests, including hematology, blood chemistry studies (including liver function tests and creatine kinase tests), urinalysis studies, and ADA assessments.

Safety endpoints are collected according to the Schedule of Activities in Appendix 2. All safety observations that occur after the first dose of study medication will be summarized regardless of how long an event occurs after the last dose of study medication. Adverse events on the day of first dose of study medication will be considered to be after the first dose; in the absence of the time of the measurement, all other safety observations on the day of the first dose will be considered before the first dose.

For safety summaries that include a comparison to baseline, baseline and all non-missing measurements after the first dose of study medication will be included in safety analyses regardless of whether or not the subject is on double-blind study medication, except as noted below.

Baseline values

For pulse rate (PR) and blood pressure (BP), the baseline will be the mean of all non-missing measurements taken prior to the first dose of randomized study medication on the last day on or before the first dose of study medication for which there is at least one non-missing value. For all other safety measurements, the baseline value will be the last non-missing value obtained on or before the first dose of randomized study medication.

Vital signs

Vital sign measurements will include PR, systolic and diastolic BP, weight, height, waist circumference and temperature.

At each visit sitting systolic and diastolic PR and BP will be measured in duplicates. The second measurement should be taken after the first measurement, according to the local standard of care. The first and second measurements will be recorded on the Case Report Form and their average (i.e., the arithmetic mean) *will serve as the value for that visit.* The post-baseline value will be the mean of all non-missing observations taken on the same day for which there is at least one non-missing value.

Clinical laboratory measurements

The following laboratory tests will be collected:

Hematology	***Chemistry***	***Urinalysis****	***Additional***
Hemoglobin *Hematocrit* *RBC count* *Mean corpuscular volume (MCV)* *Mean corpuscular hemoglobin (MCH)* *Mean corpuscular hemoglobin concentration (MCHC)* *Platelet count* *WBC count* *Total neutrophils (Abs)* *Eosinophils (Abs)* *Monocytes (Abs)* *Basophils (Abs)* *Lymphocytes (Abs)*	*BUN* *Creatinine* *Glucose* *Ca^{++}* *Na^{+}, K^{+}, Cl* *Total CO2 (Bicarbonate)* *Uric acid* *Albumin* *Total protein* *LDH* *Magnesium* *Phosphorus* *CK* *CK-isozymes** *eGFR* *HbA1c** *Liver function: AST/ALT* *Gamma-glutamyl transferase (GGT)** *Total bilirubin* *Direct bilirubin* *Indirect bilirubin* *Alkaline phosphatase* *Lipid profile (total cholesterol, LDL-C, non-HDL-C, HDL-C, RLP-C, VLDL-C, triglycerides)** *Special chemistry assessments (hs-CRP, Lp(a), Apo B, Apo A-I)**	*pH* *Specific gravity* *Bilirubin* *Urobilinogen* *Nitrite* *Leukocytes* *Glucose (qual)* *Protein (qual)* *Blood (qual)* *Ketones* *Urine albumin/creatinine ratio**	*Serum pregnancy (WCBP)** *Urine pregnancy*** (WCBP)* *Hepatitis panel*** *ADA** *PCSK9** *bococizumab**

* *Where applicable and according to the* Schedule of Activities (*SOA*).

** *Hepatitis B and C virus serologies at screening or all subjects and Hepatitis C virus serologies will be collected at EDC/EOS only for subjects from study sites in Canada. A positive or indeterminate hepatitis C serology may trigger a hepatitis C PCR test for confirmation.*

*** *Performed locally*

Qual = qualitative; WCBP= women of childbearing potential; Abs=absolute.

Cognitive testing

Cognitive testing will be performed at baseline (Visit 5), annually, and at EDC and/or EOS visits at a subset of designated North American *study sites in approximately 500 subjects (250/treatment group). The cognitive testing battery will comprise the following assessments:*

- *Wechsler Adult Intelligence Scale (WAIS-III) – Digit Span (Forward and Backward)*

  Digit Span is a test of working memory using paper and pencil. Participants are read a sequence of digits increasing in length from two to nine digits. In the Digit Span Forward test, subjects are asked to repeat the digits as they are presented, and in the

Digit Span Backward test, subjects are asked to repeat the digits in reverse. The length of the digit sequence is increased across trials until there has been a failure across two consecutive trials of a particular length.

There are eight items in the Digit Span Forward test, which is repeated twice. The score for each item in the list is the number of times the subject correctly repeats the item in the correct sequence. The Forward Digit Span Score is the sum of the score for the eight items and ranges from 0-16. A higher score indicates better cognitive function.

There are seven items in the Digit Span Backward test, which is repeated twice. The score for each item in the list is the number of times the subject correctly repeats the item in the correct sequence. The Digit Span Backward Score is the sum of the score for the seven items and ranges from 0-14. A higher score indicates better cognitive function.

- *Wechsler Adult Intelligence Scale (WAIS-III) - Digit Symbol-Coding*

  Digit Symbol - Coding is a brief motor skill and cognition test using paper and pencil. It *consists of a series of numbers, each of which is paired with its own corresponding hieroglyphic-like symbol. Using a key, the subject writes the symbol corresponding to its number. The subject's score is determined by the number of symbols correctly drawn within a 120-second time limit. Subjects are encouraged to perform the task as quickly and accurately as possible.*

  The Digit Symbol – Coding score is the number of correct symbols and ranges from 0-133. A higher score indicates better cognitive function.

- *Trail Making Test (Parts A and B)*

  The Trail Making Test (TMT) is a measure of attention, speed, and mental flexibility using paper and pencil. The TMT also tests spatial organization, visual pursuits, recall, and recognition. It consists of 25 circles distributed over a sheet of paper. In Part A of the test, the circles are numbered 1-25 and the subject is required to draw lines to connect the 25 numbered circles in ascending order. Part A tests visual scanning, numeric sequencing, and visuomotor speed. In Part B, the circles include both numbers (1-13) and letters (A-L). Part B of the test is similar to Part A except the subject must alternate between connecting the numbered and lettered circles (ie, 1-A-2-B-3-C, etc.), and it is believed to be more difficult and takes longer to complete. Part B tests cognitive demands including visual motor and visual spatial abilities and mental flexibility. Part A and Part B are timed, and scores represents the total time required to complete the tasks. Subjects are instructed to connect the circles as quickly as possible, without lifting the pen or pencil from the page. Subjects will be given up to 5 minutes to complete each task.

The Trail Making A and Trail Making B scores are the number of seconds required to complete the respective tests and range from 0-300. A shorter time indicates better cognitive function.

- *Hopkins Verbal Learning Test (HVLT)*

  The Hopkins Verbal Learning Test (HVLT) - Revised is a relatively brief test of verbal learning and memory to be used when serial testing is desired. It is composed of 12 items, organized into three semantic categories, and is presented over three consecutive learning trials as the Immediate Recall test. The subjects are asked to recall as many words as they can remember in any order. The same list of words is utilized in the consecutive trials. Delayed Recall is assessed 20 to 25 minutes after completion of the Immediate Recall test, with the subjects again to recall as many words as they can in any order. Immediately after administration of the Delayed Recall trial, a forced-choice Recognition test is administered. The Recognition test includes the 12 target words, plus 12 distractors (six semantically-related and six semantically-unrelated words). The numbers of words correctly recalled for each of the three Learning Trials are summed for the Total Recall score, which ranges from 0 to 36. The Delayed Recall Trial score, is the number of words correctly recalled on the delayed trial, and ranges from 0 to 12. The Recognition test score is the sum of the number of words correctly identified on the list for the Immediate Recall Test and the number correctly identified as not being on the list. The Recognition test score ranges from 0 to 24. On these assessments, higher scores indicate greater verbal learning and recall.

<u>Depression Assessment</u>

The assessment of depression in patients with CV disease is recommended since it may impact the quality of life and adherence to medical treatment. The Patient Health Questionnaire (PHQ) depression assessment is a validated tool to assess the presence of depression and its severity.

The PHQ-2 consists of the first two items of the PHQ-9, and constitutes the two core DSM-IV items for major depressive disorder. The PHQ-2 score ranges from 0 to 6. The operating characteristics of this ultra-brief measure are quite good; the recommended cut-point when used as a screening test is a score of 3 or greater. This study will use a screening test score of 2 or greater, as a trigger for completion of the PHQ-9 assessment, as a more conservative approach to identifying the presence of a major depressive disorder. The PHQ-2 provides depressive scores and can be used as a screening assessment for depression; the remaining 7 questions of the PHQ-9 evaluate the severity of depression. The severity is calculated by assigning scores of 0, 1, 2, and 3, to the response categories of "not at all", "several days", "more than half the days", and "nearly every day", respectively. PHQ-9 total score ranges from 0 to 27. Scores of 1-4, 5-9, 10-14, 15-19, and 20-27 represent minimal, mild, moderate, moderately severe, and severe depression, respectively.

The PHQ-2 will be performed in all subjects at Visit 5 (randomization), and in subjects with cognitive assessments only, it will be performed annually, and at EDC or EOS.

Baseline value will be the last non-missing value on or before the day of randomization.

Adverse events

The Pfizer SAE Triage Group will identify potential disease-related efficacy endpoints (listed below) that are considered by the investigator to be causally related to study drug and report these into the Pfizer Drug Safety Unit (DSU):

- *Myocardial infarction, fatal or non-fatal.*
- *CV death.*
- *All-cause death.*
- *Hospitalization for unstable angina needing urgent revascularization (PCI or CABG).*
- *Stroke, fatal or non-fatal.*
- *Hospitalization for unstable angina.*
- *Hospitalization for congestive heart failure.*
- *Arterial revascularization of any kind (eg, PCI, CABG, peripheral vascular surgery, carotid artery surgery).*

All adverse events occurring on or after the day of first informed consent will be included in reporting, regardless of whether or not the subject is on double-blind study medication. Adverse events during the screening period and adverse events with onset after the first dose of study medication will be summarized separately.

A 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 3 tiers. Different analyses will be performed for different tiers (See Section 8.2.3).

- Tier-1 events: These are pre-specified events of clinical importance and are maintained in a list in the product's Safety Review Plan;
- Tier-2 events: These are events that are not Tier-1 but are "common". A MedDRA preferred term is defined as a tier-2 event if there are at least 5% in any treatment group;
- Tier-3 events: All adverse events are tier-3 events.

6.3. Other Endpoints

Baseline characteristics, including gender, race, ethnicity, alcohol and tobacco use, cardiovascular risk factors, primary diagnosis, time since primary diagnosis, and medical history will be collected prior to randomization. The collection of primary diagnosis and time since primary diagnosis was originally collected, but discontinued following a change to the CRF.

Concomitant and pre-study medications and non-drug treatments, including statins and non-statin lipid lowering treatments, will be collected throughout the study.

The date and time of each dose of study medication and the number of injections will be collected, as will reasons for discontinuation from study therapy and from the study. Treatment duration will be calculated as (the date of last active dose – the date of first active dose +15).

After the randomization visit, subjects will be directed to bring any used and unused syringe cartons to each visit. Used syringes will be returned to the study center in a biohazard container when it is full, to receive a new container, and when directed by the study site.

Compliance is calculated as the percent of planned Investigational Product (*IP*) *doses that were actually taken. Cartons lost prior to the administration of IP, or damaged and unused syringes, should not be counted as completed dose administrations. From this information, compliance, based on the dosing schedule, will be calculated as follows:*

$$\textit{Compliance} = 100\% \times \frac{\textit{actual dose administrations}}{\textit{dose administrations planned}}$$

- The number of actual dose administrations will be derived from the dosing CRF page.
- For subjects who do not have two dose adjustments, the number of dose administrations planned is one plus the integer part of one-fourteenth of the number of days from randomization to the date the site instructs the subject to discontinue study medication. For subjects who have two dose adjustments, the number of dose administrations planned is one plus the integer part of one-fourteenth of the number of days from randomization to the visit at which the second dose adjustment takes place plus one-twenty-eighth the number of days from the visit at which the second dose adjustment takes place to the date the site instructs the subject to discontinue study medication.
- *In the event of an adverse event (AE) or reaction, subjects may be counseled to interrupt dosing permanently or temporarily. Doses not taken in such instances do not count as planned dose administrations and do not constitute lack of compliance.*

6.3.1. Pharmacokinetic/Pharmacodynamic Endpoints

Pharmacokinetic/Pharmacodynamic (PK/PD) endpoints include plasma bococizumab concentration. Samples will not be assayed for PCSK9.

Blood samples for bococizumab and PCSK9 will be collected as specified in the Schedule of Activities. On all bococizumab/PCSK9 blood sample collection days, samples must be collected prior to bococizumab dosing. After randomization, if lipid sampling has been postponed to an unscheduled visit, the corresponding ADA, PK, and PCSK9 samples should be postponed as well, and collected at the at the same time as the rescheduled lipid sample collection. Bococizumab/PCSK9 blood samples will be collected from all subjects, but only analyzed, if needed, to help understand the PK, PD, and safety profile *of bococizumab in this study population.*

Baseline PCSK9 concentration will be defined as the mean of the last two non-missing values prior to and including randomization. If only one non-missing measurement is available, that measurement will serve as the baseline.

Samples for bococizumab and PCSK9, if analyzed, will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.

6.3.2. Outcomes Research Endpoints

<u>EuroQol 5-Dimensions (EQ-5D)</u>

The EuroQol 5-Dimension (*EQ-5D*) *is a generic measure of health-related quality of life. The EQ-5D is a subject completed instrument designed to assess impact on quality of life in five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Additionally, scores from the five domains may be used to calculate a single index value. The EuroQol EQ-5D Visual Analogue Scale (VAS) is a patient-completed 20 cm scale designed to rate an individual's current health state. The Health State Profile will be administered concurrently with the VAS-HEALTH STATE component of the EuroQol EQ-5D instrument.*

The EQ-5D will be administered at Baseline and at Weeks 14, 26, 52, 104, 156, 208 and the subject's last visit (EDC or EOS). If the trial runs longer than 208 weeks, the EQ-5D will be collected every 52 weeks after Week 208.

The baseline values for the EQ-5D health index score and health state score will be the last non-missing value prior to or on the day of randomization.

The health index score will be calculated as per Shaw, Johnson and Coons (2005). Prior to calculating the health index score, the following are calculated.

- I2 = number of item scores equal to 2.
- I3 = number of item scores equal to 3.

The health index score is calculated as follows:

1. The initial health index score is 1.0.
2. If the mobility score:
    a. is 2, then 0.146016 is subtracted
    b. is 3, then 0.557685 is subtracted
3. If the self-care score:
    a. is 2, then 0.1753425 is subtracted
    b. is 3, then 0.4711896 is subtracted
4. If the usual activities score:
    a. is 2, then 0.1397295 is subtracted
    b. is 3, then 0.3742594 is subtracted
5. If the pain/discomfort score:
    a. is 2, then 0.1728907 is subtracted
    b. is 3, then 0.5371011 is subtracted
6. If the anxiety/depression score:
    a. is 2, then 0.156223 is subtracted
    b. is 3, then 0.4501876 is subtracted
7. If I2 + I3 > 1, then (I2 + I3 – 1) times 0.1395949 is added.
8. If I2 > 1, then 0.0106868 times the square of (I2 – 1) is subtracted.
9. If I3 > 1, then 0.1215579 times (I3 – 1) plus 0.0147963 times the square of (I3 –1) is added.

Health Care Resource Utilization (HCRU)

HCRU assessments will take place at each visit to collect data on the following:

- *The occurrence, primary and secondary discharge diagnoses, overall length of stay, duration of stay in different medical care units, and discharge disposition for all-cause hospitalizations;*

- *The occurrence, primary and secondary discharge diagnoses, overall length of stay, duration of stay in different medical care units, and discharge disposition for CV hospitalizations;*
- *The occurrence of emergency room visits;*
- *The occurrence of physician office visits;*
- *The occurrence of outpatient rehabilitation visits;*
- *The occurrence of all-cause hospitalizations within 30 days of a previous hospitalization, primary and secondary discharge diagnoses, length of stay, and discharge disposition;*
- *The occurrence of CV hospitalizations within 30 days of a previous hospitalization, primary and secondary discharge diagnoses, length of stay, and discharge disposition.*

The medical care units being assessed for these objectives include:

- *Cardiac Care Unit (CCU);*
- *Medical Intensive Care Unit (MICU);*
- *Neurology Intensive Care Unit (NICU);*
- *Surgical Intensive Care Unit (SICU);*
- *Thoracic Intensive Care Unit (TICU);*
- *Cardiac Step-down Unit;*
- *Pulmonary Step-down Unit;*
- *General ward;*
- *Dialysis Unit;*
- *Chemotherapy Unit;*
- *Infections disease isolation unit;*
- *Other.*

Discharge care disposition entities being evaluated for HCRU include:

- *Home self-care;*
- *Home health care;*
- *Nursing home care/skilled nursing facility;*

- *Rehabilitation facility;*
- *Hospice care;*
- *Death;*
- *And other potential disposition entities.*

6.4. Covariates

The randomization will be stratified by geographic region and complete statin intolerance. These variables will be included as stratification factors in log rank tests and Cox proportional hazards regression models and as covariates in linear models for efficacy endpoints. If the model fitting for the Cox proportional hazards model fails to converge, compete statin intolerance will be removed as a stratification factor.

Geographic region and complete statin intolerance will be obtained from the IRT system.

Complete statin intolerance is a binary variable. Subjects with complete statin intolerance will form one group; the other group will consist of subjects with partial or no statin intolerance.

The geographic regions (5 levels) are:

- USA/Canada: Canada, Puerto Rico, United States of America.
- Latin America: Argentina, Brazil, Chile, Columbia, Mexico, Peru.
- Eastern Europe/Turkey: Czech Republic, Hungary, Poland, Romania, Russia, Slovakia, Turkey.
- Asia: China, India, Japan, Korea, Taiwan, Thailand.
- Rest of World: Australia, Belgium, Denmark, Finland, France, Germany, Ireland, Israel, Italy, Netherlands, New Zealand, Republic of South Africa, Spain, Sweden, Switzerland, United Kingdom.

If a subject changes investigational sites during the study, geographic region will be assigned according to the site at which the subject was randomized.

For all linear models that involve changes from baseline, the baseline value will also be used as a covariate.

7. HANDLING OF MISSING VALUES

For the clinical endpoints, not all subjects will have adjudicated and confirmed events. Subjects who do not experience any of the components of the primary endpoint will be censored on the date of last contact or 01November2016, whichever comes first. The date of last contact is defined as the date of death, if the date is not missing. Otherwise, the date of

last contact is defined as the study discontinuation date, the date of last visit, the date of last telephone contact, the onset date of the last AE, or the randomization date, whichever occurs last. The same censoring will be done for all other clinical endpoints and for time to discontinuation from study. For analyses in the SAS, the date of first dose will be substituted for the randomization date.

Missing values for the Digit Span Forward, Digit Span Backward, Digit Symbol - Coding, Trail Making A and Trail Making B tests and the HVLT will not be imputed. For the Digit Span Forward and the Digit Span Backward, if the maximum number of digits is not reached and the last result is not a zero, the value will be missing.

Missing values for the PHQ-2 and PHQ-9 will not be imputed. If at least one item is missing, the total scores will be missing.

For all other efficacy and safety endpoints, missing values will not be imputed; missing values will remain missing.

For longitudinal analyses of circulating biomarker endpoints, a mixed model repeated measures (MMRM) model will be used for the analyses. As a likelihood method, MMRM models are valid when the data are missing at random (MAR). All subjects with a non-missing baseline value and at least one non-missing post-baseline value will be included in these analyses. Subjects with a missing baseline value will not contribute to the analyses. Consistent with MMRM model fitting, no explicit imputation of missing assessments will be performed.

Percent changes from baseline to last post-baseline value in LDL-C will be analyzed by analysis of covariance (ANCOVA). As a likelihood method, ANCOVA is valid when the data are MAR. Subjects with a non-missing baseline value and at least one non-missing post-baseline value will be included in the analyses. Subjects with a missing baseline value or without a non-missing post-baseline value will not contribute to the analyses.

When forming subgroups, subjects with a missing value on the classifying variable will not be included in a subgroup.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical Methods

8.1.1. Analyses for Continuous Data

8.1.1.1. Time-to-Event Endpoints

Time-to-event endpoints will be summarized by treatment group with the number of subjects at risk, the number and percentage of subjects with events, and event rates with 95% confidence intervals. Event rates will be calculated as the number of events per 100 subject-years at risk. The 95% confidence intervals will be calculated using an exact Clopper-Pearson method for Poisson random variables.

For the primary endpoint and the key secondary composite endpoint of cardiovascular death, non-fatal MI and non-fatal stroke, the number and percent of each component that occurs first will be summarized by treatment group. Events which occur on the day of, or the day after, the earliest event will be considered, and the following hierarchy will be applied:

1. CV Death,
2. Non-fatal MI,
3. Non-fatal stroke,
4. Hospitalization for unstable angina (if applicable).

For the primary endpoint and the key secondary composite endpoint of cardiovascular death, non-fatal MI and non-fatal stroke, the reasons for censoring will be summarized by treatment group.

Log rank test

Time-to-event endpoints will be tested with a log rank test stratified by geographic region and complete statin intolerance, and the two sided p-value from the stratified log rank test will be reported.

The log rank test is a non-parametric test of the equality of two distributions that allows for stratification and incorporates information about censoring. Stratification permits different event rates in different strata. The log rank test assumes that the censoring function is independent of the hazard function.

Cox proportional hazards regression

A Cox proportional hazards regression model for each endpoint other than time to discontinuation from therapy will be fit in the FAS with treatment group as a covariate and geographic region and complete statin intolerance as stratification factors. For time to all-cause death and time to discontinuation from study therapy, the Cox proportional hazards model will be fit in the SAS with the same covariate and stratification factors. If the model fitting fails to converge, complete statin intolerance will be removed as a stratification factor. The hazard ratios with corresponding 95% confidence intervals will be reported.

Cox proportional hazards regression is a semiparametric method for comparing hazard functions under the assumption of proportional hazards. The methodology can include adjustments for covariates for important prognostic factors, produces a point and interval estimate of the treatment effect, and allows for different baseline hazard functions in different strata to reflect different event rates in different strata. The methodology assumes that the censoring function is independent of the hazard function.

The goodness of fit of the Cox proportional hazards regression models for the primary endpoint and key secondary composite endpoint of cardiovascular death, non-fatal MI or non-fatal stroke will be assessed by plots of the cumulative expected number of events

(estimated cumulative hazard rates) versus the observed cumulative number of events for each treatment arm within each stratum formed by the combination of the two stratification factors, using the method proposed by Arjas (1988). Departures from straight lines indicate a departure from proportional hazards, which may or may not affect the interpretability of the treatment effect.

Kaplan-Meier estimates

Kaplan-Meier estimates of time to first event will be plotted for the primary endpoint, the key composite secondary endpoint of cardiovascular death, non-fatal MI and non-fatal stroke, and for all-cause death.

Kaplan-Meier estimates are non-parametric estimates of the distribution of time to first event that incorporates information about censoring. The methodology assumes that the censoring function is independent of the hazard function.

Multiple imputations for Cox proportional hazards regression

The impact of informative censoring on the primary analysis will be evaluated through multiple imputations. Imputation will only be done for surviving subjects who discontinued from the study prematurely and did not have a primary endpoint event. Several imputation models for informative censoring will be used. The Weibull distribution will be used to generate the imputed values.

Multiple imputation is a flexible technique for incorporating the uncertainty in missing data that is ignored by single imputation methods, such as LOCF or worse case imputation. The imputation model need not be identical to the analysis model, which enables the exploration for different departures from MAR. It permits the use of standard software to be used to analyze each imputed data set under intention to treat. The results of the individual analyses are then combined into a single result using standard techniques (Rubin, 1987).

The Weibull distribution with shape parameter λ and scale parameter θ has a hazard function of the form $\lambda t^{\lambda-1}/\theta^{\lambda}$, which can accommodate both increasing and decreasing hazard functions.

8.1.1.2. Other Continuous Endpoints

Other continuous endpoints will be summarized by visit and treatment group using descriptive statistics, including the mean, standard deviation, median, first and third quartiles (Q1 and Q3, respectively), and minimum and maximum.

Mixed model for repeated measures

Percent changes from baseline in all lipid endpoints and hs-CRP, and nominal changes from baseline in LDL-C will be analyzed using a mixed model repeated measures (MMRM) model with fixed effects for treatment (categorical variable), scheduled visit time point (categorical variable), baseline value (continuous variable), interaction between baseline value and scheduled visit time point, interaction between treatment and scheduled visit time point, and geographic region (categorical variable), and complete statin intolerance (categorical variable).

Restricted Maximum Likelihood (REML) estimation will be used, and the default covariance structure will be unstructured . Due to the slow onset of accrual in this event-driven trial, there will be few observations at the last several time points. One or more of the last visits may be removed to ensure convergence of the model fitting. Also, the geographic region with the fewest observations may be combined with the next smallest region to ensure convergence of the model fitting. This may be done twice. If the model fails to converge with an unstructured covariance matrix, a spatial power covariance will be used. If the model fails to converge with this covariance structure, compound symmetry will be used. Kenward-Roger degrees of freedom will be used. Estimates of treatment group means and mean treatment group differences using observed margins at Week 14 and each other visit, corresponding 95% confidence intervals, and p-value for the mean differences will be provided. The least-squares mean treatment group estimates and 95% confidence intervals will be plotted longitudinally.

For observed values of selected highly skewed circulating biomarker endpoints that are measured at more than one post-randomization visit, the same model will be fit in the same manner for log-transformed data. The data will be log-transformed prior to calculating changes. Any zero values will be replaced with 0.0001 to enable taking the logarithm. The estimated treatment group means using observed margins and corresponding 95% confidence intervals from the analysis of the log-transformed data will be transformed to percent changes for reporting. The estimated treatment group differences will be transformed to the ratio of the mean percent changes and reported with transformed 95% confidence intervals along with untransformed p-values. The transformed estimated mean percent changes and corresponding transformed 95% confidence intervals will be plotted.

Changes from baseline in cognitive test results, including the Digit Span Forward score, Digit Span Backward Score, Digit Symbol - Coding score, Trail Making A score, Trail Making B score, HVLT Total Recall score, HVLT Delayed Recall Trial score, and the HVLT Recognition score will be analyzed using an MMRM model with fixed effects for treatment (categorical variable), scheduled visit time point (categorical variable), baseline value (continuous variable), interaction between baseline value and scheduled visit time point, and interaction between treatment and scheduled visit time point.

MMRM incorporates information from multiple visits and allows for covariate adjustment of the treatment effect so as to take important prognostic factors into account. Both of these increase the precision of the estimates and the power of the tests.

MMRM is a recommended approach for confirmatory trials (Mallinckrodt et al., 2008). The MMRM analysis is unbiased under the assumption that all missing data are either missing completely at random (MCAR) or missing at random (MAR) and is often robust to departures from MAR. Siddiqui, Hung, and O'Neill (2009) have shown that under various null and alternative hypotheses, the MMRM analysis estimates the true treatment group difference at the study endpoint with negligible bias even in the presence of a 1:1:1 mixture of MCAR, MAR, and missing not at random (MNAR) missing data mechanisms.

Analysis of Covariance

Continuous measurements assessed at a single post-randomization time point (i.e., the percent changes from baseline to last non-missing post-baseline measurement in LDL-C) will be analyzed using an analysis of covariance model with treatment group and baseline value as covariates and geographic region and complete statin intolerance as factors. Kenward-Roger degrees of freedom will be used. Least squares means with corresponding 95% confidence intervals, the least-squares mean differences and corresponding 95% confidence intervals, and p-values will be presented.

ANCOVA allows for covariate adjustment of the treatment effect, increasing the precision of the estimates and the power of the tests. As a likelihood method, ANCOVA provides unbiased estimates under the MAR assumption.

8.1.2. Analyses for Categorical Data

Categorical endpoints will be summarized by treatment group with the number and percent of subjects at risk in the treatment group within each category.

8.1.3. Analyses for Binary Endpoints

For the differences between treatment groups in the percent of subjects with each Tier-1 AE, an exact method for producing 95% confidence intervals and p-values will be used (Chan and Zhang, 1999). The method is based on inverting two one-sided tests at half the significance level each. As an exact method, it is appropriate for rare events.

For the differences between the treatment groups in the percent of subjects with each Tier-2 AE, an asymptotic method for producing 95% confidence intervals as presented by Miettinen and Nurminen (1985) will be used. As an asymptotic method, it is appropriate for events that are not rare.

8.2. Statistical Analyses

Efficacy analyses, unless otherwise indicated, will be performed according to the intention-to-treat (ITT) principle. Unless otherwise indicated, all efficacy analyses will be done in the FAS.

The Safety Analysis Set (SAS) … will be used for all safety analyses, unless otherwise specified.

8.2.1. Analysis of Primary Endpoint

The primary objective is to demonstrate superiority of bococizumab over placebo with respect to the primary endpoint, the time from randomization to the first adjudicated and confirmed occurrence of a major cardiovascular event, a composite endpoint which includes CV death, non-fatal MI, non-fatal stroke, and hospitalization for unstable angina needing urgent revascularization (as defined in Appendix 1.2). Subjects who discontinue randomized study medication prematurely and have not withdrawn consent will continue to be followed in the study to assess the occurrence of endpoints. Subjects who do not experience any of the components of the primary endpoint will be censored on the date of last contact or

01November2016, whichever comes first. The date of last contact is defined as the date of death, if the date is not missing. Otherwise, the date of last contact is defined as the study discontinuation date, the date of last visit, the date of last telephone contact, the onset date of the last AE, or the randomization date, whichever occurs last.

Primary analysis

The primary endpoint will be analyzed in the FAS using a log rank test stratified by geographic region and complete statin intolerance. The overall alpha level for this trial is 0.05. The two-sided alpha level for this log rank test will be adjusted for DMC reviews of all-cause death (see Section 3) and the interim analysis for clinical benefit (see Section 3) so that a two-sided alpha of 0.04898 will be used.

Analyses supportive of the primary analysis

A Cox proportional hazards model will be fit with the treatment group as a covariate and geographic region and complete statin intolerance as stratification factors. If the model fitting fails to converge, complete statin intolerance will be removed as a stratification factor. The hazard ratio will be presented along with a 95% confidence interval. The goodness of fit of the Cox proportional hazards regression model will be assessed by visual inspection of Arjas plots. Kaplan-Meier estimates of time to first major cardiovascular event will be plotted.

Sensitivity analyses

It is assumed that there will be a premature study discontinuation rate of 1% per year.

In order to aid in the assessment of the impact of premature discontinuation from the study on the primary analysis, time from randomization to premature discontinuation from the study will be analyzed. The p-value from a log rank test stratified by geographic region and complete statin intolerance will be presented. A Cox proportional hazards model will be fit with treatment group as a covariate and geographic region and complete statin intolerance as stratification factors. If the model fitting fails to converge, complete statin intolerance will be removed as a stratification factor. The hazard ratio and a 95% CI will be presented.

The impact of informative censoring on the primary analysis of the primary endpoint only will be evaluated through multiple imputations. Imputation will be done for all surviving subjects who were administratively censored and did not have a primary endpoint event. Separate imputation models will be fit for subjects on bococizumab and subjects on placebo. Imputation for both bococizumab and placebo subjects will use the placebo imputation model under the conservative assumption of switch-to-control risk following premature discontinuation from the study.

Weibull regression models will be fit separately by treatment group. Following Rubin (1987), a completed imputed data set will be generated in two stages. First, parameters for the Weibull model will be generated from a multivariate normal distribution with mean equal to the maximum likelihood estimates (MLE) of the parameters, and the variance-covariance matrix equal to the variance-covariance matrix of the MLE. Second, the Weibull

distribution based on the generated parameters will be used to simulate a time to event for each subject requiring imputation conditional on the time of censoring, appropriate treatment group, and baseline age, gender, body mass index, geographic region, baseline smoking status, complete statin intolerance, baseline history of MI, baseline history of coronary revascularization, baseline history of coronary heart disease, baseline history of diabetes (Type I or Type II), baseline history of heFH or LDL-C≥190 mg/dL, baseline history of stroke, baseline history of congestive heart failure and baseline history of chronic kidney disease.

If an imputed time to event would put the event date after 01November2016, the event will be censored and the imputed event time will be truncated so that the time to event is on 01November2016.

The completed data sets will be analyzed with the Cox proportional hazards model used for the primary analysis. This will be repeated for 100 data sets and the estimates of the log hazard ratio and their standard errors will be combined to form point estimates and confidence intervals using standard multiple imputation methodology (Rubin, 1987). The MI-based estimates and their confidence intervals will then be back-transformed to the hazard ratio scale. The estimated hazard ratio and a 95% confidence interval will be reported.

The reasons for censoring for the primary endpoint will be summarized by treatment group.

Supplemental analyses

Investigator-reported potential primary endpoint events will be listed.

The number and percent of each component of the primary endpoint that occurs first will be summarized by treatment group.

8.2.2. Analysis of Secondary Endpoints

The secondary endpoints for clinical outcomes include the times from randomization to the first occurrence of the adjudicated and confirmed clinical endpoints described below. Time to each of these endpoints will be tested in the FAS with a log rank test stratified by geographic region and complete statin intolerance. For the key secondary endpoints, a fixed sequence testing procedure using the sequence indicated in Section 4.2 will be used with a two-sided alpha of 0.04898. For other secondary endpoints, and for analyses of the key secondary endpoints other than the log rank test, a two-sided α=0.05 will be used. A Cox proportional hazards regression model for each endpoint will be fit with treatment group as a covariate and geographic region and complete statin intolerance as stratification factors. If the model fitting fails to converge, complete statin intolerance will be removed as a stratification factor. The hazard ratio and a 95% confidence interval will be reported. The goodness of fit of the Cox proportional hazards regression model for the composite endpoint of cardiovascular death, non-fatal MI or non-fatal stroke will be assessed by visual inspection of Arjas plots. For the key secondary composite endpoint of cardiovascular death, non-fatal MI or non-fatal stroke, and for all-cause death, Kaplan-Meier estimates of time to first event will be plotted.

The reasons for censoring the key secondary composite endpoint of cardiovascular death, non-fatal MI and non-fatal stroke will be summarized by treatment group.

Key secondary endpoints

The key secondary endpoints (as defined in Appendix 1.2) are the times from randomization to the first adjudicated and confirmed occurrence of:

- A composite endpoint of CV death, non-fatal MI, and non-fatal stroke;
- A composite endpoint of all-cause death, non-fatal MI, and non-fatal stroke, and hospitalization for unstable angina needing urgent revascularization;
- A composite endpoint of all-cause death, non-fatal MI and non-fatal stroke;
- Hospitalization for unstable angina needing urgent revascularization.

Other secondary clinical endpoints

Other clinical secondary endpoints (as defined in Appendix 1.2) are the times from randomization to first adjudicated and confirmed occurrence of:

- A composite endpoint of CV death, non-fatal MI, non-fatal stroke, and hospitalization for unstable angina;
- CV death;
- Any MI (fatal and non-fatal);
- Fatal MI;
- Non-fatal MI;
- Any stroke (fatal and non-fatal);
- Any stroke (fatal and non-fatal) of any etiology;
- Fatal stroke;
- Non-fatal stroke;
- Hospitalization for unstable angina;
- Hospitalization for congestive heart failure (CHF);
- Any coronary revascularization procedure;
- CABG;

- PCI;
- Any arterial revascularizations;
- All-cause death.

Adjudicated and confirmed causes of all-cause death will be tabulated by treatment group in the FAS. The tabulation will include the event rates and 95% confidence intervals. Causes of all-cause death will be classified according to the Adjudication Committee Charter.

The number and percent of the component that occurs first for the key secondary composite endpoints of cardiovascular death, non-fatal MI or non-fatal stroke will be summarized by treatment group.

Investigator reported potential secondary endpoint events will be listed.

Circulating biomarker secondary endpoints

Percent changes from baseline in all lipid endpoints and hs-CRP and nominal changes from baseline in LDL-C will be analyzed using a mixed model repeated measures (MMRM) model with fixed effects for treatment (categorical variable), scheduled visit time point (categorical variable), baseline value (continuous variable), interaction between baseline value and scheduled visit time point, interaction between treatment and scheduled visit time point, and geographic region (categorical variable), and complete statin intolerance (categorical variable). Observations will be assigned to visits using the analysis windows in Table 3.

Restricted Maximum Likelihood (REML) estimation will be used, and the default covariance structure will be unstructured. Due to the slow onset of accrual in this event-driven trial, there will be few observations at the last several time points. One or more of the last visits may be removed to ensure convergence of the model fitting. Also, the geographic region with the fewest observations may be combined with the next smallest region to ensure convergence of the model fitting. This may be done twice. If the model fails to converge with an unstructured covariance matrix, a spatial power covariance will be used. If the model fails to converge with this covariance structure, compound symmetry will be used. Kenward-Roger degrees of freedom will be used. Consistent with MMRM model fitting, no explicit imputation of missing assessments will be performed. Estimates of treatment group means and mean treatment group differences using observed margins at Week 14 and each other visit, corresponding 95% confidence intervals, and p-values for the mean differences will be provided. The least-squares mean treatment group estimates and 95% confidence intervals will be plotted longitudinally as indicated below with an asterisk (*).

For nominal changes from baseline in Lp(a), triglycerides and hs-CRP, the same model will be fit in the same manner for log-transformed data. The data will be log transformed prior to calculating changes. Any zero values will be replaced with 0.0001 to enable taking the logarithm. The estimated treatment group means using observed margins and corresponding 95% confidence intervals from the analysis of the log-transformed data will be transformed

to percent changes for reporting. The estimated treatment group differences will be transformed to the ratio of the mean percent changes and reported with transformed 95% confidence intervals along with untransformed p-values.

The percent changes from baseline to last non-missing post-baseline measurement in LDL-C will be analyzed using an analysis of covariance model with treatment group and baseline value as covariates and geographic region and complete statin intolerance as factors. Least squares means with corresponding 95% confidence intervals, the least-squares mean differences and corresponding 95% confidence intervals, and p-values will be presented. This analysis will not use analysis windows.

Circulating biomarker endpoints include (asterisk indicates that the LS-mean treatment group estimates and 95% CI will be plotted longitudinally):

- LDL-C*;
- Total cholesterol*;
- HDL-C;
- Triglycerides;
- Non-HDL-C*;
- VLDL-C;
- RLP-C;
- Apo-A-I;
- Apo-B*;
- Lp(a);
- hs-CRP.

8.2.3. Analysis of Safety Data

Safety will be assessed through adverse events (including Type 1 and 3 hypersensitivity reactions and injection site adverse events), serious adverse events, vital signs, examination results (physical and neurologic examinations and cognitive testing), 12-lead ECG recordings, and safety laboratory tests including hematology, blood chemistry studies (including liver function tests and creatine kinase tests), urinalysis studies, and ADA assessments. The Safety Analysis Set (SAS) includes all subjects who have received at least one dose of randomized study medication and will be used for all safety analyses, unless otherwise specified. All summaries of safety data will be descriptive only, unless indicated otherwise.

For summaries by visit, observations will be assigned to visits according to the analysis windows in Table 4.

Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) will be used to classify all AEs with respect to system organ class and preferred term. AEs, AEs leading to discontinuation from treatment, and SAEs after the first dose of study medication will be tabulated by treatment group. AEs after the first dose of study medication will be summarized without any requirement that the intensity increase after the first dose of study medication. Summaries will also be provided by severity. Summaries by the relationship to study therapy will be presented for AEs and SAEs only.

In addition, a 3-tier approach will be used. Tier 1 AEs are AEs of special clinical interest, including (but not limited to) Type 1 and Type 3 hypersensitivity reactions and injection site adverse events, and will be specified in the Safety Review Plan. For these events, the number and percentage of subjects with AEs with onset after the first dose of study medication, the risk difference versus placebo, the associated 95% confidence interval, and p-value will be reported. An exact method based on inverting two one-sided tests at half the significance level each (Chan and Zhang, 1999) will be used. The confidence intervals and p-values are not adjusted for multiplicity and are provided for screening purposes only. Tier 2 AEs are those that are not Tier 1, but are common, occurring in ≥5% of subjects in any treatment arm. For these events, the number and percentage of subjects with AEs with onset after the first dose of study medication, the risk difference versus placebo and the associated 95% confidence interval will be reported. For these events, the asymptotic method of Miettinen and Nurminen (1985) will be used. The confidence intervals are for estimation purposes only. All events are Tier 3 events and will be summarized as described above.

It should be recognized that this study is not designed to reliably demonstrate a causal relationship between the use of a pharmaceutical product and an adverse event or a group of adverse events. Adverse events in this study are generally not formally adjudicated procedures for the purpose of event classification. Safety analyses are generally considered as exploratory analyses intended to generate hypotheses for further investigation. The 3-tier approach is such an exploratory analysis.

AEs with onset after the first dose of study medication will be tabulated for subjects in subgroups identified in Section 5.4.2.2.

The number and percent of investigator-reported new diagnoses of diabetes with onset after the day of the first dose of study medication will be tabulated by treatment arm in subjects without a baseline history of diabetes.

Injection site adverse events with onset after the day of the first dose of study medication will also be summarized for the bococizumab subjects according to ADA and nAb status.

Vital signs

Observed values and changes from baseline in systolic BP, diastolic BP, PR, and weight will be tabulated by visit as continuous endpoints according to sponsor standards. Height, waist circumference, and temperature will be listed.

Anti-drug antibody (ADA) and neutralizing antibody (nAb)

The number of samples analyzed for ADA and nAb will be summarized.

ADA and nAb status will be summarized as categorical endpoints by visit and overall at the subject level. The numbers and percentages of ADA positive and nAb positive subjects classified according to timing of first result with respect to last dose of bococizumab (on treatment/off treatment) and characterization of ADA and nAb response (treatment induced/treatment boosted/indeterminate) using the definitions in Section 6.2 will be presented.

In addition, the summary of nAb will be repeated with two different denominators: number of non-missing ADA samples and number of ADA positive subjects.

Antibody titers for ADA positive subjects and nAb positive subjects will be summarized by visit as continuous endpoints. Boxplots of ADA titer and nAb titer over time will be presented.

Time to first positive ADA result and time to first positive nAb result will be summarized as continuous endpoints in the subgroups listed Section 5.4.2.5.

Clinical laboratory measurements

Observed values and changes from baseline in hematology, blood chemistry, and quantitative urinalysis parameters will be tabulated by visit as continuous endpoints according to sponsor standards. Mean changes from baseline will be plotted longitudinally for selected laboratory parameters including creatine kinase, hemoglobin, HbA1c and glucose, according to sponsor standards. Qualitative urinalysis parameters will be listed.

Observed value and change from baseline in HbA1c will be tabulated by visit as continuous endpoints for the subgroup identified in Section 5.4.2.3.

Laboratory shift tables for hemoglobin, CK, glucose, and HbA1c will summarize shifts from baseline status (below lower limit of normal, normal, above upper limit of normal) to post-baseline status at each scheduled measurement. Shifts from baseline to the smallest post-baseline and largest post-baseline measurement will also be tabulated. These shift tables will also be done for the subgroups identified in Section 5.4.2.3.

Observations of potential clinical concern after the first dose of study medication for hematology, blood chemistry and all urinalysis parameters will be tabulated by treatment group as categorical variables according to sponsor standards. Subjects meeting one or more criterion for Hy's Law will be tabulated by treatment group according to sponsor standards.

The maximum post-randomization total bilirubin value will be plotted against the maximum post-randomization alanine transaminase (ALT) value (Evaluation of Drug-Induced Serious Hepatotoxicity [eDISH] plot).

Electrocardiograms

12-lead ECGs will be locally read and the interpretations will be kept at the investigation sites as source documents. Any clinically significant ECG abnormalities will be reported as AEs. As a result of the discontinuation of the bococizumab clinical development program, ECG data will not be summarized or listed.

Physical and neurological exams

As a result of the discontinuation of the bococizumab clinical development program, physical examination findings will not be listed. Also, neurological exam findings will not be summarized or listed.

Cognitive Tests

Changes from baseline in cognitive test results, including the Digit Span Forward score, Digit Span Backward Score, Digit Symbol - Coding score, Trail Making A score, Trail Making B score, HVLT Total Recall score, HVLT Delayed Recall Trial score, and the HVLT Recognition score will be analyzed using an MMRM model. The fixed effects will be treatment group (categorical variable), scheduled visit time point (categorical variable), baseline value (continuous variable), interaction between baseline value and scheduled visit time point and interaction between treatment and scheduled visit time point. REML estimation will be used and the default covariance structure will be unstructured. Due to the slow onset of accrual in this event-driven trial, there will be few observations at the last several time points. One or more of the last visits may be removed to ensure convergence of the model fitting. If the model fitting fails to converge, compound symmetry will be used as the covariance structure. Consistent with MMRM model fitting, no explicit imputation of missing assessments will be performed. Estimates of treatment group means and mean treatment group differences at each visit along with corresponding 95% confidence intervals will be provided. The confidence intervals are for estimation purposes only.

Depression assessment

The PHQ-2 score and PHQ-9 score will be summarized by treatment group at baseline as categorical variables according to sponsor standards using the following categories: scores of 0, 1-4, 5-9, 10-14, 15-19, and 20-27, which represent no depression, minimal, mild, moderate, moderately severe, and severe depression, respectively.

8.2.4. Analyses of Other Endpoints

Demographics, alcohol and tobacco use, cardiovascular risk history, medical history, pretreatment and concomitant lipid lowering medications, protocol deviations, compliance with study medication, exposure to study medication, and reasons for discontinuation from treatment and the study will be tabulated by treatment group according to sponsor standards.

The number and percent of subjects with randomized study drug dosing adjustments will be tabulated by treatment group at each visit, as well as at any time during the study. The number and percent of subjects at each dose and regimen will be tabulated by treatment group at each visit. The number and percent of subjects who maintained the dose and regimen from the previous visit and the number who changed the dose and regimen from the previous visit will be tabulated by treatment group for each post-baseline visit after the first visit.

Time from first dose of randomized study medication to premature discontinuation of randomized study medication will be analyzed in the SAS. The p-value from a log rank test stratified by geographic region and complete statin intolerance will be presented. A Cox proportional hazards model will be fit with treatment group as a covariate and geographic region and complete statin intolerance as stratification factors. The hazard ratio and a 95% CI will be presented.

Medication errors and subcutaneous injection site reaction assessments will be listed.

8.2.4.1. Pharmacokinetic/Pharmacodynamic/Immunogenicity Reporting

Pharmacokinetic/Pharmacodynamic (PK/PD) endpoints include plasma bococizumab concentration. Bococizumab blood samples will be collected from all subjects, but only analyzed for bococizumab subjects, if needed, to help understand the PK, PD and safety profile of bococizumab in this study population.

Only plasma samples for all bococizumab-treated subjects will be tested for immunogenicity; plasma samples for placebo-treated subjects will not be tested. Only ADA positive samples will be tested for nAb.

8.2.4.1.1. Definitions

ADA and nAb titers are provided to Pfizer in log2 format and will be reported in the same manner. All titles and labels used in tables and figurers should clearly indicate titer (log2).

ADA Measurement Level Status:

An ADA measurement is considered as ADA positive if the ADA titer ≥6.23; otherwise if non-missing, the measurement is considered as ADA negative.

nAb Measurement Level Status:

An nAb measurement is considered as nAb positive if the nAb titer ≥1.58 (Assay #2). An nAb measurement is considered as nAb negative if the ADA measurement from that sample is negative or if the nAb titer < 1.58.

ADA Subject Level Status – For subject level classification of ADA (positive, negative):

A subject will be considered ADA positive if:

- The subject is ADA negative at baseline and has at least 1 ADA positive post-dose measurement, or
- The subject is missing the baseline ADA measurement and has at least 1 ADA positive post-dose measurement, or
- The subject is ADA positive at baseline and has a >1.58 unit increase in ADA titer from a positive baseline titer in at least 1 post-dose measurement.

A subject will be considered ADA negative if:

- The subject is ADA negative at baseline and all post-dose measurements are negative, or
- The subject is missing the baseline ADA measurement and all post-dose measurements are negative, or
- The subject is ADA positive at baseline but does not experience >1.58 unit increase in titer from a positive baseline titer in any post-dose measurement.

nAb Subject Level Status – For subject level classification for nAb (positive or negative):

A subject will be considered nAb positive if:

- The subject is nAb negative at baseline and has at least 1 nAb positive post-dose measurement, or
- The subject is missing the baseline nAb measurement and has at least 1 nAb positive post-dose measurement, or
- The subject is nAb positive at baseline and has a >1.58 unit increase in nAb titer from a positive baseline titer in at least 1 post-dose measurement.

A subject will be considered nAb negative if:

- The subject is ADA negative, or
- The subject is nAb negative at baseline and all post-dose measurements are nAb negative, or
- The subject is nAb positive at baseline but does not experience a >1.58 unit increase in titer from a positive baseline titer in any post-dose measurement.

ADA (nAb) Response Type:

ADA (nAb) positive subjects will further be classified according to the type of ADA (nAb) response (treatment induced/treatment boosted/indeterminate):

A subject will be considered as having treatment induced ADAs (nAbs) if:

- The subject is ADA (nAb) negative at baseline with at least 1 ADA (nAb) positive post-dose measurement, or
- The subject's baseline ADA (nAb) sample is missing with an ADA (nAb) negative post-dose measurement followed by at least 1 ADA (nAb) positive post-dose measurement.

A subject will be considered as having indeterminate ADAs (nAbs) if:

- The subject's baseline ADA (nAb) sample is missing with at least 1 ADA (nAb) positive post-dose measurement that was not preceded by an ADA (nAb) negative post-dose sample.

A subject will be considered as having treatment boosted ADAs (nAbs) if:

- The subject's baseline sample was ADA (nAb) positive with an increase in ADA (nAb) titer of >1.58 unit increase in titer from a positive baseline titer in at least 1 post-dose measurement.

Timing of ADA (nAb) Positive Measurement:

ADA (nAb) positive subjects will also be classified according to the timing of the ADA (nAb) positive measurement with respect to last dose of bococizumab (on treatment/off treatment):

A subject will be considered as having on-treatment ADAs (nAbs) if:

- The subject has any ADA (nAb) detected within ≤ 14 days after last dose.

A subject will be considered as having off-treatment ADAs (nAbs) if:

- The subject has their first ADA (nAb) detected >14 days after last dose.

Duration of ADA (nAb) Response:

ADA (nAb) positive subjects will also be classified according to the duration of ADA (nAb) response (indeterminate/persistent/transient) if the date of the first post-baseline measurement to the date of the last post-baseline measurement is at least 16 weeks:

A subject will be considered as having indeterminate duration of ADAs (nAbs) if:

- The subject has a positive ADA (or nAb) detected at the last post-baseline time point only

A subject will be considered as having persistent duration of ADA (nAb) if:

- The subject has positive ADA (or nAb) detected at all post-baseline samples assayed during any period of at least 16 weeks

A subject will be considered as having transient duration of ADA (nAb) if:

- The subject has been classified as neither persistent nor indeterminate

ADA (nAb) titer response:

Subjects will also be classified according to their maximum ADA (nAb) titer as

- ADA (nAb) negative,
- Maximum ADA (nAb) titer in the 1st tertile,
- Maximum ADA (nAb) titer in the 2nd tertile, or
- Maximum ADA (nAb) titer in the 3rd tertile.

8.2.4.2. Summarization of ADA and nAb Results

1. The number of samples analyzed for ADA and nAb will be summarized.

2. ADA and nAb results will be summarized as categorical endpoints by visit and overall incidence at the subject level. The numbers and percentages of ADA positive and nAb positive subjects will be classified according to (1) timing of result with respect to bococizumab dosing (on treatment/off treatment), (2) characterization of ADA and nAb response (treatment induced/treatment boosted/indeterminate), and (3) duration of ADA and nAb response (indeterminate/persistent/transient) using the definitions in Section 8.2.4.1.1 will be presented. The summary of nAb status will be performed with two different denominators: number of subjects with non-missing ADA samples and number of ADA positive subjects.

3. ADA titers for ADA positive subjects and nAb titers for nAb positive subjects will be summarized by visit as continuous endpoints. Boxplots of ADA titer and nAb titer over time will be presented for ADA positive subjects and nAb positive subjects, respectively.

4. Time to first positive ADA result and time to first positive nAb result will be summarized as continuous endpoints in subjects who are ADA positive or nAb positive, respectively.

A listing will also be provided that details subject identifier, treatment group, ADA titer, ADA status, nAb titer, nAb status, ADA induction type, nAb induction type, duration of ADA response, duration of nAb response, relative days to first positive ADA detection, relative days to first positive nAb detection, and day on study.

8.2.4.3. Summarization of Pharmacokinetics/Pharmacodynamics Results

The following analyses will be performed for plasma bococizumab concentrations, and LDL-C response. The windows from Table 3 in Appendix 1.1 will be used.

1. Listings of all plasma bococizumab concentrations by subject and visit will be provided.

2. Descriptive summaries of observed plasma bococizumab concentrations over time will be provided. Summary statistics will include arithmetic mean, standard deviation, % coefficient of variation, median, minimum, and maximum. The number of concentrations above the lower limit of quantification (NALQ) may also be provided. Observations below the lower limit of quantification will be imputed as zero.

3. Mean (±SD) observed bococizumab concentration will be plotted over time.

The following summaries will be provided using only observations meeting the following conditions (without missed doses and prior to dose adjustment):

- Sample collection date minus the previous injection date is between 1 and 21 days.

- No dose adjustments have occurred prior to sample collection.

1. For plasma bococizumab concentrations, the descriptive summaries, longitudinal mean (±SD) plots will be repeated.

2. For plasma bococizumab concentrations and LDL-C, the descriptive summaries will be repeated by ADA status and by nAb status. For plasma bococizumab concentrations only, box plots by ADA status and nAb status will be presented. For LDL-C, box plots of percent change from baseline will be repeated by ADA status and by nAb status.

3. For plasma bococizumab concentrations and LDL-C, the descriptive summaries will be repeated by duration of ADA response (indeterminate/persistent/transient) and by duration of nAb response (indeterminate/persistent/transient). For LDL-C, and box plots of percent change from baseline will be repeated by duration of ADA response (indeterminate/persistent/transient) and by duration of nAb response (indeterminate/persistent/transient).

4. For plasma bococizumab concentrations and LDL-C, the descriptive summaries will be repeated by pre-existing ADA status (with pre-existing ADAs, without pre-existing ADAs).

5. For plasma bococizumab concentrations and LDL-C, the descriptive summaries will be repeated by ADA (nAb) titer response (ADA (nAb) negative, ADA (nAb)1st tertile, ADA (nAb) 2nd tertile, ADA (nAb) 3rd tertile.

A comprehensive listing of plasma bococizumab concentration, LDL-C, ADA status, ADA titer, nAb status, and nAb titer will be provided by subject and visit for ADA positive subjects.

8.2.4.4. Adverse Events, Serious Adverse Events, and Deaths

Adverse events and serious adverse events will be summarized by ADA status (positive, negative) and by nAb status (positive, negative).

8.2.4.5. Injection Site Adverse Events

Injection site adverse events will be summarized by ADA status (positive, negative) and by nAb status (positive, negative). The higher level term of "injection site reactions" will be used to identify the adverse events.

8.2.4.6. Clinical Laboratory Measurements

Liver function test elevations will be summarized by ADA status and by nAb status. Additionally, the maximum post-randomization total bilirubin value will be plotted against the maximum post-randomization alanine transaminase (ALT) value by ADA status (positive, negative) and by nAb status (positive, negative).

Incidence of creatinine elevations will be summarized by ADA status (positive, negative) without regard to baseline abnormality, with normal baseline, and with abnormal baseline.

8.2.4.7. Outcomes Research Endpoints

EQ-5D

As a result of the discontinuation of the bococizumab clinical development program, EQ-5D will not be summarized as described in the protocol or listed.

Health Care Resource Utilization

As a result of the discontinuation of the bococizumab clinical development program, health care resource utilization (HCRU) endpoints will not be summarized or analyzed as described in the protocol or listed.

8.2.5. Summary of Efficacy Analyses

Table 2. Tabular Summary of Efficacy Analyses

Endpoint	Analysis Set	Statistical Method	Covariates/ Strata	Objective
Time to major cardiovascular event	FAS	Log rank test	Geographic region, complete statin intolerance	Primary analysis
		Cox proportional hazards regression	Treatment group/ geographic region, complete statin intolerance*	Decision on primary objective
		Plot of Kaplan-Meier Estimates		Support of primary objective
		Arjas plot	Geographic region × complete statin intolerance	
Time to premature discontinuation from the study	FAS	Log rank test	Geographic region, complete statin intolerance	Impact of premature discontinuation from the study
		Cox proportional hazards regression	Treatment group/ geographic region, complete statin intolerance*	
Time to major cardiovascular event	FAS	Multiple imputations for Cox proportional hazards model	Cox model: Treatment group/geographic region, complete statin intolerance* Imputation model: Treatment group set equal to placebo for all subjects, age, gender, BMI, geographic region, complete statin intolerance, baseline smoking status, baseline history of MI, baseline history of coronary revascularization, baseline history of coronary heart disease, baseline history of diabetes, baseline history of heFH/LDL-C≥190 ml/dL, baseline history of stroke, baseline history of congestive heart failure baseline history of chronic kidney disease.	Impact of informative censoring under the switch-to-control assumption

Endpoint	Analysis Set	Statistical Method	Covariates/ Strata	Objective
Time to CV death, non-fatal MI or non-fatal stroke	FAS	Log rank test	geographic region, complete statin intolerance	First key secondary endpoint; tested only if the primary objective is met
		Cox proportional hazards regression	Treatment group/ geographic region, complete statin intolerance*	Decision on secondary objective
		Plot of Kaplan-Meier Estimates		Support of key secondary objective
		Arjas plot	Geographic region × complete statin intolerance	
Time to all-cause death, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina needing urgent revascularization	FAS	Log rank test	Geographic region, complete statin intolerance	Second key secondary endpoint; tested only if the primary objective is met
		Cox proportional hazards regression	Treatment group/ geographic region, complete statin intolerance*	Decision on secondary objective
Time to all-cause death, non-fatal MI, or non-fatal stroke	FAS	Log rank test	Geographic region, complete statin intolerance	Third key secondary endpoint; tested only if the primary objective is met
		Cox proportional hazards regression	Treatment group/ geographic region, complete statin intolerance*	Decision on secondary objective
Time to hospitalization for unstable angina needing urgent revascularization	FAS	Log rank test	Geographic region, complete statin intolerance	Fourth key secondary endpoint; tested only if the primary objective is met
		Cox proportional hazards regression	Treatment group/ geographic region, complete statin intolerance*	Decision on secondary objective
Time to CV death, non-fatal MI, non-fatal stroke, or hospitalization for	FAS	Log rank test	Geographic region, complete statin intolerance	Other secondary endpoint

Endpoint	Analysis Set	Statistical Method	Covariates/ Strata	Objective
unstable angina				
		Cox proportional hazards regression	Treatment group/ geographic region, complete statin intolerance*	Other secondary objective
Time to CV death	FAS	Log rank test	Geographic region, complete statin intolerance	Other secondary endpoint
		Cox proportional hazards regression	Treatment group/ geographic region, complete statin intolerance*	Other secondary objective
Time to any MI (fatal and non-fatal)	FAS	Log rank test	Geographic region, complete statin intolerance	Other secondary endpoint
		Cox proportional hazards regression	Treatment group/ geographic region, complete statin intolerance*	Other secondary objective
Time to fatal MI	FAS	Log rank test	Geographic region, complete statin intolerance	Other secondary endpoint
		Cox proportional hazards regression	Treatment group/ geographic region, complete statin intolerance*	Other secondary objective
Time to non-fatal MI	FAS	Log rank test	Geographic region, complete statin intolerance	Other secondary endpoint
		Cox proportional hazards regression	Treatment group/ geographic region, complete statin intolerance*	Other secondary objective
Time to any stroke (fatal and non-fatal)	FAS	Log rank test	Geographic region, complete statin intolerance	Other secondary endpoint
		Cox proportional hazards regression	Treatment group/ geographic region, complete statin intolerance*	Other secondary objective
Time to any stroke (fatal and non-fatal) of any etiology	FAS	Log rank test	Geographic region, complete statin intolerance	Other secondary endpoint
		Cox proportional hazards regression	Treatment group/ geographic region, complete statin intolerance*	Other secondary objective

Endpoint	Analysis Set	Statistical Method	Covariates/ Strata	Objective
Time to fatal stroke	FAS	Log rank test	Geographic region, complete statin intolerance	Other secondary endpoint
		Cox proportional hazards regression	Treatment group/ geographic region, complete statin intolerance*	Other secondary objective
Time to non-fatal stroke	FAS	Log rank test	Geographic region, complete statin intolerance	Other secondary endpoint
		Cox proportional hazards regression	Treatment group/ geographic region, complete statin intolerance*	Other secondary objective
Time to hospitalization for unstable angina	FAS	Log rank test	Geographic region, complete statin intolerance	Other secondary endpoint
		Cox proportional hazards regression	Treatment group/ geographic region, complete statin intolerance*	Other secondary objective
Time to hospitalization for congestive heart failure	FAS	Log rank test	Geographic region, complete statin intolerance	Other secondary endpoint
		Cox proportional hazards regression	Treatment group/ geographic region, complete statin intolerance*	Other secondary objective
Time to any coronary revascularization procedure	FAS	Log rank test	Geographic region, complete statin intolerance	Other secondary endpoint
		Cox proportional hazards regression	Treatment group/ geographic region, complete statin intolerance*	Other secondary objective
Time to CABG	FAS	Log rank test	Geographic region, complete statin intolerance	Other secondary endpoint
		Cox proportional hazards regression	Treatment group/ geographic region, complete statin intolerance*	Other secondary objective
Time to PCI	FAS	Log rank test	Geographic region, complete statin intolerance	Other secondary endpoint
		Cox proportional hazards regression	Treatment group/ geographic region, complete statin intolerance*	Other secondary objective

Endpoint	Analysis Set	Statistical Method	Covariates/ Strata	Objective
Time to any arterial revascularization	FAS	Log rank test	Geographic region, complete statin intolerance	Other secondary endpoint
		Cox proportional hazards regression	Treatment group/ geographic region, complete statin intolerance*	Other secondary objective
Time to all-cause death	FAS	Log rank test	Geographic region, complete statin intolerance	Other secondary endpoint
		Cox proportional hazards regression	Treatment group/ geographic region, complete statin intolerance*	Other secondary objective
		Plot of Kaplan-Meier Estimates		Support of other secondary objective
Reasons for all-cause death	FAS		Event rates and 95% CIs	
LDL-C: percent change from baseline to each post-randomization visit	FAS	MMRM	Treatment group, scheduled visit (categorical), baseline value (continuous), treatment × scheduled visit interaction, baseline value × scheduled visit interaction, geographic region, complete statin intolerance	Other secondary endpoint
		Plot of LS-Mean percent changes from baseline and 95% CI		
LDL-C: nominal change from baseline to each post-randomization visit	FAS	MMRM	Treatment group, scheduled visit (categorical), baseline value (continuous), treatment × scheduled visit interaction, baseline value × scheduled visit interaction, geographic region, complete statin intolerance	Other secondary objective
LDL-C: percent change from baseline to last post-baseline measurement	FAS	ANCOVA	Treatment group, baseline value, geographic region, complete statin intolerance	Supportive of other secondary objective

Endpoint	Analysis Set	Statistical Method	Covariates/ Strata	Objective
Total cholesterol: percent change from baseline to each post-randomization visit	FAS	MMRM	Treatment group, scheduled visit (categorical), baseline value (continuous), treatment × scheduled visit interaction, baseline value × scheduled visit interaction, geographic region, complete statin intolerance	Other secondary endpoint
		Plot of LS-Mean percent changes from baseline and 95% CI		
HDL-C: percent change from baseline to each post-randomization visit	FAS	MMRM	Treatment group, scheduled visit (categorical), baseline value (continuous), treatment × scheduled visit interaction, baseline value × scheduled visit interaction, geographic region, complete statin intolerance	
Triglycerides: nominal change from baseline to each post-randomization visit for log-transformed value	FAS	MMRM	Treatment group, scheduled visit (categorical), baseline value (continuous), treatment × scheduled visit interaction, baseline value × scheduled visit interaction, geographic region, complete statin intolerance	Other secondary objective
Non-HDL-C: percent change from baseline to each post-randomization visit	FAS	MMRM	Treatment group, scheduled visit (categorical), baseline value (continuous), treatment × scheduled visit interaction, baseline value × scheduled visit interaction, geographic region, complete statin intolerance	Other secondary endpoint
		Plot of LS-Mean percent changes from baseline and 95% CI		

Endpoint	Analysis Set	Statistical Method	Covariates/ Strata	Objective
VLDL-C: percent change from baseline to each post-randomization visit	FAS	MMRM	Treatment group, scheduled visit (categorical), baseline value (continuous), treatment × scheduled visit interaction, baseline value × scheduled visit interaction, geographic region, complete statin intolerance	Other secondary endpoint
RLP-C: percent change from baseline to each post-randomization visit	FAS	MMRM	Treatment group, scheduled visit (categorical), baseline value (continuous), treatment × scheduled visit interaction, baseline value × scheduled visit interaction, geographic region, complete statin intolerance	Other secondary endpoint
Apo-A-I: percent change from baseline to each post-randomization visit	FAS	MMRM	Treatment group, scheduled visit (categorical), baseline value (continuous), treatment × scheduled visit interaction, baseline value × scheduled visit interaction, geographic region, complete statin intolerance	Other secondary endpoint
Apo-B: percent change from baseline to each post-randomization visit	FAS	MMRM	Treatment group, scheduled visit (categorical), baseline value (continuous), treatment × scheduled visit interaction, baseline value × scheduled visit interaction, geographic region, complete statin intolerance	Other secondary endpoint
		Plot of LS-Mean percent changes from baseline and 95% CI		
Lp(a): nominal change	FAS	MMRM	Treatment group, scheduled visit	Other secondary objective

Endpoint	Analysis Set	Statistical Method	Covariates/ Strata	Objective
from baseline to each post-randomization visit in log-transformed value			(categorical), baseline value (continuous), treatment × scheduled visit interaction, baseline value × scheduled visit interaction, geographic region, complete statin intolerance	
hs-CRP: nominal change from baseline to each post-randomization visit for log-transformed value	FAS	MMRM	Treatment group, scheduled visit (categorical), baseline value (continuous), treatment × scheduled visit interaction, baseline value × scheduled visit interaction, geographic region, complete statin intolerance	Other secondary objective
* If model fitting of the Cox proportional hazards regression model fails to converge, complete statin intolerance will be removed as a stratification factor. FAS = Full Analysis Set SAS = Safety Analysis Set MMRM = Mixed Model Repeated Measures CI = confidence interval ANCOVA = analysis of covariance				

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10. APPENDICES

Appendix 1. DATA DERIVATION DETAILS

Appendix 1.1. Definition and Use of Analysis Windows in Reporting

The MMRM models for circulating biomarkers and cognitive assessments, and summaries of safety variables (including depression assessments) will require the assignment of observations to scheduled visits, i.e., analysis windows. Safety summaries and analyses will use a different set of windows than summaries and analyses of circulating biomarkers. For safety analyses, the windows will be based on the subject's date of first dose on randomized study medication; the first day of dosing is Day 1. For other summaries and analyses, the day of randomization is Day 1. For both safety and efficacy analyses, if two or more measurements fall in an analysis window, the measurement closest to the target day will be used. If two measurements are equidistant before and after the target day, the earlier measurement will be used. If there are multiple observations on the same date, the mean of the observations will be used to represent the measurements of that date.

The following table contains the analysis windows for circulating biomarkers and outcomes research variables.

Table 3. Analysis Windows for Circulating Biomarkers and PK/PD

Visit Label	Target Day	Randomization Days*
Visit 6: Week 4 (Month 1)	29	19-39
Visit 7: Week 8 (Month 2)	57	47-67
Visit 8: Week 14 (Month 3)	99	89-109
Visit 9: Week 26 (Month 6)	183	153-213
Visit 10: Week 40 (Month 9)	281	251-311
Visit 11: Week 52 (Month 12)	365	335-395
Visit 12: Week 70 (Month 16)	491	461-521
Visit 13: Week 86 (Month 20)	603	573-633
Visit 14: Week 104 (Month 24)	729	699-759
Visit 15: Week 122 (Month 28)	855	825-885
Visit 16: Week 140 (Month 32)	981	951-1011
Visit 17: Week 156 (Month 36)	1093	1063-1123
Visit 18: Week 174 (Month 40)	1219	1189-1249
Visit 19: Week 192 (Month 44)	1345	1315-1375
Visit 20: Week 208 (Month 48)	1457	1427-1487

*Randomization days = measurement date – Day 1 (randomization date) + 1

The safety windows will touch, so that all post-baseline safety observations will fall in a window. The following table contains the windows for safety analyses.

Table 4. Analysis Windows for Safety Including Cognitive Assessments

Visit Label	Target Day	Study Days*
Visit 6: Week 4 (Month 1)	29	2-42
Visit 7: Week 8 (Month 2)	57	43-77
Visit 8: Week 14 (Month 3)	99	78-140
Visit 9: Week 26 (Month 6)	183	141-231
Visit 10: Week 40 (Month 9)	281	232-322
Visit 11: Week 52 (Month 12)	365	323-427
Visit 12: Week 70 (Month 16)	491	428-546
Visit 13: Week 86 (Month 20)	603	547-665
Visit 14: Week 104 (Month 24)	729	666-791
Visit 15: Week 122 (Month 28)	855	792-917
Visit 16: Week 140 (Month 32)	981	918-1036
Visit 17: Week 156 (Month 36)	1093	1037-1155
Visit 18: Week 174 (Month 40)	1219	1156-1281
Visit 19: Week 192 (Month 44)	1345	1282-1400
Visit 20: Week 208 (Month 48)	1457	1401-Open ended

* Study days = measurement date – Day 1 (date of first dose of randomized study medication) + 1

Appendix 1.2. Further Definition of Endpoints

The specific criteria for clinical endpoint definitions outlined below, and the source documentation necessary to qualify for the adjudication and confirmation of a clinical endpoint event, are described in the Adjudication Committee Charter.

Cardiovascular Death

Cardiovascular death is defined as sudden cardiac death, fatal myocardial infarction (MI), death due to heart failure, death due to stroke (fatal ischemic stroke or fatal stroke of undetermined etiology), or death due to other cardiovascular causes.

Myocardial Infarction

The MI categories contributing to the MI endpoints for this study are those defined in the Third Universal Definition of Myocardial Infarction, as Type 1 (plaque rupture with thrombus), Type 2, (MI due to an ischemic imbalance, ie, an increase in oxygen demand or a decrease in oxygen supply resulting in cardiac injury), Type 3 (MI resulting in cardiac death, when symptoms of ischemia, or ECG evidence of ischemia are present, but death occurred before biomarkers could be obtained), Type 4 (MI related to PCI [Type 4a], stent thrombosis [Type 4b], stent restenosis [Type 4c]), or Type 5 (MI related to CABG), consistent with the draft endpoint definitions of the Standardized Data Collection for Cardiovascular Trials Initiative.

Hospitalization for unstable angina needing urgent revascularization

Hospitalization for unstable angina needing urgent revascularization is defined as an unscheduled hospitalization for unstable angina in a subject needing urgent coronary revascularization. The *criteria and documentation requirements for this endpoint are defined by the Adjudication Committee Charter and the draft endpoint definitions of the Standardized Data Collection for Cardiovascular Trials Initiative.*

Coronary revascularization

Coronary revascularization for the purpose of this study comprises procedures of coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI).

Stroke

For the purposes of this study, any stroke is defined as strokes of ischemic or undetermined etiology, including strokes of ischemic etiology that have had subsequent hemorrhagic transformation. Stroke of any etiology will include all of the above and hemorrhagic stroke. Hemorrhagic stroke events will also be reported as a safety endpoint.

Arterial revascularizations

For the purposes of this study, arterial revascularizations will comprise any peripheral artery revascularizations of any type.

Hospitalization for unstable angina

Hospitalization for unstable angina must be qualified as being with or without urgent revascularization. The criteria for the diagnosis of hospitalization for unstable angina include clinical symptoms and ECG or imaging evidence of ischemia, in the absence of evidence of permanent myocardial injury.

Hospitalization for congestive heart failure

The criteria for hospitalization for congestive heart failure include a constellation of symptoms, physical examination findings, laboratory evidence, of heart failure, as well as the institution of heart failure therapy.

Appendix 2. SCHEDULE OF ACTIVITIES

Visit Schedule/Flowchart:

Study Period	***Pre***	***Scr***	***Run in period***			***R***																
VISITS[1]	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*	*19*	*20*	*EDC*[28]*/ EOS*[29]
Week[1]	*NA*	*NA*	*-6*	*-4*	*-2*	*0*	*4*	*8*	*14*	*26*	*40*	*52*	*70*	*86*	*104*	*122*	*140*	*156*	*174*	*192*	*208*	
Informed Consents[1]	*X*	*X*																				
Contact IRT[2]	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*
Med hx/Demog.		*X*																				
Inclusion/exclusion criteria		*X*	*X*		*X*	*X*																
Counseling[3]		*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*
Vital signs,T, BP/PR[4]		*X*				*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*
Physical Exam[5]						*X*						*X*			*X*			*X*			*X*	*X*
Cognitive assessment[6]						*X*						*X*			*X*			*X*			*X*	*X*
12 Lead ECG[7]						*X*						*X*			*X*			*X*			*X*	*X*
Laboratory																						
Chemistry Group[8]		*X*				*X*			*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*
Liver function[9]		*X*				*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*
Creatine kinase[10]		*X*				*X*						*X*			*X*			*X*			*X*	*X*
ADA/PK/PCSK9[11]				*X*		*X*	*X*		*X*		*X*		*X*		*X*			*X*			*X*	*X*
Hematology[12]		*X*				*X*						*X*			*X*			*X*			*X*	*X*
Urinalysis[13]		*X*				*X*						*X*			*X*			*X*			*X*	*X*
Pregnancy Test[14]		*X*				*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*
Biospecimens[15]						*X*						*X*										
Lipid Profile[16]	*X*			*X*		*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	
Special Studies[17]		*X*				*X*			*X*			*X*										
HbA1c[18]						*X*						*X*										*X*
Hepatitis[19]		*X*																				*X*
Dispense IP[20]			*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	
Injection in clinic[20]			*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	
Con Med Check[21]		*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*
Adverse Event/SAE Collection[22]	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*
Potential Endpoint Assessment[22]						*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*
Compliance Check[23]			*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*
Contraception Chk.[24]		*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*
EQ-5D assessment[25]						*X*			*X*	*X*		*X*			*X*			*X*			*X*	*X*
PHQ-2/PHQ-9[26]						*X*						*X*			*X*			*X*			*X*	*X*
HCRU assessment[27]							*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*

Key: Pre=pre-screening visit; *Scr* ***= screening; R = randomization; EDC = early discontinuation of investigational product; EOS = End of Study/Study Completion; IRT= Interactive Response Technology System; T = temperature; BP=blood pressure; PR=pulse rate; hx= history; ECG=electrocardiogram; ADA/PK/PCSK9=anti-drug antibody/pharmacokinetic; and PCSK9 sampling; IP=investigational product; Con Med=concomitant medication; EQ-5D= EuroQol Group quality of life assessment; HCRU=health care resource utilization; PHQ-2/PHQ-9 = patient health questionnaire for depression; Chk.= check.***

Footnotes:

1 ***Visit Schedule****:*

Visits should be scheduled by the numbered weeks above.

Subjects should be fasting for at least 10 hours prior to all visits during which fasting blood samples will be collected, with the following exceptions. Unscheduled assessments limited to measures of creatine kinase (CK), liver function tests (including alanine amino transferase [ALT], aspartate amino transferase [AST], alkaline phosphatase, and total and direct bilirubin), hepatitis C polymerase chain reaction (PCR), or pregnancy testing, do not require fasting. At Visit 0, where required, or where pre-clinic visit fasting is not the general practice, subjects will need to return for Visit 0 blood sampling, at a subsequent unscheduled visit, so that 10 hour fasting only takes place after informed consent has been obtained. Subjects are permitted to take concomitant medications, on the morning of a visit, taken as prescribed with water. When a subject has missed a scheduled visit, every attempt should be made to contact him/her, to reschedule the visit, by phone, e-mail, text message, and if necessary, by letter and/or certified mail, in instances where the subject is not responsive to contact attempts.

Informed consent:

The subject should be consented prior to any pre-screening procedures being completed at Visit 0. A study specific informed consent will be obtained at Visit 1, the screening visit if not obtained previously. Some study sites may have alternative informed consent requirements as specified by their institutional review board (IRB)/ethics committee (EC), but the general principle is that informed consent must have been obtained prior to the conduct of any study procedure.

Visit 0, Pre-screening visit:

A pre-screening visit will be conducted to collect data which will help the investigator ascertain if a potential subject qualifies for this study. The subject should be consented prior to any pre-screening procedures being completed at Visit 0. At this visit, subjects will have consented to have had lipid levels assessed and provide medical records for review, only, so as to determine if the subject qualifies for this study. At Visit 0, where required, or where pre-clinic visit fasting is not the general practice, subjects will need to return for Visit 0 blood sampling, at a subsequent unscheduled visit, so that 10 hour fasting only takes place after informed consent has been obtained. No data for the subject will be recorded in the pre-randomization visit case report form (CRF) until the cholesterol laboratory results are received, unless the subject experiences an AE or SAE.

The time interval between the Pre-screening Visit (Visit 0) and the Screening Visit (Visit 1) is a maximum of 30 days.

Visit 1:

Visit 1, the screening visit, should be scheduled after the pre-screening data (lipid results and medical records) are available to ascertain eligibility for the study. Study-specific informed consent should be obtained at Visit 1 before all other procedures. Starting at Visit 1, study centers should attempt to schedule each subject's visits at the same time of day, and day of the week for that subject, if possible. Visits should be scheduled based on the week in the Schedule of Activity Table and coordinated with the subject's dosing schedule, so that the visit day is coordinated with a subject's relevant dose day, if possible. Starting at Visit 5 (randomization/baseline visit), and all subsequent visits, if a visit coincides with a scheduled injection of investigational product (IP), the injection should be performed after all other study procedures have been completed.

***Lipid, ADA, PK, and PCSK9 testing requirements after randomization**:*

Lipid (direct LDL-C and lipid panel), ADA, PK, and PCSK9 testing, after randomization, when required, should be scheduled ***no sooner than 10 days after the subject's prior dose****, even if this requires an unscheduled visit. If a subject has a visit that is scheduled less than 10 days after the last dose, the visit procedures may take place, but lipid, ADA, PK, and PCSK9 testing should be postponed and performed at the earliest possible time, at an unscheduled visit, no sooner than 10 days after the subject's last dose. A lipid profile will not be collected at EDC/EOS visits. ADA, PK, and PCSK9 samples will be collected at EDC/EOS visits.*

Visit windows:

The run-in period is of up to 6 weeks duration, starting at Visit 2, so that there is some flexibility for scheduling the subjects. The run-in visits should take place no less than 7 and no more than 14 days apart. The run-in period continues until Visit 5, randomization. Visit 5 should be scheduled no more than 14 days after Visit 4, the final run-in visit.

After Visit 5, all visits will have a visit window ±14 days, except for Visits 8 (the Week 14 visit), 11 (the Week 52 visit), both which will have visit window of ±3 days, and EDC/EOS visits, which will not have visit windows. It will be important to ascertain that the lipid level testing requirement stated above, is met.

Dosing windows:

After randomization, IP dosing windows are 1 day before or up to 4 days after the scheduled dosing date. If more than 4 days after the scheduled day have passed, the subject should skip the dose and resume dosing following the dosing schedule provided by site personnel for the next injection.

***Visit 2,** start of run-in: Run-in Visit 2 can occur up to 14 days after Visit 1, depending upon the availability of Visit 1 lab results, additional medical records, if they are needed, and the schedule of the subject and clinical site. At Run-in Visit 2, the initiation of the run-in period, the subject will be shown how to self-inject IP (placebo). Only during the run-in period (Visits 2, 3, and 4), subjects will be seen up to two weeks apart (0.5 month periods), to ascertain the subjects' ability to self-inject IP. The other run-in procedures specified in this Schedule of Activities will be adhered to.*

***Visit sequences:** After Visit 5 (Week 0) subjects will be seen at Visit 6 (Week 4), Visit 7 (Week 8), Visit 8 (Week 14), Visit 9 (Week 26), Visit 10 (Week 40), and Visit 11 (Week 52). After Visit 11, subjects will be seen as indicated in the Schedule of Activities. Subjects who discontinue IP early (EDC), will be encouraged to be followed, according to the visit schedule and activities, until study completion (EOS). If the study is not completed by Visit 20, visits will continue every 4 months in accordance with the Schedule of Activities for annual (Visits 11, 14, 17, 20) and interim visits (eg, Visits 12, 13, 15, 16, 18, and 19) until study completion (EOS). The study may end sooner than Visit 20, if the primary endpoint event accrual rate is faster than anticipated or the trial is terminated for other reasons. Subjects who have had an IP dose frequency modification to dosing every 4 weeks, will need to have their visit frequency increased to every 8 weeks, approximately, for the purposes of direct LDL-C measurement and an assessment for adverse events; both serious and non-serious (*Protocol *Section 6.4.5). If the per-protocol scheduled visit falls within the 8 week window, the scheduled visit will reset the scheduling of the next 8 week direct LDL-C measurement visits.*

2 *IRT. The subjects' visits will be registered at Visit 0 and every visit thereafter, unless they have discontinued treatment with IP.*

3 *Counseling: drug self-injection counseling and therapeutic lifestyle change counseling (diet, exercise) as per NCEP-ATP III or ESC/EAS guidelines or per local medical practice.*

4 *Vital Signs: Vital signs (temperature, pulse rate and blood pressure) shall be recorded at each visit, except for Visits 2, 3, and 4 (unless clinically indicated), as described in* Protocol *Section 7.2.3.1.*

5 *Physical Exam: Periodic examinations, including a physical exam and basic neurology exam will be performed at baseline (Visit 5), annually, and at the EDC or EOS visit. The physical exam will include the measurement of weight, height and waist circumference at Visit 5 (*Protocol *Section 7.2.3.2.1). Waist circumference will also be measured at EOS or EDC. Whenever a physical exam is performed, it must include the measurement of weight and a basic neurology exam as described in* Protocol *Section 7.2.3.*

6 *Cognitive Testing: Cognitive testing will be performed in a subset of designated North American (U.S. and Canada) study sites, at baseline (Visit 5), annually, and EDC or EOS visits only as described in* Protocol *Section 7.2.3.4.*

7 *ECG: Regularly scheduled ECGs are to be recorded locally, anonymized, saved in the study file, and a copy of the ECG should be sent to the study central ECG file for storage. If a subject experiences a nonfatal adjudicated and confirmed CV event after randomization, a new baseline ECG should be performed following the event. It may be done at a regularly scheduled visit if the visit is to occur within that time frame. If not, a new ECG should be performed at an unscheduled study visit.*

8 *Chemistry Group: At indicated visits only: sodium, potassium, chloride, bicarbonate, creatinine, blood urea nitrogen (BUN; serum urea), glucose. All chemistry studies are to be performed by central laboratory.*

9 *Liver function tests: Liver function tests, including ALT, AST, alkaline phosphatase, and total and direct bilirubin, should be performed at the designated visits. Unplanned visits for reassessing liver function test abnormalities may be required (*Protocol *Section 8.6.2 and* Protocol *Appendix 8) and do not require fasting.*

10 *Creatine Kinase: Scheduled CK tests are only drawn at screening, baseline, and, annually thereafter. If a subject complains of muscle discomfort at a visit, a CK level should be drawn. If at any time a CK level is >5X the upper limit of normal (ULN), an unscheduled visit should be scheduled for a repeat CK, within 48 hours if possible, with CK fractionation for isozymes (to assess CK-MM and CK-MB) and urine dipstick. Unscheduled measurements of CK do not require fasting. See* Protocol *Section 7.2.5,* Protocol *Section 7.6 and* Protocol *Appendix 7. Prior to obtaining blood for a CK assessment, investigators should enquire about recent intramuscular injections, heavy exercise, or recent musculoskeletal trauma, and defer CK testing until the next visit or repeat testing at an unscheduled visit, no less than 7 days after the IM injection, heavy exercise, or musculoskeletal trauma, so as to avoid spuriously elevated values.*

11 *ADA/PK/PCSK9 sampling: Anti-drug antibody (ADA), bococizumab drug, and PCSK9 blood samples should be collected in all subjects, at the baseline and designated visits as described in* Protocol *Section 6 For Visit 3, only a PCSK9 sample is needed. No PK or ADA sample is needed at Visit 3. After randomization, if lipid sampling has been postponed to an unscheduled visit, the corresponding ADA/PK/PCSK9 samples should be postponed as well, and collected at the same time as the rescheduled lipid sample collection. ADA, PK, and PCSK9 samples will be collected at EDC/EOS visits.*

12 *Hematology: Complete blood count (CBC) with white blood cell (WBC) and red blood cell (RBC) counts, hemoglobin, hematocrit, WBC differential and platelet count. All hematology studies are to be performed by central laboratory.*

13 *Urinalysis: Dipstick urinalysis will be performed by study site, locally. Details describing what is evaluated in the urinalysis are described in* Protocol *Section 7.2.1.2, Table 2. At the screening visit a central lab urine albumin/creatine ratio assessment may be evaluated, in subjects who have had a cardiovascular event more than 5 years prior to screening and in subjects without a prior qualifying cardiovascular event.*

14 Pregnancy Test: *A woman is of childbearing potential if, in the opinion of the investigator, she is biologically capable of having children, with her partner, and is sexually active (*Protocol *Section 4.1, inclusion criterion 8). For women of childbearing potential, serum pregnancy tests, performed at the central laboratory, and urine pregnancy tests, tested locally, are performed at the screening visit (Visit 1), before IP administration, at the baseline visit (Visit 5), at all visits after randomization, and at the EDC/EOS visit. Subjects who have missed a menstrual period or who show an indeterminate or positive result on the urine test may not further progress in the study until pregnancy is ruled out using further diagnostic testing (eg, a negative quantitative serum pregnancy test conducted at the central laboratory). At all visits, a negative urine pregnancy result is required before the subject may receive the IP. In the case of a positive confirmed pregnancy, the subject will be withdrawn from study medication but may remain in the study. In addition, pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected). Pregnancy tests may also be repeated as per request of institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. Unscheduled visits for pregnancy testing do not require fasting.*

15 Biospecimens: *Banked biospecimen collection will include a 4 mL whole blood specimen at Visit 5, and 10 mL blood samples processed to plasma at Visits 5 and 11, as specified in* Protocol *Section 7.5.*

16 Lipid profile: *The fasting lipid profile includes total cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), very low density lipoprotein cholesterol (VLDL-C), remnant lipoprotein cholesterol (RLP-C), and triglycerides, performed by a central laboratory. After randomization lipid level tests should be scheduled no sooner than 10 days after the subject's prior dose, even if this requires an unscheduled visit. If a subject has a visit that is scheduled less than 10 days after the last dose, the visit procedures may take place, but lipid testing should be postponed and performed at the earliest possible time, at an unscheduled visit, no sooner than 10 days after the subject's last dose. Subjects who have had an IP dose frequency modification to dosing every 4 weeks, will need to have their visit frequency increased to every 8 weeks, approximately, for the purposes of direct LDL-C measurement. A lipid profile will not be collected at EDC/EOS visits.*

17 Special Lipid and Efficacy Assessments: *At the screening visit hs-CRP and Lp(a), and may be evaluated, in subjects who have had a cardiovascular event more than 5 years prior to screening and in subjects without a prior qualifying cardiovascular event. Apolipoprotein (apo) B and apo A-I will not be collected at the screening visit. Special lipid and efficacy blood samples will be collected in all subjects, at Visits 5, 8, and 11, for apo B, apo A-I, Lp(a), and hs-CRP, as described in* Protocol *Section 6, and measured by a central laboratory.*

18 HbA1c: *HbA1c will be collected, for all subjects, at baseline, Visit 11, and EDC/EOS. HbA1c may be collected at any time, at an unscheduled visit, if necessary for additional safety assessments, as determined by the investigator.*

19 Viral hepatitis serologies. *Hepatitis B and hepatitis C virus screening serologies will be collected at Visit 1 in all subjects and evaluated as per* Protocol *Appendix 3. Hepatitis C virus serologies will be collected at the EDC/EOS visit, only for subjects from study sites in Canada. A positive or indeterminate hepatitis C serology may trigger a hepatitis C polymerase chain reaction (PCR) test for confirmation. Unscheduled visits for hepatitis C PCR testing do not require fasting.*

20 Dispense investigational product: *IP will be dispensed as designated in the table. During the run-in period (Visits 2, 3, and 4) subjects will self-administer or be administered study drug by a caregiver, during the study visit. At Visit 5, Subjects will be observed during injection of IP, either by self-injection, or as performed by a care giver and observed for a period of 30 minutes, to determine if any signs or symptoms develop. The observation period may be extended, if any signs or symptoms become apparent. After Visit 5, the randomization visit, study sites should try to coordinate the visit schedule with the subject's dosing schedule, when possible. After study procedures are completed, at each visit, subjects should self-inject IP only after blood samples have been collected and the physical exam has been performed.*

21 Con Med Check: *Concomitant medication assessment, including assessment of background lipid lowering medication (see* Protocol *Section 5.8).*

22 *Adverse events and Potential Endpoint Assessments: Adverse events (AEs) will be reported at every visit. Serious adverse events (SAEs) will be reported from the time of informed consent (see* Protocol *Section 8.2). Potential disease-related efficacy endpoint assessment will be done at every visit after randomization.*

23 *Compliance Check: The subject's compliance with IP administration, as described in* Protocol *Section 5.3 will be assessed. After the randomization visit, subjects will be directed to bring any used and unused syringe cartons to each visit. Used syringes will be returned to the study center in a biohazards container, as needed. Compliance with lifestyle guidelines should be reviewed (*Protocol *Section 4.4) and recorded in the CRF.*

24 *Contraception Check: At these visits, a contraception check should be made for male and female subjects, who, with their partner(s), are of childbearing potential (*Protocol *Section 4.4.2).*

25 *Health-Related Quality of Life Assessment: EuroQol Group quality of life (EQ-5D) assessments (*Protocol *Section 7.3.1) at visits 5, 8, 9, 11, 14, 17, 20, and EDC or EOS.*

26 *Patient Health Questionnaire: A Patient Health Questionnaire 2 (PHQ-2) will be performed at Visit 5 (*Protocol *Section 7.3.2*), *in all subjects, and in the subset of subjects with cognitive assessments, only, it will also be performed annually, and at EDC or EOS. If at the baseline PHQ-2 assessment, a subject scores ≥2, the remaining 7 questions of the PHQ-9 will be answered. If the PHQ-9 score is ≥10, the subject should be referred back to his/her primary care physician for further assessment and/or treatment of potential major depression. If the PHQ-9 score is ≥15 or there is a positive score in question 9, the subject should be excluded from participation, the subject's primary care physician (PCP) should be informed, and the subject should be referred to a mental health professional, either by the PCP or the investigator. Such subjects may be rescreened, at a later date, if they were evaluated and treated as appropriate, and the repeat PHQ scores permit inclusion. Any adverse events should be documented in the case report form as appropriate.*
Only subjects participating in the cognitive assessment sub-study will have annual, and end of treatment or end of study PHQ assessments, in addition to the baseline assessment. If at any the visits after the baseline assessment, a subject scores ≥2, the remaining 7 questions of the PHQ-9 will be answered. If the PHQ-9 score is ≥10, consideration should be given to referring the subject back to his/her primary care physician for further assessment of potential major depression and recommendations. If the PHQ-9 score is ≥15 or there is a positive score in question 9, the subject's primary care physician (PCP) should be informed, and the subject should be referred to a mental health professional, either by the PCP or the investigator. Any adverse events should be documented in the case report form as appropriate.

27 *Health care resource utilization: Subjects will be queried for hospitalizations, emergency room visits, and physician office visits, and the appropriate CRFs completed.*

28 *Early discontinuation (EDC) procedures should be done upon the permanent early discontinuation of double-blind IP. Study sites must contact the study retention team, or delegate, or EDC retention hotline, by telephone or email, for all potential or actual EDC subjects. Subjects should continue to have visits (either in person or via phone visit) with study personnel according to the study schedule until study completion. Subjects who continue in the study, after EDC, should also complete EOS procedures, at the time of study completion.*

29 *The EOS will be announced to study sites, when the Sponsor estimates that criteria for stopping the study in* Protocol *Section 3 have been satisfied. EOS visits should be scheduled as soon as possible after that announcement. The EOS visit should occur no sooner than 14 days after the last dose of IP was administered for subjects taking IP. The safety follow-up period is 40 days after the last dose of IP was administered. If their EOS visit has occurred less than 40 days after the last dose of IP was administered, subjects should be contacted by telephone to determine if any serious adverse events have occurred. All EOS procedures should be done for all randomized subjects when the study is completed, including those who had an EDC visit, if they continued in the study, ie, EOS procedures should be completed, whether or not the subject is taking double-blind IP.*