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

Compound:	PF-04950615 (RN-316)
Compound Name:	Bococizumab
United States (US) Investigational New Drug (IND) Number:	104,872
European Clinical Trial Database (EudraCT) Number:	2013-002795-41
Universal Trial Number	U1111-1151-0616
Protocol Number:	B1481038
Phase:	3

[redacted]

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 2	12 February 2016	Visit dates in months were replaced by visit dates in weeks, throughout the protocol, for clarity and consistency. Unplanned visits were described as unscheduled visits, throughout the protocol, for clarity and consistency. The protocol background information was updated to include more updated Phase 2 anti-drug antibody data based on a more sensitive assay, so as to provide additional safety information. Clinical Secondary Objectives and Endpoints were updated to reflect an upgrading of the secondary endpoint of a composite endpoint of all-cause death, non-fatal MI and non-fatal stroke to a KEY secondary endpoint, in consideration of its clinical importance. The secondary endpoint of nominal change in hs-CRP was changed to percent change in hs-CRP. The schedule of activities and its footnotes were modified to describe more clearly which procedures were to be conducted and when they were to be conducted. Statements have been added which state that 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. The study design language was modified to clarify that the end of study visit should occur no sooner than 14 days after the last dose of investigational product (IP) was administered. The safety follow-up period is 40 days after the last dose of IP was administered and if the EOS

Document	Version Date	Summary of Changes and Rationale
		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 occurred. The proposed indication was modified so that the major cardiovascular events reflected components of the primary endpoint. Section 1.2.2, Rationale was updated to include more recent references of PCSK9 inhibitors. The summary of safety for completed studies with bococizumab was updated to reflect the updated Phase 2 anti-drug anti-body data based on a more sensitive assay, so as to provide additional safety information. The safety reporting section was revised to reflect the fact that a Pfizer Internal Serious Adverse Event Triage Group will ensure the correct reporting of SAEs to the Pfizer Drug Safety Unit. The protocol section describing external committees was updated to reflect the fact that the Joint Operations Committee and Joint Leadership Committee were merged into a single oversight committee. Modifications were made to the study's inclusion criteria, as described below. The inclusion criterion for age was modified to state that subjects who have not had a prior CVD event, but who have a conditions of elevated LDL-C, (heterozygous familial hypercholesterolemia [heFH] or a history of LDL-C ≥190 mg/dL [4.9 mmol/L]) should be ≥35 years of age if a man, and ≥45 years of age, if a woman, given observational studies which demonstrate that it is at these ages at which patients with heFH have an increased risk of incurring a CV event. Clarifying language was added to the requirements for background lipid lowering

Document	Version Date	Summary of Changes and Rationale
		treatment, to permit the use of intermediate doses of statins. Clarifying language was added to permit the inclusion of subjects with complete statin intolerance who were treated only with preventative cardiology lifestyle change guidance since some countries have no alternative non-statin lipid lowering drugs which are approved for the indication of reducing cardiovascular risk. The definition of complete statin intolerance was expanded to include subjects with a history of documented statin allergy, which would preclude rechallenge with an alternative statin. Clarifying language was added to the inclusion criteria that the diagnosis of a prior myocardial infarction could not be made solely on the basis of the presence of new Q waves reported on an ECG. There would need to be additional evidence of a silent MI, such as imaging data showing a fixed regional wall motion abnormality which correlated with such ECG changes. Clarifying language was added to indicate that a diagnostic arterial catheterization, without revascularization, did no qualify as a revascularization event. The inclusion criterion of peripheral vascular disease was expanded to permit the inclusion of subjects with imaging evidence of a >50% stenosis of a carotid or lower extremity artery or imaging evidence of a high carotid artery plaque burden. Clarifying language as added to the inclusion criterion of imaging evidence of significant coronary artery disease which states that a previously stenotic coronary artery, which was subsequently revascularized, cannot be counted as a CVD risk factor. Exclusion criteria were modified to exclude

Document	Version Date	Summary of Changes and Rationale
		subjects who have an SAE of a cardiovascular disease event between Visit 0 and Visit 5. The cerebral hemorrhage risk exclusion was modified to clarify that a prior lacunar infarct refers to a prior lacunar stroke, ie, a lacunar infarct which resulted in a stroke. Imaging evidence of a lacunar infarct, in the absence of a historical neurologic deficit is not exclusionary. Exclusion criteria were modified to exclude subjects who may take or have taken a marketed PCSK9 inhibitor, since such drugs are now available in some countries. Exclusion criteria were modified to exclude subjects with a Patient Health Questionnaire score ≥15 or who have a positive score in question 9 of that assessment, since such scores suggest a high risk of depression with suicidality. The exclusion criterion of intramuscular injections was removed from the protocol, since the sole concern of these injections was the potential for triggering an elevated value of creatine kinase due to tissue trauma, which might complicate the analysis of safety. A provision was added in the description of the hepatitis inclusion criterion, to permit a confirmatory hepatitis C polymerase chain reaction in subjects who have a positive hepatitis C screening test. An exclusion criterion of gastric bypass surgery was added, since its presence could complicate the interpretation of metabolic efficacy and safety data. The definition of IP was added to Section 5, Study Treatments. The blood sampling schedule for levels of LDL-C, anti-drug antibodies, PCSK9, and bococizumab was modified to ensure that it takes place no sooner than 10 days after the last dose of

Document	Version Date	Summary of Changes and Rationale
		bococizumab, so as to prevent the unnecessary triggering of dose modifications. Lipid testing is no longer required at early discontinuation and EOS visits since the time intervals between the discontinuation of IP and the sampling will be highly variable and not reflective of the pre-specified dose administration schedule. A requirement was added to the protocol that study sites contact the early discontinuation hotline when they become aware of a potential discontinuation of a subject's participation, so as to enhance the retention of subjects in the study, for the purposes of maintaining the study's scientific integrity. A requirement was added to the protocol that IP should not be administered, if a subject is prescribed a marketed PCSK9 inhibitor during the conduct of the study. A provision was added to the study, for subjects who are traveling, to obtain study required lab tests when they cannot visit the study site. Urine pregnancy tests were added to all visits, for women of childbearing potential. The blood pressure measurement requirements were modified to reflect locally accepted practice, to enhance compliance. The blood sampling requirements for creatine kinase (CK) testing were modified, such that such sampling should take place no sooner than one week after an intramuscular injection, to avoid spurious elevations of CK due to local muscle injury. The requirements for anti-drug antibody blood sampling were modified so that anti-drug antibody measurements would be obtained for an injection site reaction that lasts more than 3 days. Section 7.6, Triggered requirements was modified

Document	Version Date	Summary of Changes and Rationale
		with the removal of the section describing the management of low-LDL-C with the concomitant dose modification paradigm, since this would happen automatically, through the IRT system and would not require direct study site involvement. Section 7.6, Triggered requirements was modified with the removal of the section describing the management of positive ADAs, since the analysis of ADA is done in the laboratory and not at the study site. Section 7.6, Triggered requirements was modified with the removal of the section requiring the site to seek approval from the medical monitor, to continue dispensing IP if the subject experiences unexplained muscle tenderness or weakness in the absence of a CK elevation, since there is no known relationship between PCSK9 inhibition and myopathy. While such symptoms are known to be related to statin administration, it is up to the investigator to follow local requirements for the administration of statins as described in the Section 5.8, concomitant medications. In Safety Section 8.2, clarification was added that serious adverse event reporting includes the period between pre-screening and randomization. Section 8.6.1 was modified to indicate that Protocol Specified Adverse Events were now to be described as Disease Related Efficacy Endpoints and that they would be identified by the Pfizer SAE triage group. In Safety Section 8.14.1, Serious Adverse Event Reporting Requirements, the operations of an internal Pfizer Serious Adverse Event Triage Group are described, to improve the reporting of serious adverse events. Section 9, Data Analysis/Statistical Methods, was updated to be consistent with other changes made for this amendment.

Document	Version Date	Summary of Changes and Rationale
		The sample size of the study was modified and increased from 9,000 subjects to 11,000 subjects, so as to complete the study sooner, given the expected rate of accrual of primary endpoint events. This will shorten the duration of the trial, so as to preserve the study's integrity, given the risk that subjects may be started on a marketed PCSK9 inhibitor during the conduct of the study, or drop out of the study if they suspect that they are receiving placebo (eg, if a primary care physician obtains lipid levels). The definition of the efficacy cutoff date was modified to accommodate the possibility of changes to the stopping criteria outlined in Section 3. As a result of EMA Scientific Advice, the minimum number of events required to perform subgroup analyses was deleted. As a result, language was added to indicate that the subgroups would be finalized in the Statistical Analysis Plan. Also the language around the interaction p-value model was modified to include subjects from all subgroups. The method of controlling Type 1 error for the key secondary endpoints was changed to fixed sequence testing from the Hochberg procedure, to increase the power for more important endpoints. Section 9.5, Interim Analysis was modified to reflect the addition of an interim analysis for clinical benefit, which will be performed when 75% of the primary endpoint events have accrued. The rationale for such an analysis is that if overwhelming efficacy can be demonstrated at that point in time, it would be difficult to justify the continuation of the study, as equipoise would be lost. Minor additional modifications of text were made, to ensure compliance with the most current Pfizer protocol template for Phase 3 studies, dated 16-Feb-2015.

Document	Version Date	Summary of Changes and Rationale
		The appendices were updated as follows: Appendix 3, Hepatitis B Assessment was modified to reflect the laboratory nomenclature for the central lab; Appendix 4, Clinical Endpoints was modified to reflect the addition of the MI type 4c, stent stenosis; Appendix 7, Safety algorithm: Myopathy, was modified so that it was no longer necessary for investigators to contact the study medical monitor to resume IP, for unexplained muscle symptoms without an elevation in creatine kinase levels. Such events would be reported as adverse events usually would be, with clinical follow-up as needed; Appendix 9 was modified to reflect the updated safety reporting processes; Appendix 10 was modified to reflect updated inclusion criteria.
Amendment 1	01-Oct-2014	The generic name, bococizumab, replaces compound number PF-04950615; Schedule of activities was modified to reflect changes in protocol and provide additional detail to study sites; An efficacy endpoint of any stroke (fatal and non-fatal), of any etiology which includes hemorrhagic stroke, was added; Modified inclusion and exclusion criteria language to enhance study site compliance and acknowledge the inclusion of other factors known to confer cardiovascular risk; Clarified language regarding background concomitant lipid lowering treatments, to enhance clarity for the investigators; Modified contraception language in Inclusion Criteria (4.1) and Lifestyle Guidelines (4.4.2), to reflect additional pre-clinical reproductive safety

Document	Version Date	Summary of Changes and Rationale
		data, and to enhance clarity for the investigators; Modified study design to include a pre-screening direct low density lipoprotein cholesterol (LDL-C) measurement, to permit investigators to identify subjects who might qualify for inclusion, before other study procedures are completed; Required that lipid assessments be done no sooner than 10 days after prior dose, to ensure that lipid values are evaluated at the end of the dosing period; Added more frequent visits for assessment of direct LDL-C and adverse events (AEs)/serious adverse events (SAEs), for subjects who have had investigational product (IP) dose frequency modifications to Q4wks so that the data monitoring committee (DMC) can monitor more closely, lipid levels in subjects with a history of low levels of LDL-C during the trial; Added endpoint of calculated remnant lipoprotein cholesterol, in consideration of scientific interest in this parameter; Clarified that very low density lipoprotein cholesterol (VLDL-C) is a calculated value, so that reviewers understand the measurement was not made by ultracentrifugation; Added depression assessments so as to capture baseline risk for the disorder, given that depression is found fairly frequently in subjects at high risk of cardiovascular events and its presence may alter performance on the planned cognitive assessments; Added Hopkins Verbal Learning Testing to the cognitive assessment panel, to get additional information on the subjects' memory function; Added health care utilization assessments and endpoints, to evaluate the potential impact of

Document	Version Date	Summary of Changes and Rationale
		bococizumab on health care resource utilization; Added to screening laboratory tests, hs-CRP and Lp(a) for subjects who had not had a prior cardiovascular event, since these are established risk factors for the occurrence of cardiovascular events; Modified safety section to clarify further, how serious adverse events are to be reported; Modified statistical assumptions, event rate and sample size as well as analysis plan, including subgroups, to enhance the scientific value of the study; Added safety appendices that include flow charts describing actions which should occur in cases of potential drug induced liver injury or myopathy to clarify the intent of the protocol procedures, for the investigators; Added an appendix facilitating the understanding of screening hepatitis serologies, to enhance the clarity of the protocol for the investigators; Added Appendix 9, describing safety reporting and potential endpoint reporting, to enhance the clarity of the protocol for the investigators; Added Appendix 10, describing the assessment of CVD risk for inclusion, to enhance the clarity of the protocol for the investigators.
Original Protocol	26 August 2013	Not applicable

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.

PROTOCOL SUMMARY

Background

Bococizumab (previously numbered PF-04950615, RN-316, and J16) is a humanized monoclonal antibody against the proprotein convertase subtilisin kexin type 9 (PCSK9) enzyme responsible for the regulation of the low density lipoprotein receptor (LDLR), being developed for the following indications: (1) the treatment of primary hyperlipidemia or mixed dyslipidemia and (2) cardiovascular (CV) risk reduction, in subjects at high and very high risk of major cardiovascular events.

Cardiovascular disease (CVD) due to atherosclerosis continues to be the leading single cause of death in industrialized countries. High serum lipid levels, and especially high low density lipoprotein cholesterol (LDL-C) levels, have been demonstrated to strongly and directly correlate with cardiovascular disease risks by numerous epidemiological studies. Moreover, large prospective clinical outcome trials have demonstrated that lowering LDL-C decreases cardiovascular morbidity and mortality.[45] Despite the availability of highly effective lipid lowering therapies such as statins and ezetimibe, a significant percentage of patients remain at high risk for CVD.

PCSK9 is the ninth member of the subtilisin family of kexin like proconvertases to be identified[14] and is closely related to proteinase K. PCSK9 is linked to serum LDL-C levels by binding to and down regulating LDLR levels on hepatocytes. This reduction in LDLR results in reduced cellular uptake of LDL-C and, consequently, higher LDL-C levels in serum.[17] In contrast, a decrease in active PCSK9 leads to an increase in hepatocyte LDLR, causing an increase in LDL uptake from circulation and consequently a subsequent reduction in serum LDL-C levels.[15,16] Loss of function mutations lead to higher levels of the LDLR, and consequently lower plasma LDL-C levels, and protection from coronary heart disease.[18,19,20,21,22] This loss of PCSK9 appears to have no discernible adverse consequences in the affected subjects.[21,22]

Bococizumab targets the evolutionarily conserved LDLR binding domain of PCSK9 with high affinity. Bococizumab administered either as a single or multiple doses, either alone or in combination with current lipid lowering agents, was generally well tolerated in completed studies. No subjects in completed studies met the categorical criteria of drug-induced liver injury according to the Hy's law definition. Using a highly sensitive and drug tolerant anti-drug antibody (ADA) assay, 42.5% of subjects (201/473) exposed to bococizumab in three recently completed studies (B1481024, B1481015, and B1481036) developed ADAs. The presence of ADAs was not associated with any clinical signs or symptoms of hypersensitivity. In 98.7% of ADA positive subjects treated with multiple doses of bococizumab, no adverse effects on clinical pharmacokinetics (PK) or pharmacodynamics (PD) were evident. A potential impact on PK and/or PD was noted in 5 of 398 subjects (1.3%) treated with multiple doses.

Results from the completed Phase 2b study (Study B1481015) showed that bococizumab was generally well tolerated at each dose, with an adverse event profile similar to previous

findings in the clinical program, and clear evidence of efficacy was established in all bococizumab treatment groups.

Study Objectives (Refer to Section 2.1 for Complete List)

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 (myocardial infarction), non-fatal stroke, and hospitalization for unstable angina with urgent revascularization (as defined in Appendix 4), 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 (non-high density lipoprotein cholesterol) ≥130 mg/dL (3.36 mmol/L).

Clinical 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 4) 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.

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 adjudicated and confirmed secondary endpoints (as defined in Appendix 4) 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.

Circulating Biomarker Objectives

A circulating lipid biomarker secondary objective is to evaluate bococizumab compared with placebo, for LDL-C, with respect to the percent change and nominal change from baseline at Week 14 and the percent change from baseline to the last available post randomization measure of LDL-C (direct measure).

Additional circulating lipid biomarker objectives are evaluating the percent change from baseline at Week 14, in:

- 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 sole circulating inflammatory secondary objective is to evaluate bococizumab compared with placebo, for high sensitivity C-reactive protein (hs-CRP) with respect to its percent change from baseline at Week 14.

Health Care Resource Utilization Objectives

Health care resource utilization objectives include comparing bococizumab to placebo with respect to 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 to describe the safety, tolerability, and immunogenicity of bococizumab and placebo, including assessments of adverse events (including Type 1 and 3 hypersensitivity reactions and injection site reactions), serious adverse events, vital signs, physical and neurological examinations, cognitive testing, 12-lead electrocardiogram (ECG) recordings, and safety laboratory tests including hematology, urinalysis, blood chemistry studies, and anti-drug antibody (ADA) assessments. See Section 7.2 for details.

Study Endpoints (refer to Section 2.2 for complete list and Appendix 4 for clinical endpoint definitions).

Primary Endpoint

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

Key Secondary Endpoints

Key secondary endpoints are defined as 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, 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

The times from randomization to the first adjudicated and confirmed occurrence of the following endpoints:

- A composite endpoint of CV death, non-fatal MI, and 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.

Other Secondary Circulating Biomarker Endpoints

The LDL-C biomarker endpoints are the percent change and nominal change from baseline at Week 14 (Visit 8) and the percent change from baseline to the last available post-randomization value, of LDL-C (direct measurement).

Other lipid endpoints include the percent change from baseline at Week 14 (Visit 8) in levels of:

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

Inflammatory biomarker endpoint

The sole inflammatory biomarker endpoint is the percent change from baseline at Week 14 (Visit 8), in levels of hs-CRP.

Health Care Resource Utilization Endpoints

Health care resource utilization endpoints being evaluated include:

- The occurrence, primary and secondary discharge diagnoses, overall length of stay, duration of stay in different medical care units, and discharge disposition, of 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, of 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.

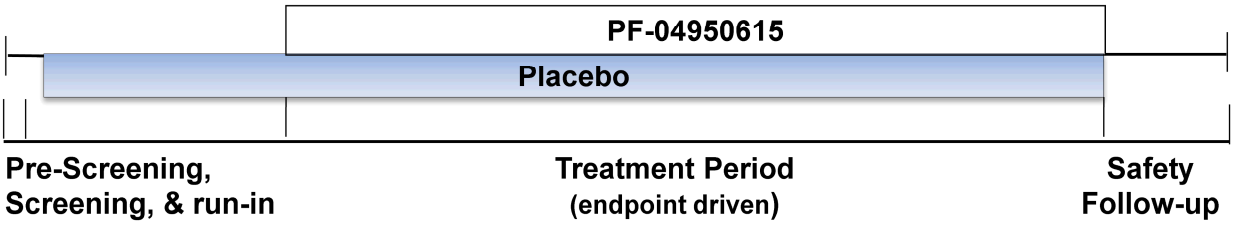
Safety Endpoints

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. See Section 7.2 for details.

Study Design (details found in Section 3)

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 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 qualifies for this study. The 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.

Study Schematic



Approximately 55,000 subjects may be screened and approximately 11,000 will be randomized. 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 duration of the trial is expected to be approximately 3.9 years (see Section 9.1). The End of Study (EOS) will be announced to study sites, when the Sponsor estimates that criteria for stopping the study in Section 3 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) is administered. The safety follow-up period is 40 days after the last dose of 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 occurred. 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.

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.

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.

Potential endpoint events will be adjudicated by an independent and blinded adjudication committee. Subject safety will be monitored by an independent data monitoring committee (DMC). An independent statistical data analysis center will provide analyses to the DMC according to the DMC charter.

Study Treatments

Subjects will be randomized to bococizumab 150 mg or placebo Q2wks in a 1:1 ratio. Randomization will be stratified by geographic region and complete statin intolerance. Subjects will self-inject, or if unable to self-inject, have IP administered by a caregiver (eg, a family member or health care assistant).

Statistical Methods and Sample Size Determination

Data analyses and statistical methods are described in Section 9. A more detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be maintained by the sponsor.

A sample size estimate of 11,000 randomized subjects (5,500 on bococizumab and 5,500 on placebo) has approximately 90% power to detect a 25% reduction in the risk of experiencing the primary endpoint, by means of a two-sided α=0.05 log rank test. The required number of subjects with an adjudicated and confirmed event is 508. The sample size calculation is based on an annual event rate of 2.7% and a premature study discontinuation rate of 1% per year. Assuming that the trial will recruit in 2.5 years, with approximately 50% of the subjects in the last six months, the study will finish in another approximately 1.4 years for a trial duration of approximately 3.9 years. These results were derived via the software package EaST® (version 6.3.1).

As above, 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. 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. 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.

Primary Endpoint Event Rate Estimate

Given the power and the alpha level, the expected duration of the trial will be driven by the assumed rate of accrual of adjudicated and confirmed primary endpoint events in the placebo group, the assumed hazard ratio, the subject accrual rate and the premature study discontinuation rate. To produce an estimate of the primary endpoint event rate in the placebo group, meta-analyses, published and unpublished, were considered and a review of lipid lowering clinical trial literature was conducted (Section 9.1.3). These trials vary considerably with respect to their temporal execution, background cardioprotective medications, and differences in enrichment of various risk factors, any of which may impact CV event rates. Furthermore, the component of the primary endpoint for the present study, hospitalization for unstable angina needing urgent revascularization, did not appear to be a predefined component of the trials that were reviewed, some of which had endpoint components comprising hospitalization for unstable angina, irrespective of the need for revascularization, and for other clinical trials, revascularization rates were reported separately, as a secondary endpoint.

Given the uncertainty of the primary endpoint event rate in the placebo group, estimates of trial duration and event accrual will assume a placebo event rate of 2.7%/year, which is the lower bound of the 80% prediction interval for a baseline LDL-C of 100 mg/dL (2.59 mmol/L) from an unpublished meta-analysis.

Efficacy Analysis

The primary analysis set for efficacy analyses will be the Full Analysis Set, which includes all randomized subjects and all post-randomization data. The primary endpoint will be analyzed using a log rank test stratified by geographic region and complete statin intolerance and will use a two-sided α=0.04898 after an adjustment for an interim analysis for clinical benefit (see Section 9.5) and a single Bonferroni adjustment for DMC reviews of all-cause death (see Section 9.6). The hazard ratio and a 95% confidence interval will be reported from a Cox proportional hazards model stratified by geographic region and complete statin intolerance with treatment group as a covariate. Kaplan-Meier estimates will be plotted.

A gatekeeping procedure will be applied; the key secondary endpoints will be formally tested only if the null hypothesis for the primary analysis is rejected (See Section 9.2.2 for details). A fixed sequence procedure with a two-sided alpha of 0.04898 will be applied for the key secondary endpoints. Aside from the fixed sequence procedure, the methodology for the key secondary endpoints will be the same as that for the primary endpoint. The methodology for the remaining clinical endpoints will be identical to that for the primary endpoint except that an alpha=0.05 will be used.

Percent and/or nominal changes from baseline in circulating biomarkers, as indicated in the objectives, will be analyzed using a mixed model repeated measures (MMRM) model with fixed effects for treatment, scheduled visit time point (categorical), baseline value, interaction between the baseline value and scheduled visit time point, interaction between the treatment and scheduled visit time point, geographic region and complete statin intolerance. An unstructured covariance matrix will be used. Estimates of the treatment group means and

mean treatment group differences at each visit with corresponding 95% confidence intervals will be reported, as will the p-values for the mean treatment group differences. The estimated treatment group means and the corresponding 95% confidence intervals will be plotted. For Lp(a), triglycerides and hs-CRP, the same model will be fit for log-transformed data. The estimated treatment group means and corresponding 95% confidence intervals 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 95% confidence intervals along with p-values. The estimated mean percent changes and corresponding 95% confidence intervals will be plotted.

Safety Analysis

Safety will be assessed through adverse events (including Type 1 and 3 hypersensitivity reactions and injection site reactions), 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. Details of the safety analysis are found in Section 9.4.

SCHEDULE OF ACTIVITIES

The Schedule of Activities Flowchart provides an overview of the protocol visits and procedures. Refer to STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (designated in this protocol as unscheduled visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the subject.

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 (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 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 (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 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 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 (Section 8.6.2 and 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 Section 7.2.5, Section 7.6 and 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 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 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 (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 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 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 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 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 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 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 (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 (Section 4.4.2).

25 Health-Related Quality of Life Assessment: EuroQol Group quality of life (EQ-5D) assessments (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 (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 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.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

1. INTRODUCTION

Bococizumab (previously numbered PF-04950615, RN-316, and J16) is a humanized monoclonal antibody that is a potent and selective inhibitor of proprotein convertase kexin (PCSK9). Bococizumab enhances the expression of LDL receptors on hepatocytes, lowering LDL-C levels substantially, with or without concomitant statin treatment. It has the potential to be an effective therapy for patients with primary hyperlipidemia or mixed dyslipidemia and may reduce the occurrence of cardiovascular (CV) events. The purpose of this study is to establish the superior efficacy and safety of bococizumab, compared to placebo, in reducing the risk of major CV events in subjects at high or very high risk of incurring a CV event, who are on background lipid lowering therapy, and have an LDL-C ≥100 mg/dL (2.59 mmol/L) or non-HDL-C ≥130 mg/dL (3.36 mmol/L).

1.1. Indication

In patients at high risk of coronary events due to a history of CV disease (myocardial infarction, ischemic stroke, or arterial revascularization) or in high-risk patients without CV disease (diabetes mellitus, familial hypercholesterolemia, symptomatic peripheral vascular disease, or chronic kidney disease), bococizumab, when added to the existing standard of care, is indicated to reduce the risk of the following major CV events:

- CV death
- Non-fatal myocardial infarction;
- Non-fatal stroke;

  and;

- Hospitalization for unstable angina needing urgent revascularization.

1.2. Background and Rationale

1.2.1. Overview of the Disease State

Cardiovascular disease due to atherosclerosis (CVD), including myocardial infarction and stroke, is currently the leading cause of morbidity and premature mortality worldwide, contributing 17 million (8.6 million among women) deaths annually and 10% of the global disease burden, despite the availability of highly effective treatments.[1,2] By the year 2020, heart disease and stroke are estimated to become the leading causes of both death and disability, worldwide, with the number of fatalities projected to increase to over 20 million a year.[3,4]

Risk factors for CVD are well characterized and include age, gender, family history of CVD, hypertension, diabetes, smoking, dyslipidemia (increased levels of low density lipoprotein cholesterol [LDL-C] and non-high density lipoprotein cholesterol [non-HDL-C], and low levels of high density lipoprotein cholesterol [HDL-C]), and elevated levels of high sensitivity C-reactive protein (hs-CRP) a circulating biomarker of vascular inflammation.[5,6] Various vascular imaging modalities have also been used to identify the risk of CVD.[7]

Cholesterol, an insoluble fat, is transported through the bloodstream on lipoproteins. Non-HDL-C, and its components, very low density lipoprotein cholesterol (VLDL-C), intermediate density lipoprotein cholesterol (IDL-C), remnant cholesterol, and LDL-C represent those moieties that lead to the development of atherosclerosis. LDL-C is the main contributor to the accumulation of cholesterol in arterial walls and the cause of systemic atherosclerosis.[8] Low density lipoprotein (LDL) particles within the vessel wall can become oxidized and modified, within monocyte/macrophages, leading to local inflammation and vessel injury.[9] When the intravascular accumulation of plaque becomes unstable, plaque rupture can be triggered, leading to thrombotic occlusion of a vessel and potential irreversible end organ damage to the heart or brain.[10]

LDL-C cholesterol is presently a key treatment target for reducing the risk of CVD event occurrence.[5,6] Over the decades, numerous studies assessing the safety and efficacy of different treatments that lower total cholesterol (TC) and LDL-C have consistently shown a strong relationship between LDL-C lowering a reduction in the risk of major CV events.[11] As dyslipidemia treatments have become more potent, leading to lower LDL-C on-treatment values and lower CV event rates, the LDL-C treatment recommendations continue to evolve.[5,6,12,13]

The most effective LDL-C lowering treatments, for the prevention of cardiovascular events, to date, are statins. They reduce levels of LDL-C by inhibiting hepatocyte 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase and the intracellular synthesis of cholesterol. This action triggers the production of more hepatocyte LDL receptors, which remove circulating LDL-C from the bloodstream. The cholesterol is ultimately excreted in the bile. Statins also reduce levels of non-HDL-C, which includes VLDL-C and triglyceride rich remnant lipoproteins, and modestly increase levels of HDL-C.

1.2.2. Rationale

Despite currently available treatments for dyslipidemia, many patients do not reach therapeutic LDL-C goals and others sustain major CV events, even while being treated with adequate doses of medication. LDL-C lowering by inhibiting the action of proprotein convertase subtilisin kexin type 9 (PCSK9) appears to be a promising new dyslipidemia treatment. Among the genetic polymorphisms that alter LDL metabolism and LDL-C levels are mutations of the PCSK9 gene. PCSK9 is the ninth member of the subtilisin family of kexin-like proconvertases to be identified and is closely related to proteinase K.[14] It is expressed in liver, neuronal tissue, kidney, and intestinal cells. The PCSK9 gene is regulated by sterols and regulates the level of LDL receptor. The mechanism by which PCSK9 is linked to serum LDL-C levels has been elucidated by biochemical and genetic studies in cell cultures and rodents. These studies have demonstrated that PCSK9 binds to and down regulates LDL receptor (LDLR) levels on hepatocytes. This reduction in LDL receptor density results in reduced cellular uptake of LDL cholesterol and, consequently, higher levels of LDL-C. In contrast, a decrease in active PCSK9 leads to an increase in the number of hepatocyte LDL receptors, causing an increase in LDL uptake from circulation and lower levels of LDL- C.[15,16]

As would be predicted, naturally occurring gain of function mutations in PCSK9 reduce LDLR levels in the liver, resulting in high levels of plasma LDL-C in the plasma and increased susceptibility to coronary heart disease.[17] Loss of function mutations lead to higher levels of the LDLR, and consequently lower plasma LDL-C levels, and protection from coronary heart disease.[18,19,20,21,22] This loss of PCSK9 appears to have no discernible adverse consequences in the affected subjects.[21,22]

The LDLR and PCSK9 are coordinately regulated by sterol regulatory element binding protein 2 (SREBP 2), a transcription factor that activates many genes involved in cholesterol metabolism in a coordinated manner.[23,24] Statin administration, in addition to the HMG-CoA inhibition of cholesterol synthesis, induces SREBP 2 expression, which induces the expression of LDLR.[25,26] However, the statin induction of SREBP 2 also increases PCSK9 messenger ribonucleic acid (mRNA) expression and protein levels.[27,28] The increase in PCSK9 expression would be expected to attenuate the LDL cholesterol lowering effect of statins. Thus, the pharmacologic inhibition of PCSK9 activity may augment statin induced LDLR expression and increase LDL-C clearance, as was observed when statins were administered to PCSK9 knockout mice.[27] This hypothesis, combined with the supportive epidemiologic findings in patients with loss of function PCSK9 mutations, underlies the development of LDL-C lowering pharmacologic inhibitors of PCSK9.[29,30,31] The Phase 1, Phase 2, and Phase 3 published studies of injectable anti-body inhibitors of PCSK9, in normal subjects and subjects with dyslipidemia have shown robust LDL-C lowering, with and without background statin therapy.[32,33,34,35,36,37,38,67,68,69,70,71,72,73,74,75,76] There is also evidence from meta-analyses of some of those studies, that suggests that PCSK9 inhibitors may reduce the occurrence of CV events.[75,76]

Bococizumab is a humanized monoclonal antibody that is a potent and selective inhibitor of PCSK9.[39] Bococizumab lowers LDL-C levels substantially, with or without concomitant statin treatment.[39,40,74] It has the potential to be an effective therapy for patients with dyslipidemia and may reduce the risk of major CV events including CV death, non-fatal myocardial infarction (MI), non-fatal stroke, and hospitalization for unstable angina needing urgent revascularization.

Consequently, the proposed target population for this study is subjects at high or very high risk of incurring a CV event, who are on background lipid lowering therapy and have an LDL-C ≥100 mg/dL (2.59 mmol/L) or non-HDL-C ≥130 mg/dL (3.36 mmol/L). The clinical characteristics of the study population are based on the key features of published guidance documents and prognostic tools used to determine CV risk including the American Heart Association/American College of Cardiology Foundation (AHA/ACCF) guidelines of 2011,[13] National Cholesterol Education Program/Adult Treatment Panel (NCEP/ATP) III guidelines of 2004,[12] and the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines for the treatment of dyslipidemia, published in 2011,[5] and are consistent with the more recent European Guidelines on Cardiovascular Disease Prevention in Clinical Practice, published in 2012,[59] and the International Atherosclerosis Society Global Recommendations for the Management of Dyslipidemia, published in 2014.[60]

1.2.3. Summary of Safety from Completed Studies with Bococizumab

Bococizumab administered either as a single or multiple doses, either alone or in combination with current lipid lowering agents, was generally well tolerated in completed studies. No subjects in completed studies met the categorical criteria of drug-induced liver injury according to the Hy's law definition. Using a highly sensitive and drug tolerant anti-drug antibody (ADA) assay, 42.5% of subjects (201/473) exposed to bococizumab in three recently completed studies (B1481024, B1481015, and B1481036) developed ADAs. The presence of ADAs was not associated with any clinical signs or symptoms of hypersensitivity. In 98.7% of ADA positive subjects treated with multiple doses of bococizumab, no adverse effects on clinical pharmacokinetics (PK) or pharmacodynamics (PD) were evident. A potential impact on PK and/or PD was noted in 5 of 398 subjects (1.3%) treated with multiple doses.

Complete information for this compound may be found in the Single Reference Safety Document (SRSD), which for this study is the *Investigators Brochure*.

Complete information for background treatments may be found in the country specific local label (such as the United States Package Insert [USPI], Summary of Product Characteristics [SPC] or Local Product Document [LPD]).

1.2.4. Benefits and Risks of Participation

The potential benefit of participation, for all subjects in this study, is close monitoring of their medical condition and safety. Those randomized to the active treatment arm may have a benefit of a lower risk of major CV events. Those randomized to the placebo arm are not expected to obtain any additional benefit, beyond close monitoring of their medical condition and safety. A potential risk of participation, for all subjects, is the occurrence of injection site reactions. For those receiving active treatment, there may be an additional risk of achieving a very low LDL-C. It is not known if there are any risks associated with very low LDL-C.

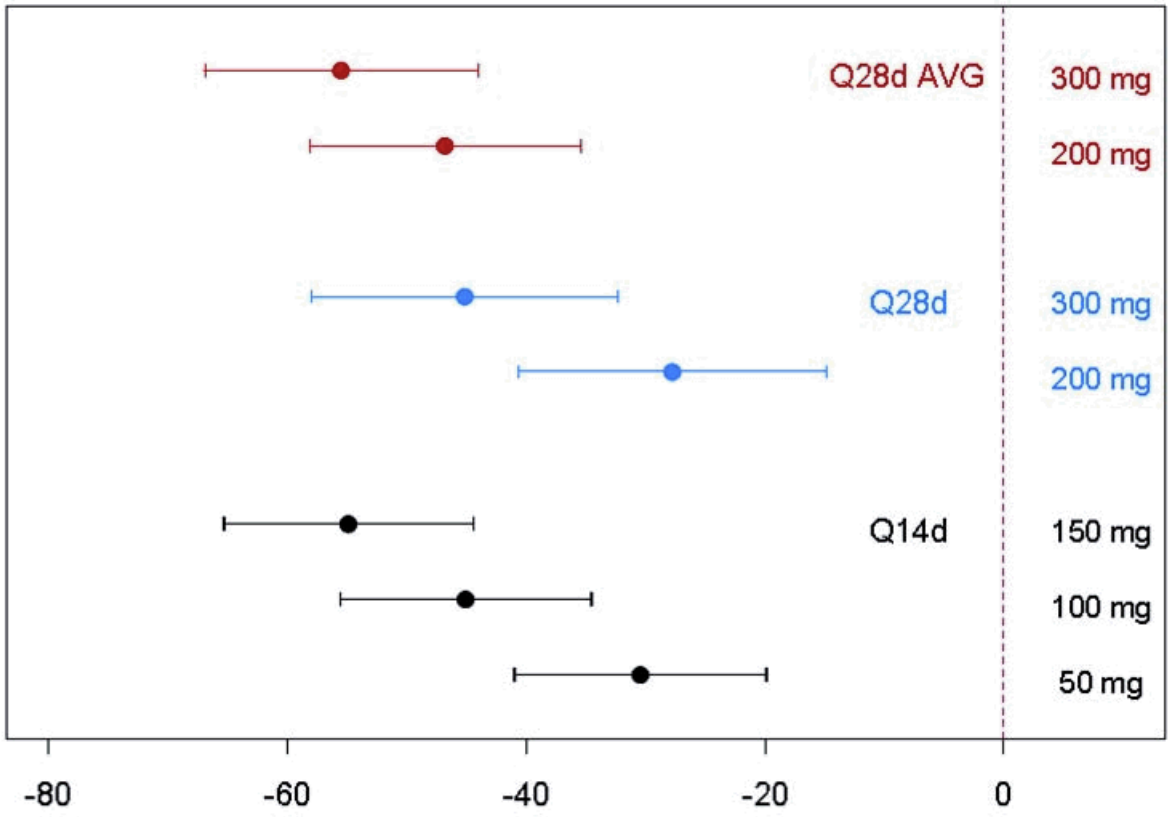
1.2.5. Interim Analysis from Study B1481015

An interim analysis, for the primary endpoint of the now completed study B1481015, was conducted after subjects completed 12 weeks of treatment, for the purpose of Phase 3 dose selection. The study was a randomized, double-blind, placebo-controlled, parallel-group, dose-ranging trial that enrolled 354 subjects, with a treatment duration of 24 weeks. Subjects were randomized to one of 7 dose groups (placebo, 50, 100, 150, once every 2 weeks [Q2wks] and placebo, 200, 300 mg, once every 4 weeks [Q4wks]) delivered by the subcutaneous (SC) route. The dosing strategy in this study allowed for downward dose adjustment when LDL-C ≤25 mg/dL (0.65 mmol/L). The primary efficacy endpoint was the absolute change in LDL-C at 12 weeks following Q2wks or Q4wks dosing as compared to study Day 1 pre-dose baseline LDL-C.

Clear evidence of efficacy was established in all bococizumab treatment groups as shown in Figure 1, below. At the primary timepoint of Week 12, the Q2wks adjusted mean treatment group differences for change in LDL-C from baseline ranged from −30.4 to −54.9 mg/dL at

the end of the dosing period (Q14d in Figure 1). The Q4wks adjusted mean treatment group differences for change in LDL-C ranged from −27.8 to −45.2 mg/dL at the end of the dosing period (Q28d in Figure 1). The Q4wk LDL-C adjusted mean treatment group difference, based on the means of the observed nadir (Week 10, peak effect) and trough (Week 12, end of dosing period) values, ranged from −46.8 to −55.5 mg/dL (Q28d AVG in Figure 1).

Figure 1. Study B1481015 LS-Mean Treatment Difference (mg/dL) and 95% Confidence Interval



Bococizumab was generally well tolerated at each dose, with an adverse event profile similar to previous findings in the clinical program. The overall proportion of subjects experiencing adverse events was similar among all treatment groups. The incidence of moderate and severe injection site reactions and of serious adverse events was low in all treatment groups. Downward-dosing titrations were more frequent in higher dose groups.

1.2.6. Rationale for Dose Selection

The dose selected for Phase 3 is a starting dose of 150 mg administered SC, every two weeks (Q2wks), with a potential modification to a dose of 75 mg Q2wks for subjects with two consecutive low LDL-C concentrations (≤10 mg/dL or 0.26 mmol/L) at the end of the dosing interval. Additionally, subjects with two consecutive low LDL-C concentrations ≤10 mg/dL

(0.26 mmol/L), even after a dose reduction, will have their dose frequency modified to 75 mg every four weeks (Q4wks).

In study B1481015, multiple subcutaneous (SC) doses of bococizumab as high as 150 mg Q2wks and 300 mg Q4wks (up to 24 weeks) were safe and well-tolerated. The primary rationale for dose selection was based on the pharmacokinetic/pharmacodynamic (PK/PD) model-predicted LDL-C percent change from baseline (CFB) and the estimate of the proportion of subjects with very low LDL-C at the end of the dosing interval. The probability of achieving a target effect (risk reduction in CV events) was also estimated by taking into consideration the uncertainty in the dose response profile, clinical relevance of the magnitude of effect, and the desired level of confidence in the effect size.

Based on population PK/PD modeling, a dose of 150 mg Q2wks is approximately equivalent to the dose associated with 80% of the maximal LDL-C lowering response (ED80). This dose is predicted to result in a -68.2 percent CFB, and is a dose where the percentage of subjects with LDL-C concentrations ≤10 mg/dL (0.26 mmol/L), at the end of a dosing interval, is expected to be approximately 5%. Clinical trial simulations where the proposed dose modification rules for this protocol are implemented for subjects with an LDL-C ≤10 mg/dL (0.26 mmol/L) predict that 7.7% of subjects will be titrated to 75 mg Q2wks and a further 0.4% will have dose frequency modified to 75 mg Q4wks. Assuming a mean LDL-C baseline of 119 mg/dL (3.08 mmol/L), which is expected with an LDL-C inclusion criterion of ≥100 mg/dL (2.59 mmol/L), the mean absolute LDL-C change from baseline is predicted to be -79.5 mg/dL (2.06 mmol/L). A model-based meta-analysis of the relationship between on-trial LDL-C differences and relative risk (RR) for (1) "any" CV event (a composite endpoint of CV death, MI, and stroke, revascularizations, and/or hospitalizations due to unstable angina) and (2) CV events with end organ injury (a composite endpoint limited to CV death, MI, and/or stroke, sometimes described as a "hard"endpoint) was used to simulate the probability distribution of risk reduction for CV events for bococizumab vs. control, given the trial design and subject characteristics proposed for this protocol. The estimated RR for "any" CV event was 0.61 (90% PI: 0.50, 0.76) with an 85.4% probability the observed RR ≤0.70 (one-sided α=0.025). The estimated RR for CV events with end organ injury was 0.62 (90% PI: 0.48, 0.81) with a 77.4% probability the observed RR ≤0.70 (one-sided α=0.025).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. 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 4), 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).

2.1.2. Secondary Objectives

2.1.2.1. Clinical 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 4) 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.

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 4) 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.

2.1.2.2. Circulating Biomarker Secondary Objectives

2.1.2.2.1. LDL-C

To 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.

2.1.2.2.2. Other Circulating Lipid Biomarkers

To 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).

2.1.2.2.3. Inflammatory Circulating Biomarker

To 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.

2.1.2.3. Health Care Resource Utilization Objectives

To 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, 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.

2.1.2.4. Safety Objectives

To 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 ADA assessments.

2.2. Endpoints

This protocol will use an independent endpoint adjudication committee to determine whether certain investigator-reported events meet the definition of disease-related efficacy endpoints, using pre-defined endpoint criteria. For all clinical endpoints listed below, a description of qualifying outcome events can be found in Appendix 4. The criteria determining whether a potential clinical event qualifies as an adjudicated and confirmed clinical outcome event are defined in the Adjudication Committee Charter.

2.2.1. Primary Endpoint

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

2.2.2. Key Secondary Endpoints

Key secondary endpoints are defined as 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, non-fatal stroke, and hospitalization for unstable angina needing urgent revascularization;
- A composite endpoint of all-cause death, non-fatal MI, non-fatal stroke;
- Hospitalization for unstable angina needing urgent revascularization.

2.2.3. Other Clinical Secondary Endpoints

Other clinical secondary endpoints are defined as 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, 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.

2.2.3.1. Circulating Biomarker Endpoints

2.2.3.1.1. LDL-C

The percent change and nominal change, from baseline at Week 14 (Visit -8) and percent change from baseline to the last available post-randomization value, in LDL-C (direct measurement).

2.2.3.1.2. Other Circulating Lipid Biomarker Endpoints

The percent change from baseline at Week 14 (Visit 8) in levels of:

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

2.2.3.1.3. Inflammatory Circulating Biomarker

- The percent change from baseline at Week 14 (Visit 8), in levels of hs-CRP.

2.2.3.2. Health Care Resource Utilization Endpoints

The HCRU endpoints include:

- The occurrence, primary and secondary discharge diagnoses, overall length of stay, duration of stay in different medical care units, and discharge disposition, of 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, of 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, and discharge disposition.

2.2.4. 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. See Section 7.2 for details.

2.2.5. Assessment of Clinical Efficacy and Safety Endpoints

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 (as defined above), 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 4. The Adjudication Committee will confirm whether potential disease-related efficacy endpoints 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*.[41] Other endpoint definitions will be based upon the *Standardized Definitions for Cardiovascular and Stroke End Point Events in Clinical Trials*.[42]

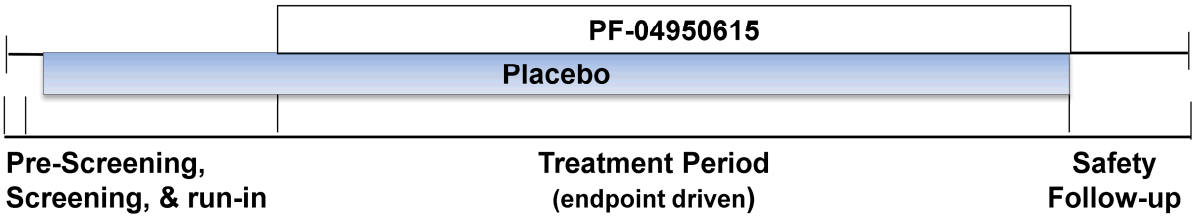
For those Serious Adverse Events (SAEs) that are handled as disease-related efficacy endpoints (which includes death), a data monitoring committee (DMC) will conduct unblinded reviews on a regular basis throughout the trial (see the Data Monitoring Committee, Section 3.4.3). The DMC is responsible for ongoing analysis of these events and for informing the sponsor of recommendations made (eg, to continue the study or to stop the study). Disease-related efficacy endpoints are described in Section 8.6.1.

Pfizer will utilize an internal serious adverse event (SAE) triage group to ensure the correct reporting of SAEs to the Pfizer Drug Safety Unit (as defined in Section 8.14.1).

3. 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 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 qualifies for this study. The interactive response technologies (IRT) system will determine if the subject qualifies for the 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 2).

Figure 2. B1481038 Study Diagram



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 IP administered by a caregiver (eg, 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 duration of the trial is expected to be approximately 3.9 years (see Section 9.1). The End of Study (EOS) will be announced to study sites, when the Sponsor estimates that criteria for stopping the study in Section 3 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 IP is administered for subjects taking IP. The safety follow-up period is 40 days after the last dose of IP was administered. 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.

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. For more information on the interim analysis, see Section 9.5.

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.

3.1. Number and Location of Study Sites

The study will be conducted in North America, Latin America, Europe, Africa, Asia, and Australia in approximately forty countries.

3.2. Study Population

Subjects will be men and women with a high risk or very high risk of incurring major CV events based on the study inclusion and exclusion criteria (Section 4).

3.3. Treatment Periods

3.3.1. Pre-screening Visit

A pre-screening visit is required for all subjects. Sites will obtain informed consent from potential subjects to evaluate baseline lipids and obtain medical records for review, only, so as to determine if the subject qualifies for this study. The lipid assessments will be done using the central laboratory.

3.3.2. Screening Visit

The time interval between the Pre-screening Visit (Visit 0) and the Screening Visit (Visit 1) is a maximum of 30 days. At the screening visit, after obtaining consent for participation in study B1481038, potential subjects will be fully evaluated for eligibility, based on the prescreening lipid values and medical records obtained after the pre-screening visit, and a review of the complete study specific inclusion/exclusion criteria, as described in Section 4.

3.3.3. Run-In Period

After the screening visit, qualified subjects will begin a run-in period of up to six weeks duration during which they will receive SC injections of open-label placebo IP no less than 7 and no more than 14 days apart.

The primary objectives of the run-in period are to ensure (1) compliance with the SC administration of a parenteral agent, (2) that subjects meet inclusion and exclusion criteria and (3) can follow study procedures.

3.3.4. Active Treatment Period

At the randomization visit, the subject will be assigned to either active treatment or placebo IP in a blinded fashion. IP will be administered SC by self-injection, or by a trained caregiver, Q2wks during the course of the study, unless there has been an IP dose modification to a frequency of Q4wks (Section 5.4.1.1). Subsequent visits for assessments of

efficacy, safety, and tolerability will be scheduled according to the Schedule of Activities, unless there has been an IP dose modification to Q4wks, in which case subjects will be seen every 8 weeks, approximately, until the completion of the study.

Subjects may return to the study site for unscheduled visits, or to replenish IP supplies, if necessary. Subjects who discontinue IP will be followed until the completion of the study. 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.

3.3.5. Safety Follow-up Period

The safety follow-up period will comprise 40 calendar days after the last administration of the IP.

3.4. External Committees

3.4.1. Executive Committee

An Executive Committee will be responsible for providing overall guidance to Pfizer on the study protocol. This will include evaluation of the scientific merit of proposed sub-studies, execution of the trial, review of recommendations from the Data Monitoring Committee (DMC) and oversight of study publications. A separate charter will document specific policies and procedures of the Executive Committee.

3.4.2. Adjudication Committee

An Adjudication Committee will perform a blinded review of all potential primary, secondary, and tertiary endpoints (as specified in the Adjudication Committee Charter) to confirm that the data support the endpoint designation. The Adjudication Committee Charter describes the Adjudication Committee's responsibilities and how it will function.

3.4.3. Data Monitoring Committee

Subject safety will be monitored by an independent data monitoring committee (DMC). An independent statistical data analysis center will provide analyses to the DMC according to the DMC charter. In addition, the DMC will review the interim analysis for clinical benefit. The same independent statistical data analysis center will provide the analyses to the DMC. Refer to Section 9.6 for a full description of the functions of the DMC.

3.4.4. Steering Committee

The Steering Committee comprises medical representatives from each country of study operations and will oversee recruitment, retention and quality issues within the country. This committee will work jointly with the Executive Committee, to ensure that operational issues are effectively addressed on a national level.

3.4.5. Joint Leadership/Operations Committee

The Joint Leadership/Operations Committee will be responsible for the operational aspects of study execution, global site initiation and monitoring, recruitment and data quality issues across the different academic and clinical research organizations. It will make recommendations to the Executive Committee and Steering Committee members on quality issues within countries or across regions. A separate charter will document specific policies and procedures of the Joint Leadership/Operations Committee.

4. SUBJECT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled and followed throughout the completion of the trial irrespective of whether they are maintained on IP. All efforts should be made to follow all subjects for the entire duration of the study. Importantly, discontinuation of IP does not imply or constitute withdrawal of the subject from the study. Section 6.5 describes the follow-up procedures for Subjects who withdraw from IP. In general, Investigators should try to obtain the most complete collection of data as possible from subjects who discontinue IP, weighing the subject's willingness to participate with the scientific integrity of the protocol. Those subjects who are *a priori* unwilling to agree to the collection of this information in the event that they discontinue IP should not be enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

4.1. Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team, before subjects are included in the study. Appropriately qualified members of the investigator's study team are defined in the study site's delegation of authority log.

A key element of eligibility is the investigator's documentation that the subject is at high or very high risk of incurring a CVD event. Adequate documentation of objective evidence of the criterion that qualifies the subject as being at high risk or very high risk for CVD events must be available in the investigational site's source documents including medical records, copies of such records from other institutions, or a letter from a referring physician that specifically provides diagnostic information and/or diagnosis and date of a qualifying CV event, when relevant.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Informed Consent

There must be evidence of personally signed and dated informed consent documents for both the pre-screening and screening visits, indicating that the subject (or a legal representative) has been informed of all pertinent aspects of the study. The pre-screening visit informed consent form will be limited to study activities up until the screening visit. The screening

visit informed consent form will cover all aspects of the study. Subjects should be reconsented if there are modifications to the original informed consent document, at the next available opportunity.

2. Compliance

Subjects must be willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

3. Age

Subjects who have had a prior CVD event, must be men or women age ≥ the legal age of majority (legal adulthood), in the subject's country.

Subjects who have not had a prior CVD event, must be age ≥50 years, if a man, and must be age ≥60 years, if a woman, with the following exceptions:

Subjects who have not had a prior CVD event, but who have a conditions of elevated LDL-C, (heterozygous familial hypercholesterolemia [heFH] or a history of LDL-C ≥190 mg/dL [4.9 mmol/L]) should be ≥35 years of age if a man, and ≥45 years of age, if a woman.

4. Acceptance of administration of investigational product

Subjects must be willing and able to self-administer or be administered sub-cutaneous injections of IP.

5. Requirements for background lipid lowering treatment

There should be no plans at the time of pre-screening and randomization to modify the dose of statin for the duration of the trial. Unless the background lipid lowering treatment exceptions described below are met, subjects must be treated with one of the following highly effective statins at the specified daily doses for ≥4 weeks prior to the pre-screening visit:

- atorvastatin, at least 40 milligrams (mg) once a day;
- rosuvastatin, at least 20 mg, once a day;
- simvastatin, at least 40 mg, once a day or, if a subject has been on that dose for >1 year, 80 mg, once a day.

Combination medications that contain atorvastatin, rosuvastatin, or simvastatin components described at the aforementioned doses will be permitted.

Background lipid lowering treatment exceptions

The following background lipid lowering treatment exceptions are permitted:

- **Lower doses of statins due to partial statin intolerance**

  Subjects may be on a lower dose of one of the highly effective statins described above if there is documented intolerance to any one of them (atorvastatin, rosuvastatin, or simvastatin) at the aforementioned, or lower, doses.

  Intolerance to any dose of any statin must be documented as historical adverse events attributed to the statin in question, in the source documentation and case report form (CRF).

- **Regulatory limitations**

  Subjects may be on a lower dose of one of the highly effective statins described above if the highest locally approved dose for one of the stated statins is lower than those doses shown above (eg, in Japan, atorvastatin 20 mg, once a day, is the highest locally approved dose) or due to label restrictions.

- **Alternative statins**

  Subjects may be treated with other statins (pravastatin, fluvastatin, pitavastatin, or lovastatin), different from the highly effective statins listed above, if there is documented intolerance to any two different highly effective statins (atorvastatin, rosuvastatin, simvastatin) at the lowest available daily dose for at least one of those highly effective statins. Intolerance to any statin must be documented as historical adverse events attributed to the statin in question, in the source documentation and CRF.

- **No background statin therapy**

  Subjects may be enrolled who are only on non-statin lipid lowering therapy (drug and/or preventive cardiology lifestyle change guidance), if complete statin intolerance has been documented. Subjects with complete statin intolerance must be unable to tolerate at least two statins: one statin at the lowest available daily dose AND another statin at any dose. Intolerance to any statin must be documented as historical adverse events attributed to the statin in question, in the source documentation and CRF. The sole exception, for which a subject may participate in the study with documentation of intolerance to only one statin, is a documented history of rhabdomyolysis attributed to that statin or a history of documented statin allergy, precluding challenge with an alternative statin.

6. Qualifying cardiovascular disease risk

Qualifying cardiovascular disease (CVD) risk must be documented by supporting source documentation such as, but not limited to, copies of a hospital discharge summary, copies of medical records, or other documents that can be used to confirm the qualifying CVD risk event or diagnosis and its approximate date of occurrence or onset. Ideally, this

documentation should be acquired before Visit 1. A subject may qualify for inclusion according to the following (see Appendix 10):

a. Myocardial infarction

- A subject may qualify for inclusion if he/she had a prior myocardial infarction >30 days and ≤5 years, prior to screening;
- A subject may qualify for inclusion if he/she had an MI >5 years before screening if he/she also has an additional CVD risk condition and one additional CVD risk factor, two additional CVD risk conditions, or two additional CVD risk factors, (CVD risk conditions and CVD risk factors are described below in e);
- The diagnosis of a silent MI based solely on ECG criteria of new Q waves, without additional imaging evidence showing a corresponding fixed regional wall motion abnormality, is **not** considered sufficient evidence for a qualifying MI CV event.

OR

b. Ischemic stroke

- A subject may qualify for inclusion if he/she had a prior ischemic stroke, as documented by hospital discharge summary or medical records which have evidence of confirmatory brain scan imaging, >30 days, and ≤5 years prior to screening;.
- A subject may qualify for inclusion if he/she had a prior ischemic stroke, as documented by hospital discharge summary or medical records which have evidence of confirmatory brain scan imaging, >5 years before screening, he/she also has an additional CVD risk condition and one additional CVD risk factor, two additional CVD risk conditions, or two additional CVD risk factors (CVD risk conditions and CVD risk factors are described below in e);

OR

c. Coronary artery revascularization

- A subject may qualify for inclusion if he/she had a prior coronary artery revascularization >90 days, but ≤5 years prior to screening, including PCI, thrombolysis, or CABG, as documented by hospital discharge summary or medical records. For a PCI performed during the same hospitalization as an MI, the date of the PCI (not the date of the MI) determines whether the subject is qualified for inclusion);
- If the prior coronary artery revascularization was >5 years before screening, the subject may qualify for inclusion if he/she also has an additional CVD risk

condition and one additional CVD risk factor, two additional CVD risk conditions, or two additional CVD risk factors (CVD risk conditions and CVD risk factors are described below in e);

- A purely diagnostic coronary angiogram or cardiac catheterization without revascularization (eg, angioplasty, stent placement, or thrombolysis) does **not** qualify as a prior CV event;

OR

d. Non-coronary arterial revascularization

- A subject may qualify for inclusion if he/she had a prior non-coronary arterial revascularization, >30 days, and ≤5 years prior to screening documented as a carotid, abdominal aortic aneurysm repair, or peripheral artery revascularization, by either open surgery, endovascular catheterization, or thrombolysis, with or without stent placement;

- A purely diagnostic angiogram or catheterization without revascularization (eg, angioplasty, stent placement, or thrombolysis) does **not** qualify as a prior CV event;

- If the prior non-coronary arterial revascularization was more than five years before screening, the subject may qualify for inclusion if he/she also has an additional CVD risk condition and one additional CVD risk factor, two additional CVD risk conditions, or two additional CVD risk factors (CVD risk conditions and CVD risk factors are described below in e);

OR

e. CVD risk conditions and CVD risk factors

- Subjects may qualify for inclusion if they have two CVD risk conditions,

OR

- one CVD risk condition and two CV risk factors (described below),

OR

- a condition of elevated LDL-C as specified below.

- **CVD Risk Conditions**

  - **Diabetes**

    A subject may qualify for inclusion if he/she has Type I or Type II diabetes mellitus, (as defined per local diabetes guidelines, eg, American Diabetes Association in the United States of America (USA)., European Association for the Study of Diabetes [EASD] in the European Union [EU]) and one other CVD risk condition listed here, or two additional CVD risk factors (see below);

  - **Peripheral vascular disease**

    A subject may qualify for inclusion if he/she has:

    - peripheral vascular disease with current or historical documentation of a measured ankle brachial index (ABI) of <0.85; or
    - significant (> 50%, or reported as hemodynamically significant) peripheral artery stenosis in at least one limb, using any kind of imaging technology; or
    - a prior amputation for peripheral vascular disease; or
    - imaging evidence of a significant (>50%) stenosis in at least one carotid artery; or
    - a high carotid plaque burden, using ultrasound, with a total plaque area >119 mm^2 of plaque or equivalent plaque volume; and

    one other CVD risk condition listed here, or two additional CVD risk factors (see below);

  - **Chronic kidney disease**

    Chronic kidney disease with an estimated glomerular filtration rate of ≥30 and ≤60 mL/min/1.73m^2, based on the screening visit measurement of creatinine, as calculated by the Modification of Diet in Renal Disease [MDRD] formula, and not on dialysis and one other CVD risk condition listed here, or two additional CVD risk factors (see below);

  - **Conditions of elevated LDL-C**

    Conditions of elevated LDL-C are defined as:

    - a history of heterozygous familial hypercholesterolemia (heFH) as described in Appendix 2

or

- a history of LDL-C ≥190 mg/dL (4.9 mmol/L) regardless of whether or not the subject was taking background lipid lowering therapy at the time the measurement was made.

Subjects with a condition of elevated LDL-C **with a prior CV event** only need to be of legal age. For subjects with a condition of elevated LDL-C **and without a prior CV event**, they should be at least 35 years old if a man and 45 years old if a woman as specified in the age criteria, above.

Subjects who have a condition of elevated LDL-C **without a prior CV event** must have at least one additional risk condition or risk factor, and they must meet the age criteria as specified above, to qualify for inclusion.

- **CVD risk factors**

  - **Imaging evidence of significant coronary artery disease**

    Current or historical evidence of coronary artery stenoses of >50% narrowing in the left main coronary artery or at least two major coronary arteries (left anterior descending, circumflex, or right coronary arteries) as documented by any type of coronary artery imaging with the exception that a previously stenotic coronary artery, which was subsequently revascularized, cannot be counted as a CVD risk factor;

    or,

    A coronary artery calcium score of ≥300 Agatston units or ≥75th percentile for age, sex, and ethnicity;

- **Smoking**

  Current cigarette smoking, defined as smoking for 30 days or more (any number of cigarettes) at the time of screening;

- **Low levels of HDL-C**

  HDL-C <40 mg/dL (<1.03 mmol/L) as measured at the pre-screening visit;

- **Elevated levels of hs-CRP**

  hs-CRP >2.0 mg/L documented within one year of the screening visit;

- **Microabluminuria**

  A positive measure of microalbuminuria (a spot urine albumin-to-creatinine ratio >30 mg/g) at the screening visit;

- **Lipoprotein (a)**

  Any history of Lp(a) cholesterol ≥50 mg/dL.

7. Qualifying lipid levels (LDL-C or non-HDL-C)

Subjects must have a direct LDL-C measurement of ≥100 mg/dL (2.59 mmol/L) or non-HDL-C ≥130 mg/dL (3.36 mmol/L) at the pre-screening visit, to qualify for inclusion in the study. The lipid values collected at Visit 3 are not used to determine qualification.

8. Contraception requirements

Male subjects able to father children and female subjects of childbearing potential, who (with their partners) are at risk for pregnancy, or male subjects with pregnant partners who are sexually active, must agree to use a highly effective method of contraception throughout the study and for at least 63 days after the last dose of assigned treatment. A male subject need not use contraception with his partner who is not of childbearing potential as defined below.

Female subjects who are not of childbearing potential should meet at least one of the following criteria:

- Have undergone a documented hysterectomy and/or bilateral oophorectomy;
- Have medically confirmed ovarian failure, or
- Achieved post-menopausal status, defined as: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed by having a serum follicle stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal females.

All other female subjects (including female subjects with tubal ligations) will be considered to be of childbearing potential.

4.2. Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

1. Personnel involved in the conduct of the study

Subjects who are investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the

Investigator, or subjects who are Pfizer employees directly involved in the conduct of the trial.

2. Exclusionary prior CV events or planned revascularization procedures

A planned coronary (PCI or CABG) or other arterial revascularization;

Myocardial infarction, stroke, or any non-coronary arterial revascularization ≤30 days prior to screening;

Coronary revascularization ≤90 days prior to screening;

Subjects with SAEs that would have potentially met the criteria for a CVD event (as defined in Appendix 4), between Visit 0 and Visit 5, should be excluded. Such subjects may be rescreened at a later date.

3. Participation in prior clinical research studies

Participation in other studies involving small molecule investigational drug(s) (Phases 1-4) within 1 month, or five half-lives, of Visit 1, whichever is longer; any participation in a cholesteryl ester transfer protein (CETP) inhibitor within 1 year of Visit 1; or any biological agents within 6 months or 5 half-lives, of Visit 1, whichever is longer (the investigator should refer to documents provided by the subject on the other study to determine the IP half-life). If the blind of the prior study has been broken and the investigator provides documentation that the subject received placebo, the potential subject can be included, regardless of when participation occurred.

4. Other exclusionary conditions

Other severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or IP administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

5. Childbearing potential and/or breast feeding

Pregnant female subjects; breastfeeding female subjects; male subjects with partners currently pregnant who are sexually active; male subjects able to father children and female subjects of childbearing potential, who are at risk of pregnancy with their partners and are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for 63 days after last dose of IP (refer to Section 4.4.2).

6. Latex sensitivity

Latex sensitive individuals (due to potential for exposure to natural dry rubber in the pre-filled syringe cap of IP, during administration).

7. Apheresis

Undergoing lipid apheresis, within 6 weeks of pre-screening, or planned start of lipid apheresis.

8. Severe congestive heart failure

Congestive heart failure of New York Heart Association (NYHA) Class IV, or if there is prior documentation of left ventricular ejection fraction (LVEF) of <25%, measured by imaging. For subjects who have had serial assessments of LVEF, only the most recent study is used for the purposes of this exclusion requirement.

9. Dialysis

Potential subjects with end stage renal disease on dialysis.

10. Chronic renal insufficiency

Potential subjects with an eGFR of <30 ml/min/1.73m^2 by MDRD formula at Visit 1.

11. Hypertension

Poorly controlled hypertension at any screening visit or at randomization, defined as the average of two systolic blood pressure (BP) measurements >180 mmHg or the average of two diastolic BP measurements >110 mmHg even with treatment. Subjects who have hypertension and are controlled on stable doses of anti-hypertensive medications may be included. An additional set of BP measurements may be performed within the hour or at the completion of the office visit, to determine if a subject may be included in the study, given the potential for "white coat hypertension." The final set of measurements will be the measurements of record.

12. Cerebral hemorrhage risk

A prior history of hemorrhagic stroke or lacunar infarct resulting in a stroke (a lacunar infarct which was seen with cerebral imaging is not exclusionary in the absence of a clinical stroke). A prior ischemic stroke which resulted in hemorrhagic transformation is not exclusionary.

13. Tissue donation

Plans to donate any tissues (eg, blood, sperm, or other tissues, including participating in *in vitro* fertilization) during the study.

14. Substance abuse

Current history of alcoholism or drug addiction according to diagnostic and statistical manual of mental disorders (DSM) IV criteria within 12 months prior to screening. Use of any recreational drugs within 12 months prior to screening.

15. Human immunodeficiency virus

Medical history of positive testing for human immunodeficiency virus (HIV).

16. Prior or anticipated exposure to a PCSK9 inhibitor

Subjects with prior exposure to bococizumab or other PCSK9 inhibitors;

Subjects who, in the opinion of the investigator, are likely to be treated with a marketed PCSK9 inhibitor at any time during the conduct of the study.

17. Depression

If the subject's Patient Health Questionnaire (PHQ-9) score is ≥15 or there is a positive score in question 9 (Section 7.3.2), 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.

18. Hypersensitivity to monoclonal antibodies

History of allergic or anaphylactic reaction to any therapeutic or diagnostic monoclonal antibody (immunoglobulin G [IgG] protein) or molecules made of components of monoclonal antibodies (eg, Enbrel® which contains the fragment crystallizable [Fc] portion of an antibody or Lucentis® which is a monoclonal antibody fragment).

19. Hepatitis

- Hepatitis B

  Positive hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (anti-HBc), or tests indicative of present or prior infection. NOTE: If a subject tests negative for HBsAg, but positive for anti-HBc, the subject would be considered eligible only if the subject tests positive for antibody to HBsAg (anti HBs) upon reflex testing (see Appendix 3).

- Hepatitis C

  Serologic tests indicative of past or present hepatitis C virus infection. A positive or indeterminate hepatitis C serology may trigger a hepatitis C polymerase chain reaction (PCR) test for confirmation. If the hepatitis C PCR is negative, the subject may be included.

20. Creatine kinase elevations

Creatine kinase (CK) ≥3.0 x upper limit of normal (ULN) at Visit 1. A measurement ≥3.0 x ULN may be repeated once, no later than Visit 2, and if <3.0 x ULN the subject is eligible.

21. Amino transferase elevation

Alanine amino transferase (ALT) or aspartate amino transferase (AST) >2 x ULN, at Visit 1. These labs may be repeated once for values >2 x ULN, no later than Visit 2, and if ≤2 x ULN the subject is eligible.

22. Bilirubin elevation

Direct bilirubin >1.5 X ULN, at Visit 1. This may be repeated once for values >1.5 X ULN, no later than Visit 2, and if ≤1.5 x ULN the subject is eligible.

23. Malignancy

Subjects with cancer who are actively receiving chemotherapy. Potential subjects with a prior history of malignancy should have thorough documentation of the malignancy type and the extent of disease. Potential subjects considered at high risk of recurrence or the development of metastatic disease within the time frame of the conduct of the clinical trial should be excluded.

24. Gastric bypass surgery

Planned or previous gastric bypass surgery.

4.3. Randomization Criteria

Subjects will be randomized into the trial upon satisfactory completion of the run-in period if they have demonstrated 100% compliance with all injections of placebo and satisfied all subject selection criteria (Sections 4.1 and 4.2), unless there are extenuating circumstances which require further evaluation (see Section 5.1.5). A computer-generated randomization schedule will be used to assign subjects to treatment with bococizumab or placebo in a 1:1 ratio. The randomization schedule will be stratified by geographic region and complete statin intolerance.

4.4. Life Style Guidelines

During protocol feasibility activities, study teams should become familiar with acceptable contraception wording in the countries in which the protocol will be conducted to ensure protocol acceptability during the Ethics review.

4.4.1. Nutritional Counseling

All subjects will be provided with counseling for diet and therapeutic lifestyle change recommendations for the prevention of CV disease, in accordance with ESC/EAS[5] or

NCEP-ATP-III[6] guidelines at all study visits, from screening to EOS. Documentation of such counseling will be recorded in the CRF for each visit.

4.4.2. Contraception

All male subjects able to father children and female subjects of childbearing potential, who, in the opinion of the investigator, are biologically capable of having children and are sexually active, and are at risk for pregnancy with their partners, and male subjects with pregnant partners who are sexually active must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 63 days after the last dose of IP. The investigator or his/her designee, in consultation with the subject, will confirm the subject has selected the most appropriate method of contraception, for the individual subject, from the permitted list of contraception methods (see below) and instruct the subject in its consistent and correct use. Subjects must affirm that they meet the criteria for the correct use of at least one of the selected methods of contraception. The investigator or his/her designee will discuss with the subject the need to use highly effective contraception consistently and correctly. These discussions will take place according to the Schedule of Activities (SOA) will be documented in the subject's chart. In addition, the investigator or his/her designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject, or the subject's partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include:

1. Established use of hormonal methods of contraception associated with oral inhibition of ovulation (eg, inserted, injected, implanted, or transdermal) provided the female subject or male subject's partner plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper containing intrauterine device (IUD).

3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate: eg, For male subjects from Denmark, condom use WITH a spermicide is acceptable. For female subjects from Denmark, condom use WITH a spermicide is not acceptable and other highly effective methods of contraception described in this section should be used.

4. Male sterilization with absence of sperm in the post-vasectomy ejaculate.

5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

4.5. Sponsor Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the trial is documented in the study contact list located in the coordinator's manual. Appropriately qualified members of the investigator's study team are defined in the study site's delegation of authority log. To facilitate access to appropriately qualified medical personnel, on study related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, subject study number, contact information for the investigational site and contact details for a help desk in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The help desk number can also be used by investigational staff if they are seeking advice on medical questions or problems, however it should only be used in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace the established communication pathways between the investigational site and study team for advice on medical questions or problems that may arise during the study. The help desk number is not intended for use by the subject directly and if a subject calls that number they will be directed back to the investigational site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonization (ICH) guidelines investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

Investigational product will comprise placebo and bococizumab. During the run-in period, subjects will be receiving placebo. After completion of the run-in period the subjects will be randomized into two parallel groups. One group will receive bococizumab and the other group will continue to receive placebo, both delivered by the SC route every two weeks.

During the run-in and treatment periods, subjects will be taking their prescribed background lipid lowering treatment(s). Lipid lowering treatment doses, frequency, and changes in dose or frequency will be recorded in the CRF at each visit. When background lipid lowering treatment changes occur, the reason for those changes should be documented in both the source documentation and CRF.

5.1. Allocation to Treatment

5.1.1. Interactive Response Technology Registration

Allocation of subjects to treatment groups will proceed through the use of an Interactive Response Technology (IRT) System (Interactive Web Response [IWR]/Interactive Voice Response [IVR] system). The site personnel (study coordinator or specified designee) will

be required to enter or select information including, but not limited to, the user's identification (ID) and password, and protocol number to access the system. For each subject, at the initial registration call, the site personnel will be provided with a subject identification number that will be used to track the subject throughout the study.

At each study visit, the site personnel will be provided with a treatment assignment as a dispensable unit (DU) number. The IRT system will provide a confirmation report containing the subject number and DU or container number assigned. The confirmation report must be stored in the site's files.

There is a 24 hour a day, 7 days a week, IRT helpdesk available for any questions or issues. The study specific IRT reference manual will provide the contact information and further details on the use of the IRT.

An IRT operations manual will be provided to the study site. The IRT operations manual will describe the IRT functions for each visit, and will serve as the reference manual throughout the conduct of the study.

5.1.2. Visit 0, Pre-screening Visit

Each subject will be assigned a unique identifier number at Visit 0 by the IRT for Study B1481038.

5.1.3. Visit 1, Screening Visit and Run-In Period

If the subject continues to qualify for this study, based on the pre-screening lipid values and medical history, the subject will continue to be assigned to Study B1481038, otherwise the subject will be screen failed.

5.1.4. Run-in Period Visits

For subjects continuing in Study B1481038, the run-in period starts at Visit 2. The objectives of the run in period are to ensure (1) compliance with the SC administration of a parenteral agent, (2) that subjects meet inclusion and exclusion criteria and (3) can follow study procedures. There will be IRT interactions at each run-in visit.

5.1.5. Visit 5, Randomization Visit and Active Treatment Period

At Visit 5, if the subject meets all randomization criteria and has 100 percent compliance with injections during the run-in period, the system will randomize the subject to receive the administration of subcutaneous injections of IP, either bococizumab (I) or placebo (II) (Table 1). If extenuating circumstances arise during run-in phase preventing 100 percent compliance with injections (eg, the subject is prevented from getting to a scheduled study site visit or the study site is unable to provide IP), such cases should be discussed with the Sponsor to determine if the subject should continue on to randomization. Randomization will use a permuted block design stratified by geographic region and complete statin intolerance. Subjects, who are disqualified from allocation to blinded treatment, will be registered as screen failures in the system.

Table 1. Treatments

Group	
I	bococizumab, 150 mg SC, Q2wks
II	Placebo injection, SC, Q2wks

The IRT system will be used for each study visit, during the active treatment period, to assign IP for each subject. For subjects who are randomized to the active treatment arm, blinded bococizumab will initially be administered at a dose of 150 mg SC Q2wks. For subjects who are randomized to placebo, blinded placebo will initially be administered SC Q2wks. Blinded dose modifications may take place, through the IRT system, based on trigger measurements of LDL-C (5.4.1.1).

At Visit 5, after the subject has been randomized, and all other procedures and assessments completed, the first active treatment period dose will be self-injected, or injected by a care-giver, at the clinic. The subject will be observed at the study site, by the study site personnel, for 30 minutes after the self-injection. Subjects will be provided with a dosing schedule by site personnel based on the date of randomization. Subjects will receive sufficient pre-filled syringes (PFSs) to self-inject between clinic visits. As noted in the Schedule of Activities, many of the scheduled doses will also coincide with scheduled visits. When a scheduled dose occurs on the same day as a scheduled visit, subjects should hold their self-injected dose until they are at the clinic and self-inject or be administered an injection by a care provider only after all other study procedures for that visit have been completed.

Injections 1 day before or up to 4 days past the scheduled day of administration are allowed. 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.

Subjects should adhere to their treatment schedule even if their scheduled clinic visit is rescheduled or missed due to unforeseen circumstances.

Subjects will continue to receive their prescribed, background lipid lowering therapy, at the dose that they had taken at the last visit of the run-in period prior to the randomization visit.

5.2. Breaking the Blind

The study will be subject, investigator, and sponsor blinded.

At the initiation of the study, the study site will be instructed on the method for breaking the blind. When appropriate, the Principal Investigator or designee must interact with the IRT to obtain the treatment assigned to the subject. Blinding codes should only be broken in emergency situations for reasons of subject safety. Whenever possible, the investigator or sub-investigator should contact a member of the study team, prior to breaking the blind. It is understood that in an emergency situation, it may not be possible to communicate with the study team, prior to breaking the blind. The safety of the subject should be of primary

concern. When the blinding code is broken, the reason must be fully documented and entered on the CRF.

To protect the blind, the subject, investigator, sub-investigators, and sponsor should be blinded with respect to lipid values and under no circumstances should more than one carton of IP be opened to compare unused syringe fill volumes, at any one time. In addition, to protect the blind, any IP dose adjustments made in the blinded active treatment arm, will be matched by a sham dose adjustment in the blinded placebo arm, through the IRT system.

5.3. Subject Compliance

Compliance will be evaluated at all visits beginning with Visit 2. During the run-in period visits (Visits 2, 3, 4) and at the randomization visit (Visit 5), compliance refers to the observation of the correct administration of study drug, since dose administration will be observed at the study site. The criterion for acceptable IP compliance during the run-in period is as follows:

Run-in period compliance will be checked at each visit after Visit 2 (beginning of the run-in period). Any subject found to be taking less than 100 percent of the prescribed IP will be considered non-compliant and should be discontinued prior to randomization, unless there are extenuating circumstances which require further evaluation (see Section 5.1.5).

From Visit 5, the randomization visit, onward, subjects will be dispensed study drug, to take home with them. 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 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:

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

Following randomization, should subjects have less than 100% compliance, the investigator or designee should assess potential factors leading to less than complete compliance and take steps to improve compliance.

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.

5.4. Investigational Product Supplies

5.4.1. Dosage Form and Packaging

Blinded IP, placebo or bococizumab 100 mg/mL, will be presented as a sterile solution, in pre-filled syringes, for subcutaneous injection, throughout the trial. Each syringe will be packaged in an individual carton and sealed with a tamper-evident closure. Both syringes and cartons will be labeled in accordance with local regulations. The cartons should not be opened until the drug is to be administered. Each subject should receive enough pre-filled syringes to cover the number of doses until the next scheduled clinic visit.

Prefilled syringes containing sterile blinded IP (placebo solution), for subcutaneous injection will also be provided during the run-in period. The run-in period syringes may be of different volumes compared to those provided during the treatment period.

Dose volumes for IP (placebo or active treatment arms) may change during the conduct of the study when dose modifications in the active treatment arm occur (Section 5.4.1.1) and comparable sham dose modifications are triggered by the IRT in the placebo treatment arm.

Protection of the blind is to be ensured by the guidance that (1) no more than one syringe carton should be opened at any one time, (2) syringes should be discarded, into the provided biohazard sharps container, immediately after use, (3) the subject and the members of study site and study team should remain blinded to lipid values, and by the design elements whereby (1) IP dose modifications are made in both the active and placebo treatment arms of the trial and (2) active and placebo are blinded in appearance, packaging, labeling, and storage conditions.

The subjects will continue to take their prescribed lipid lowering and other treatments as background medications. None of these treatments will be provided as clinical trial drug supply.

5.4.1.1. Dose Adjustments

Lipid levels will be blinded to the investigator and staff, subject and sponsor study team. Lipid level values from study visits will be transmitted directly from the central laboratory to the IRT system. Dose modifications will be conducted through the IRT system to preserve the study blind.

If a subject randomized to bococizumab has two consecutive end of dosing interval LDL-C measurements ≤10 mg/dL (0.26 mmol/L), the dose of bococizumab, for that subject, will be adjusted to 75 mg SC Q2wks. If a bococizumab subject, again, has two consecutive end of dosing interval LDL-C measurements ≤10 mg/dL (0.26 mmol/L), after a dose modification to 75 mg SC Q2wks, the dose frequency will be modified to bococizumab, 75 mg SC Q4wks for the remainder of the study. For each bococizumab subject who has a dose adjustment or dose frequency change, a placebo subject with similar baseline LDL-C will be selected for the same dose adjustment or dose frequency change at the visit with the same visit number.

5.4.2. Preparation and Dispensing

See the Dosage and Administration Instructions (DAI), package insert or equivalent, for instructions in how to prepare the IP for administration. Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance. Only qualified personnel (Section 4.5) should dispense IP to subjects. At each study visit, subjects will be given multiple cartons of IP, for the purpose of ongoing treatment. Since some study visit intervals are as long as 18 weeks after the first year of treatment, subjects may need to return to the study site for re-supply, so that they have a sufficient quantity of IP to continue dosing, prior to each study visit.

The following procedures should be followed to help protect the blind:

Under no circumstances should more than one syringe carton be opened at a study center, at any one time. Similarly, neither the subject, nor the care-giver, should open more than one syringe carton, at any one time, in any location. Used syringes should be placed immediately after use, whenever or wherever dosing occurs, in a biohazard sharps container and the container will be returned to the study site, as needed, eg, when the biohazard sharps container is full, or at early discontinuation (EDC)/EOS visits.

5.5. Administration

In general, it is expected that subjects will self-administer IP during the run-in period and after randomization.

Qualified study site personnel will be trained on how to instruct subjects or care-giver in the proper administration of IP. Subjects, who are not capable of the self-administration of IP, may have the injections administered by a care-giver (eg, a family member or health care assistant) who has been trained in the procedure, during the run-in period. New or replacement caregivers will be trained for the administration of IP to a subject.

Instructions on the administration of IP will be provided at Visit 2, during the run-in period, and after randomization if re-training is necessary. Investigational product will be administered as a single SC injection as outlined on the subject dosing cards. The drug will be injected into the upper or lower quadrant of the abdominal wall. Study staff, care givers, and subjects should refer to the subject dosing instructions on the handling and administration of IP.

5.6. Investigational Product Storage

The investigator, or an approved representative, eg, pharmacist, will ensure that all investigational products, including any comparative agents and/or marketed products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational product should be stored in its original container and in accordance with the drug label. See the package label for storage conditions of the product. All IP should be

stored at 2 to 8° centigrade and protected from excessive shaking. Single use syringes should remain in the protective carton until the time of dosing.

Storage conditions stated in the SRSD (Investigator Brochure) will be superseded by the storage conditions stated in the labeling.

Site systems must be capable of measuring and documenting , at a minimum, daily minimum and maximum temperatures for all site storage locations. This should be captured from the time of IP receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to labeled storage conditions, as described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor.

Once an excursion is identified, the IP must be quarantined and not used until the sponsor provides documentation of permission to use the IP. It will not be considered a protocol deviation if the sponsor approves the use of the IP after the temperature excursion. Use of the IP prior to sponsor approval will be considered a protocol deviation.

Specific details regarding information the site should report for each excursion will be provided to the site.

Site staff will instruct subjects on the proper storage requirements for take home IP.

5.7. Investigational Product Accountability

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of IP supplies. All unused IP (kits, prefilled syringes, used and unused) must be returned to the investigator by the subject.

5.7.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused IP (eg, at the site). If destruction is authorized to take place at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

5.8. Concomitant Medication(s)

All permitted concomitant medication administration, as described below, should be recorded at each study visit; details as specified on the CRF and/or the CRF completion guidelines.

Subjects should take prescribed permitted concomitant medication, as needed, prior to the clinic visit, if it can be administered with water only. Prescribed permitted concomitant

medications that must be taken with food or after meals should not be taken until after the visit procedures have been completed.

5.8.1. Lipid Lowering Medication(s)

Subjects will continue to take their prescribed background lipid lowering treatment. It is expected that statin treatment (type, dose, and frequency) will not be modified for the duration of the trial. Each subject's primary health care provider needs to be informed that the subject's lipid levels should not be checked outside the clinical trial and prescribed lipid lowering treatment doses should not be changed on the basis of an unblinded measurement of lipid levels. If a dose adjustment in prescribed background lipid lowering therapy needs to take place because of an AE, such as partial or complete statin intolerance, the dose change and AE must be recorded in the appropriate CRF (Section 5.8.1.1).

During the study, subjects may continue to take additional, locally approved, non-statin lipid lowering treatment (eg, ezetimibe), during the conduct of the study, if they were taking such treatment at the time of screening.

During the study, if subjects are prescribed a commercially available PCSK9 inhibitor, they must not take IP at the same time. Wherever possible these subjects should remain in the study and have all study procedures, until the study is concluded. Should a subject discontinue a prescribed commercially available PCSK9 inhibitor, they may resume treatment with IP, after consultation with the study team, regarding the timing of doing so.

5.8.1.1. Statin Intolerance

It is possible, that, during the clinical trial, subjects will become statin intolerant due to AEs attributed to the background statin treatment. Subjects, who develop statin intolerance, due to a documented AE, may be switched to another locally approved statin treatment or, if intolerant to two statins, due to documented AEs, treatment with other approved lipid lowering therapies such as niacin, ezetimibe, or bile acid sequestrants. During the trial, subjects who are only able to tolerate a submaximal dose of any statin, due to a documented AE, will be designated as partially statin intolerant. During the trial, subjects who are not able to tolerate two different statins, due to documented AEs, will be designated as completely statin intolerant. In instances of partial or complete statin intolerance, the causative AEs triggering (background statin dose adjustments, changes in background statin type, or complete discontinuation of background statin treatment) must be recorded in the CRF.

5.8.2. Other Concomitant Medication(s)

The administration of concomitant medications required to treat concurrent medical conditions is permitted during the course of the study, consistent with local regulatory labeling, at the discretion of the investigator. Medications that are contraindicated with concomitant lipid lowering therapy, according to local regulatory labeling, should be avoided. In these subjects at high risk or very high risk of CV events, it is expected that subjects will be treated according to local guidelines, in the absence of contraindications.

6. STUDY PROCEDURES

The specific procedures (including specific laboratory tests) to be performed at all study visits are shown in the Visit Schedule/Flowchart.

Scheduling:

The visit window for all post-randomization visits will be ±14 days, except for visits 8 and 11, for which the visits windows are ±3 days, and EDC/EOS visits, which will not have visit windows. Study sites should attempt to schedule each subject's visits at the same time of day for that subject. 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, and all subsequent visits, if a visit coincides with a scheduled injection of IP, the injection should be performed after all other study procedures have been completed.

Ideally, after randomization, visits should be scheduled to take place on a dosing day, so that dosing can take place at the end of the study visit. Lipid level tests (direct LDL-C and lipid panel) 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 labs should be postponed and drawn at the earliest possible time, at an unscheduled visit, no sooner than 10 days after the last dose.

Subjects will be required to fast (water only) for at least 10 hours prior to all study visits during which blood samples will be collected, with the following exceptions. Unscheduled assessments limited to measures of CK, liver function tests (including ALT, AST, alkaline phosphatase, and total and direct bilirubin), hepatitis C PCR testing, or pregnancy testing, do not require fasting. Subjects should take prescribed permitted concomitant medication, as needed, prior to each study visit if it can be administered with water only; prescribed permitted concomitant medications that must be taken with food or after meals should NOT be taken until after the visit procedures have been completed. Subjects who do not fast will be required to return for fasting laboratory tests, at the earliest possible time, before the next scheduled study visit.

6.1. Visit 0: Pre-screening visit

A pre-screening visit should 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 to provide medical records for review, only, so as to determine if the subject qualifies for this study. The IRT system will determine if the subject is eligible for the study or if the subject should be screen failed. The following activities should take place at this visit:

- Obtain informed consent for access to historical records and lipid laboratory testing; 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;

- Register the subject in the IRT system;
- Obtain a fasting lipid blood sample (per Section 7.1.2.1) for analysis of LDL-C and non-HDL-C;
- Evaluate the subject for adverse and serious adverse events.

No data for the subject will be recorded in the pre-screening visit CRF until the cholesterol laboratory results are received, unless the subject experiences an AE or SAE.

The Pre-screening Visit 0 and Screening Visit 1, may be up to 30 days apart, since it may take time for the study site to obtain the subject's medical records.

6.2. Visit 1: Screening Visit

Visit 1, the screening visit, should be scheduled after the pre-screening data (lipid results and medical records) are available to ascertain eligibility for study B1481022 or Study B1481038. The time interval between the Pre-screening Visit (Visit 0) and the Screening Visit (Visit 1) is a maximum of 30 days.

Study specific informed consent should be obtained at Visit 1, before all other procedures, 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.

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.

Investigator Level Assessments

- **Informed Consent:** At Visit 1, the investigator will obtain written informed consent from each subject or the subject's legally acceptable representative before any study-specific activity is performed (see Section 12.3). This informed consent covers the period from Visit 1 until the end of the subject's participation in the study. The investigator should ascertain that the subject's primary care provider has been informed of the subject's participation in the trial, that safety will be monitored, and that it will be important for the health care provider to not perform lipid chemistry analyses during the subject's participation in the trial.
- **Demographics:** Information such as date of birth, race, and gender will be collected.
- **Criteria for Eligibility:** If the subject meets all the applicable inclusion criteria (see Section 4.1) and none of the exclusion criteria apply (see Section 4.2) the subject

should be scheduled for Visit 2 to occur no more than 14 days after the screening visit.

- **Medical History:** Qualifying cardiovascular disease (CVD) risk must be documented by supporting source documentation such as, but not limited to, copies of a hospital discharge summary, copies of medical records, or other documents that can be used to confirm the qualifying CVD risk event or diagnosis and its approximate date of occurrence or onset. Ideally, this documentation should be acquired before Visit 1.

- **Vital Signs:** (1) Temperature, (2) pulse rate (PR), and (3) BP will be recorded as described in Section 7.2.3.1.

- **Prior and Concomitant Medications:** Any medications (over-the-counter or prescribed), including lipid lowering medications, vitamins, and herbal supplements taken in the last 3 months should be recorded. Start and stop dates for medications should be recorded as accurately as possible.

- **IRT interaction:** Subjects will be registered in the IRT, Visit 1, Screening Visit, and assigned a screening number by the system.

- **Laboratory tests:** At Visit 1, laboratory specimens will be obtained for analysis as specified in the Schedule of Activities (Visit Schedule/Flowchart and Section 7.2.1): chemistry group tests (including liver function tests [LFTs] and creatine kinase [CK]), hematology tests, urinalysis, and urine and serum pregnancy tests (in female subjects of childbearing potential, only). At the screening visit hs-CRP, Lp(a), and a central lab urine albumin/creatine ratio may be evaluated, only in subjects who have had a cardiovascular event more than 5 years prior to screening and in subjects without a prior qualifying cardiovascular event. Hepatitis B and C virus serologies will be collected for all subjects at the screening visit. A positive or indeterminate hepatitis C serology may trigger a hepatitis C PCR test for confirmation.

- **Adverse Events (including SAEs):** Subjects will be asked if any AEs have occurred. During the run-in period AEs (serious and non serious) should be recorded on the CRF. SAEs should be reported as per the safety requirements of the study (Section 8.6). Subjects should be questioned, specifically, about the occurrence of potential new cardiovascular events, since their occurrence, after screening but before randomization, might be exclusionary (Section 4).

- **Lifestyle guidance:** Subjects will be provided with educational information describing therapeutic life style change guidelines that are recommended for patients at risk of major CV events (Section 4.4). The particular guidelines used will be documented in the CRF, and their review with the subject by the investigator or his/her designee Run-in period visits.

- **Contraception check:** A contraception check should be made for male and female subjects, who, with their partner, are of childbearing potential (Section 4.4.2).

Re-screening is permitted for subjects who were screened previously, but now meet inclusion/exclusion criteria. Rescreening is also permitted in the event of lost or damaged laboratory samples, in which case only the lost or damaged laboratory tests need to be replaced. Additionally, subjects who cannot complete screening procedures between the date of screening and the planned Visit 2 date, due to unforeseen circumstances, such as but not limited to, delays in study drug shipment to the clinical site or acts of nature (eg, weather disasters), may be re-screened. In this case all eligibility criteria need to be reviewed, and the fasting lipid profile, pregnancy test (if applicable), medical history and concomitant medications need to be redone/updated.

6.3. Run-in Period

The primary objectives of the run-in period are to ensure (1) compliance with the SC administration of a parenteral agent, (2) that subjects meet inclusion and exclusion criteria and (3) can follow study procedures.

For run-in Visits 2, up to and including Visit 5 (the randomization visit), visits should be scheduled 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.

All subjects will be assessed for AEs, SAEs, and potential CV events at every visit during the trial, including the run-in period.

6.3.1. Visit 2: Run-in Visit

The following procedures should be completed:

- **Assessment of inclusion/exclusion criteria:** Subjects should be reassessed to confirm that meet the applicable inclusion/exclusion criteria.

- **Concomitant medication assessment**: Subjects will have a concomitant medication assessment which will include prescribed background lipid lowering treatment. The medication names and doses will be recorded in the CRF.

- **Assessment of AEs (including SAEs)**: Subjects will be asked if any AEs have occurred. During the run-in period AEs (serious and non serious) should be recorded on the CRF. SAEs should be reported as per the safety requirements of the study (Section 8.6). Subjects should be specifically interrogated with respect to the occurrence of potential outcome events. Subjects should be questioned, specifically, about the occurrence of potential new cardiovascular events, since their occurrence, after screening but before randomization, might be exclusionary (Section 4).

- **Vital signs (only if clinically indicated):** Temperature, PR, and BP will be measured and recorded in the CRF as described in Section 7.2.3.1.

- **IRT interaction:** At the time of the visit, the visit will be registered in the IRT which will trigger an allocation of IP (placebo) for the subject.

- **Dispensing of open-label placebo investigational product:** At Visit 2, subjects or their care giver, will be instructed on the storage and administration of the injectable IP. They will not be provided with IP to take home at this visit. They will be given the opportunity to practice self-injection during the study visit. They will also be instructed on what to do with used injection materials after the administration of IP. They will be informed on how to identify and report potential injection site reactions. Optimally, subjects should be able to self-inject the IP, but if that is not possible, a trained care giver may administer the IP.

  Subjects will be informed on how the IP will be supplied and that there may be a need for interval trips to the study site, solely for the purpose of drug re-supply, during the conduct of the study. Documentation of IP usage will be recorded in the CRF and the IRT.

- **Compliance check:** The subject's compliance with IP administration, as described in Section 5.3, will be assessed. Compliance with lifestyle guidelines should also be reviewed (Section 4.4) and recorded in the CRF.

- **Contraception check:** A contraception check should be made for male and female subjects, who, with their partner, are of childbearing potential (Section 4.4.2).

6.3.2. Visit 3: Run-in Visit

The following procedures and assessments should be made before subject self-injection:

- **Concomitant medication assessment:** Subjects will have a concomitant medication assessment which will include prescribed background lipid lowering treatment. The medication names and doses will be recorded in the CRF.

- **Assessment of AEs (including SAEs):** Subjects will be asked if any AEs have occurred. During the run-in period AEs (serious and non serious) should be recorded on the CRF. SAEs should be reported as per the safety requirements of the study (Section 8.6). Subjects should be questioned, specifically, about the occurrence of potential new cardiovascular events, since their occurrence, after screening but before randomization, might be exclusionary (Section 4).

- **Vital signs (only if clinically indicated):** Temperature, PR, and BP will be measured and recorded in the CRF as described in Section 7.2.3.1.

- **Laboratory tests:** All subjects will have a fasting lipid profile measured. These values will not be used to ascertain lipid eligibility for the study, but will be used in the calculation of the baseline lipid values. A blood specimen should be acquired for analysis of a PCSK9 level.

- **IRT interaction:** At the time of the visit, the visit will be registered in the IRT which will trigger an allocation of IP (placebo) for the subject.

- **Dispensing of open-label placebo investigational product:** At Visit 3, subjects or their care-giver, will be re-instructed on the storage and administration of the injectable IP. They will not be provided with IP to take home at this visit. They will be given the opportunity to practice self-injection during the study visit. They will also be instructed on what to do with used injection materials after the administration of IP. They will be re-instructed on how to identify and report potential injection site reactions. Documentation of IP usage (placebo), will be recorded in the CRF and the IRT.

- **Compliance check:** The subject's compliance with IP administration, as described in Section 5.3, will be assessed. Compliance with lifestyle guidelines should also be reviewed (Section 4.4) and recorded in the CRF.

- **Contraception check:** A contraception check should be made for male and female subjects, who, with their partner, are of childbearing potential (Section 4.4.2).

6.3.3. Visit 4: Run-in Visit

The following procedures and assessments should be made before subject self-injection:

- **Concomitant medication assessment:** Subjects will have a concomitant medication assessment. The medication names and doses will be recorded in the CRF.

- **Assessment of AEs (including SAEs):** Subjects will be asked if any AEs have occurred. During the run-in period AEs (serious and non serious) should be recorded on the CRF. SAEs should be reported as per the safety requirements of the study (Section 8.6. Subjects should be questioned, specifically, about the occurrence of potential new cardiovascular events, since their occurrence, after screening but before randomization, might be exclusionary (Section 4).

- **Vital signs (only if clinically indicated):** Temperature, PR, and BP will be measured and recorded in the CRF as described in Section 7.2.3.1.

- **IRT interaction:** At the time of the visit, the visit will be registered in the IRT which will trigger an allocation of IP (placebo) for the subject.

- **Dispensing of open-label placebo investigational product:** At Visit 4, subjects or their care giver, will be re-instructed on the storage and administration of the injectable IP. They will not be provided with IP to take home at this visit. They will be given the opportunity to practice self-injection during the study visit. They will also be instructed on what to do with used injection materials after the administration of IP. They will be re-instructed on how to identify and report potential injection site reactions. Documentation of IP usage (placebo), will be recorded in the CRF and the IRT.

- **Compliance check:** The subject's compliance with IP administration, as described in Section 5.3, will be assessed. Compliance with lifestyle guidelines should also be reviewed (Section 4.4) and recorded in the CRF.

- **Contraception check:** A contraception check should be made for male and female subjects, who, with their partner, are of childbearing potential (Section 4.4.2).

- **Review of inclusion/exclusion criteria:** At Visit 4 a determination will be made to confirm if the subject fulfills all inclusion criteria (Section 4.1, and that there are no exclusion criteria present (Section 4.2).

6.4. Treatment Period

Visit windows for the treatment period are ±14 days for all visits except Visit 8 (Week 14) and Visit 11 (Week 52), each of which has a visit window of ±3 days.

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, until study completion, and the EOS. Subjects who discontinue IP early (EDC), will be encouraged to be followed, according to the Schedule of Activities, until the EOS. If the study is not completed by Visit 20, visits will continue in accordance with the Schedule of Activities for annual visits (Visits 11, 14, 17, 20) and interim visits (eg, Visits 12, 13, 15, 16, 18, and 19) until 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 (Section 5.4.1.1) and an assessment for adverse events, both serious and non-serious (Section 6.4.5). These more frequent visits should be instituted after the visit at which the subject was informed of the decreased dose frequency. Such subjects should maintain the original visit schedule, with an additional visit scheduled approximately half-way between.

6.4.1. Visit 5 (Week 0) Randomization (Baseline) Visit

The following procedures and assessments should be made before subject self-injection of IP:

- **Assessment of inclusion/exclusion criteria:** The subject should be re-evaluated to ensure that he/she have met the inclusion/exclusion criteria, for the study, prior to randomization using the IRT system.

- **IRT interaction:** At the randomization visit, the subject will be registered in the IRT and assigned a randomization number by the system. The IRT will assign the subject to blinded IP.

- **Concomitant medication assessment:** Subjects will have a concomitant medication assessment. At the randomization visit, and all subsequent visits, subjects should continue their prescribed background medications, including their lipid lowering treatment. Any changes in background medications should be recorded in the CRF.

- **Assessment of AEs (including SAEs) or potential CVD outcome events:** Subjects will be asked if any AEs have occurred. AEs (serious and non serious)should be recorded on the CRF. SAEs should be reported as per the safety requirements of the study (Section 8.6). Subjects should be specifically interrogated with respect to the occurrence of potential outcome events. Potential CVD outcome events should be reported as required (Section 8.6.1). Subjects with SAEs that would have potentially met the criteria for a CVD event (as defined in Appendix 4), between Visit 0 and Visit 5, should be excluded. Such subjects may be rescreened at a later date.

- **Vital signs:** Temperature, PR, and BP will be measured and recorded in the CRF as described in Section 7.2.3.1.

- **Examinations:** Randomized subjects will have a complete physical exam and a neurologic exam, as described in Section 7.2.3. Cognitive assessments are only to be performed at designated study sites (Section 7.2.3.4). The subject's weight, height, and waist circumference will also be measured as described in Section 7.2.3.2.1. All findings will be recorded in the CRF.

- **Laboratory tests:** At the randomization visit subjects will have the following laboratory tests: chemistry group tests (including LFTs and CK level), hematology tests, urinalysis, urine and serum pregnancy tests (in female subjects of childbearing potential only), lipid profile, special lipid and efficacy studies, and hemoglobin A1c (HbA1c).

- **Blood specimens:** Blood specimens will be acquired for ADA, bococizumab level, and PCSK9 level.

- **Biospecimens:** Biospecimens will be collected as described in Section 7.5.

- **12-Lead ECG:** A 12-lead ECG should be recorded and saved (Section 7.2.2).

- **EuroQol 5-Dimensions Health State Profile (EQ-5D)**: Subjects will complete brief EQ-5D questionnaire as described in Section 7.3. Results will be transcribed to the CRF.

- **Depression assessment:** A Patient Health Care Questionnaire 2 (PHQ-2) will be completed at the randomization visit in all subjects and if the score is ≥ 2, the remaining 7 PHQ questions will be completed as the PHQ-9 (see Section 7.3.2. 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 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.

- **Dispensing of investigational product:** At Visit 5, Subjects will be dispensed IP according to the IRT allocation. At the visit, subjects or their care giver, will be re-instructed on the storage and administration of the injectable IP, as well as how to store, safely, used injection materials, after the administration of IP. The self-injection process will be reviewed with the subject. 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. They will be re-instructed on how to identify and report potential injection site or hypersensitivity reactions.

- **Compliance check:** The subject's compliance with IP administration, as described in Section 5.3, will be assessed. Subjects will be instructed 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, as described in Section 5.3. Compliance with lifestyle guidelines should also be reviewed (Section 4.4) and recorded in the CRF.

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

6.4.2. Visits 6 (Week 4) and 7 (Week 8)

The following procedures and assessments should be made before subject self-injection:

- **Laboratory test review:** There should be a review of results from laboratory values of the previous visit.

- **Vital signs:** Temperature, PR, and BP will be measured and recorded in the CRF as described in Section 7.2.3.1.

- **Concomitant medications:** Background prescribed lipid lowering treatment (drug name and dose) and all other concomitant treatments will be recorded in the CRF. Instruct subjects on the use of concomitant medications (Section 5.8).

- **Health care resource utilization:** Assessment of health care resource utilization (Section 7.7)

- **Assessment of AEs (including SAEs) or potential CVD outcome events:** Subjects will be asked if any AEs have occurred. AEs (serious and non serious) should be

recorded on the CRF. SAEs should be reported as per the safety requirements of the study (Section 8.6). Subjects should be specifically interrogated with respect to the occurrence of potential outcome events. Potential CVD outcome events should be reported as required (Section 8.6.1).

- **IRT interaction:** At the time of the visit, the visit will be registered in the IRT which will trigger an allocation of IP for the subject.

- **Investigational product:** Dispense IP based on IRT randomization code. If there is dosing during the visit, subjects will be observed, at the visit, during the injection of IP, either by self-injection, or as performed by a care giver, after all other procedures have been completed.

  Subjects will be provided with IP kits to bring home with them and will be reminded about storage conditions.

- **Compliance check**: The subject's compliance with IP administration, as described in Section 5.3, will be assessed. Subjects will be instructed 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, as described in Section 5.3. Compliance with lifestyle guidelines should also be reviewed (Section 4.4) and recorded in the CRF.

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

The following laboratory tests will be collected:

- Blood for fasting lipid profile:

  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;

- LFTs;

- Blood specimens acquired for ADA, bococizumab level, and PCSK9 level in all subjects at Visit 6 only;

  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;

- Urine and serum for pregnancy testing (if indicated).

6.4.3. Visits 8, 9, 10, 12, 13, 15, 16, 18, and 19

At weeks 14, 26, 40, 70, 86, 122, 140, 174, and 192, the following procedures and assessments should be made before subject self-injection:

- **Laboratory test review:** There should be a review of results from laboratory values of the previous visit.
- **Vital signs:** Temperature, PR, and BP will be measured and recorded in the CRF as described in Section 7.2.3.1.
- **Concomitant medications:** Background prescribed lipid lowering treatment (drug name and dose) and all other concomitant treatments will be recorded in the CRF. Instruct subjects on the use of concomitant medications (Section 5.8).
- **Health care resource utilization:** **A**ssessment of healthcare resource utilization (Section 7.7)
- **Assessment of AEs (including SAEs) or potential CVD outcome events:** Subjects will be asked if any AEs have occurred. AEs (serious and non serious) should be recorded on the CRF. SAEs should be reported as per the safety requirements of the study (Section 8.6). Subjects should be specifically interrogated with respect to the occurrence of potential outcome events. Potential CVD outcome events should be reported as required (Section 8.6.1).
- **EQ-5D:** Subjects will complete brief questionnaire as described in Section 7.3 at Visits 8 and 9 only. Results will be transcribed to the CRF.
- **IRT interaction:** At the time of the visit, the visit will be registered in the IRT which will trigger an allocation of IP for the subject.
- **Investigational product:** Dispense IP based on IRT randomization code. If there is dosing during the visit, subjects will be observed, at the visit, during the injection of IP, either by self-injection, or as performed by a care giver, after all other procedures have been completed.

  Subjects will be provided with IP kits to bring home with them and will be reminded about storage conditions.

- **Compliance check:** The subject's compliance with IP administration, as described in Section 5.3, will be assessed. Collect all used and unused syringe cartons in a biohazards container Subjects will be instructed 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, as described in Section 5.3. Compliance with lifestyle guidelines should also be reviewed (Section 4.4) and recorded in the CRF.

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

The following laboratory tests should be collected:

- Blood for fasting lipid profile;

  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;

- Special lipid and efficacy studies, as described in Section 7.1.2.2, will be collected at Week 14, Visit 8.

- Chemistry group;

- LFTs;

- Blood specimens acquired for ADA, bococizumab level, and PCSK9 level in all subjects at Visits 8, 10, and 12;

  After randomization, if lipid sampling has been postponed to an unscheduled visit, the corresponding ADA/PK/PCSK9 tests should be postponed as well, and collected at the same time as the rescheduled lipid sample collection;

- Urine and serum for pregnancy testing (if indicated).

6.4.4. Visits 11, 14, 17, 20, and Early Study Discontinuation or End of Study Visit

At the annual visits (Weeks 52, 104, 156, and 208) or early study discontinuation or end of study visit, the following procedures and assessments should be completed. Except for the EDC or EOS visits, all of the procedures should be completed before the self-administration of IP. When the criteria for stopping the trial outlined in Section 3 have been met, the study sites will be contacted by the study team and told to instruct their subjects to discontinue taking IP. EOS visits should be scheduled as soon as possible after that announcement. The EOS visit should be scheduled to occur no sooner than 14 days after the last dose of IP was administered. The safety follow-up period is 40 days after the last dose of IP was administered for subjects taking IP. If their EOS visit has occurred less than 40 days after the last dose of IP was administered, 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.

All EDC procedures should be done upon the permanent early discontinuation of double-blind IP. Subjects should continue to have visits with study personnel according to the study schedule until study completion. If a subject has not fully withdrawn consent for further contact with the study site, the subject should be encouraged to remain in contact with the investigator, either by attending study visits or via phone visit, throughout the remainder of the study. The study management team will provide to the study site, an EDC retention hotline, and a study retention toolkit, to define potential levels of the subject's continued participation in the study. Every effort must be made to retain subjects in the study, even if they are no longer taking IP.

- **Laboratory test review:** There should be a review of results from laboratory values of the previous visit.

- **Vital signs:** Temperature, PR, and BP will be measured and recorded in the CRF as described in Section 7.2.3.1.

- **Examinations:** Subjects will have a complete physical exam and a neurologic exam, as described in Section 7.2.3.2. Waist circumference will be measured only at the EDC or EOS visits. Cognitive assessments are only to be performed at designated study sites, in those subjects who had baseline assessments (Section 7.2.3.4), annually and at EDC and/or EOS visits.

- **12 Lead ECG:** A 12-Lead ECG will be recorded (Section 7.2.2).

- **Concomitant medications:** Background prescribed lipid lowering treatment (drug name and dose) and all other concomitant treatments will be recorded in the CRF. Instruct subjects on the use of concomitant medications (Section 5.8).

- **Health care resource utilization:** **A**ssessment of healthcare resource utilization (Section 7.7).

- **Assessment of AEs (including SAEs) or potential CVD outcome events**: Subjects will be asked if any AEs have occurred. AEs (serious and non serious) should be recorded on the CRF. SAEs should be reported as per the safety requirements of the study (Section 8.6). Subjects should be specifically interrogated with respect to the occurrence of potential outcome events. Potential CVD outcome events should be reported as required (Section 8.6.1).

- **EQ-5D:** Subjects will complete a brief questionnaire as described in Section 7.3. Results will be transcribed to the CRF.

- **Depression assessment:** 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 (Section 7.3.2). 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.

- **IRT interaction:** At the time of the visit, the visit will be registered in the IRT which will trigger an allocation of IP for the subject, except at the EDC or EOS visit. At the EDC or EOS visit, the EDC or EOS status will be registered.

- **Investigational product:** Dispense IP based on IRT randomization code (except for EDC or EOS visit). If there is dosing during the visit, subjects will be observed, at the visit, during the injection of IP, either by self-injection, or as performed by a care giver, after all other procedures have been completed. Except for EDC or EOS visit, subjects will be provided with IP kits to bring home with them and will be reminded about storage conditions.

- **Compliance check:** The subject's compliance with IP administration, as described in Section 5.3, will be assessed. Subjects will be instructed 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, as described in Section 5.3. Compliance with lifestyle guidelines should also be reviewed (Section 4.4) and recorded in the CRF.

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

The following laboratory tests will be collected:

- Blood for fasting lipid profile;

  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;

  A lipid profile will not be collected at EDC/EOS visits.

- Special lipid and efficacy studies as described in Section 7.1.2.2, at Month 12, Visit 11;

- Biospecimens as described in Section 7.5, at Week 52, Visit 11;

- Chemistry group (including LFTs and CK level);
- Hematology;
- Urinalysis;
- HbA1c for all subjects at Visit 11 and EDC and/or EOS;
- Blood specimens acquired for ADA, bococizumab level, and PCSK9 level in all subjects at Visits 14, 17, 20, and EDC or EOS;

  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;
- Urine and serum for pregnancy testing (if indicated);
- Hepatitis C virus serologies will be collected at the EDC or EOS visit for all subjects at study sites in Canada. A positive hepatitis or indeterminate C serology may trigger a hepatitis C polymerase chain reaction (PCR) test for confirmation.

6.4.5. Visits After Second Dose Modification of Investigational Product

Subjects who have had dosing of IP modified by the IRT system to Q4wks (Section 5.4.1.1), will need to have their visit frequency changed to obtain a direct LDL-C level every 8 weeks (Q8wks), approximately. The first visit of increased frequency should take place 6 weeks after the visit at which the subject was informed of the change in IP dose frequency. This will permit the DMC to perform an independent safety review, in an ongoing fashion so as to ascertain if there are any potential safety issues, consequent to the modification of IP dosing.

The direct measurement of LDL-C 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, 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.

Since all subjects with a dose frequency modification (both those on placebo and those receiving bococizumab) will have more frequent direct LDL-C monitoring, the blinding of the study should be preserved.

At these visits for direct LDL-C assessment the following additional assessments should take place:

- **Health care resource utilization:** Assessment of healthcare resource utilization (Section 7.7).

- **Assessment of AEs (including SAEs) or potential CVD outcome events:** Subjects will be asked if any AEs have occurred. AEs (serious and non serious) should be recorded on the CRF. SAEs should be reported as per the safety requirements of the study (Section 8.6). Subjects should be specifically interrogated with respect to the occurrence of potential outcome events. Potential CVD outcome events should be reported as required (Section 8.6.1).

- **Compliance check**: The subject's compliance with IP administration, as described in Section 5.3, will be assessed. Subjects will be instructed 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, as described in Section 5.3. Compliance with lifestyle guidelines should also be reviewed (Section 4.4) and recorded in the CRF.

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

6.4.6. Discontinuation of Investigational Product

Subjects who temporarily or permanently discontinue IP, should remain in the study and continue to be followed at all scheduled visits, for the duration of the study. Subjects with the temporary discontinuation of IP should resume its administration when deemed appropriate by the investigator and, if necessary, with consultation of the Sponsor. Only subjects who have permanently discontinued IP are classified as Off Drug In Study (ODIS) subjects. ODIS subjects are not expected to, or planned to resume the administration of IP. ODIS subjects should remain in contact with the investigator, either by attending study visits or via phone visit, throughout the remainder of the study. The sole exception to continuing some level of contact with the investigator is if a subject fully withdraws consent, as described in Section 6.5. Temporary or permanent discontinuation of IP and/or resumption of IP after a temporary discontinuation, must be registered in the IRT.

For all ODIS and Withdrawn Consent subjects the study site must discuss the case with a study team member, ie, retention hotline or delegate to discuss the subject status and ensure continued follow-up in the study. The study management team will provide to the study site, an EDC retention hotline and a study retention toolkit, to define potential levels of the subject's continued participation in the study, even if the subject is no longer taking IP (ie, an ODIS subject). Every effort must be made to retain subjects in the study, even if they are no longer taking IP.

6.5. Subject Withdrawal

6.5.1. Withdrawal of Consent

Subjects who withdraw consent are defined as those subjects who refuse any further contact with the investigator or persons authorized by the subject, previously, to receive the subject's study information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up in writing, whenever possible. The reason for withdrawal of

consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. The investigator should document thoroughly, the efforts by the site to retain the subject by offering the subject the opportunity to remain in the study as an ODIS subject with complete study visits or lesser degrees of follow up (ie, phone contact). In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the subject to comply with the protocol required schedule of study visits or procedures at a given study site, with the exception noted in Section 6.5.3. In such circumstances, subjects should be encouraged to remain in contact with the investigator, and to be followed as ODIS subjects, either by attending study visits or via phone visit throughout the remainder of the study in order to provide safety information as it occurs.

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

6.5.2. Lost to Follow-Up

Lost to follow-up is defined by the inability to reach the subject by the end of the study only. No subject should be considered lost to follow-up, until the study has been completed. If a subject does not return for a scheduled visit, every effort should be made to contact the subject. Attempts to reschedule the visit should be completed 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. This includes follow-up with persons authorized by the subject as noted above. The study retention team must be contacted, through the retention hotline or delegate, to discuss strategies available for assistance with locating subjects who are potentially lost to follow-up. All efforts to retain a subject, should continue throughout the course of the study and should be documented in the subject's medical source records. Every effort should be made to have the subject complete an EDC or EOS visit and to document subject's vital status, if possible.

If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death. If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then

the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

6.5.3. Individual Subject Dosing Stopping Criteria

No subjects will be withdrawn from the study because of lack of compliance with IP administration (Section 5.3).

During the double-blind, active treatment phase subjects will have clinic visits at regular intervals. The following individual dosing stopping criteria will be followed:

- Dosing with blinded IP (bococizumab, matching placebo) may be temporarily discontinued or stopped for intolerable adverse events, or if the Investigator believes that continuing dosing will be detrimental to the subject's mental or physical health;

- Dosing with blinded IP should be stopped if the subject starts taking a marketed PCSK9 inhibitor;

- Subjects with CK values >5 x ULN confirmed by repeat test (Refer to Section 7.2.5), for whom the CK elevation is associated with muscle pain, muscle tenderness and/or muscle weakness, or new onset renal dysfunction, must be discontinued from study treatment and asked to complete the remainder of the scheduled visits without receiving blinded IP (bococizumab or placebo).

7. ASSESSMENTS

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However it is anticipated that from time to time there may be circumstances, outside of the control of the investigator, which may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

In order to completely and accurately assess the primary and secondary clinical efficacy endpoints and the safety profile of the treatment groups, the vital status of each randomized subject must be obtained at the completion of the study. The occurrence of potential clinical outcome events as defined in Section 2.2 will trigger the compilation of a dossier that includes anonymized supporting medical record information that will be sent to the clinical Adjudication Committee.

7.1. Efficacy Assessments

7.1.1. Clinical Endpoints

Clinical endpoints defined as primary or secondary efficacy parameters will be assessed beginning with the day of randomization. Cardiovascular adverse events occurring between pre-screening (the time of pre-screening informed consent) and randomization should be

reported as adverse events and not submitted for adjudication. 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 IP. A complete description of these endpoints, their definition, the documentation that needs to be provided for review, and the processes whereby the documentation is prepared and transmitted for adjudication by the Adjudication Committee are detailed in a separate Adjudication Committee Charter. Potential endpoint documentation should include, but is not limited to, any of the following: hospital discharge summaries, operative reports, clinic notes, ECGs, diagnostic test data and/or results, autopsy reports and death certificate information.

The identification of a potential clinical endpoint will be made by the study site and communicated to Pfizer or designated representative immediately (within 24 hours).

7.1.1.1. Primary Clinical Endpoint

The primary endpoint is the time from randomization to the first occurrence of the 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 4).

7.1.1.2. Key Secondary Clinical Endpoints

The times from randomization to the first adjudicated and confirmed occurrence of the endpoints below (as defined in Appendix 4):

- 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.

7.1.1.3. Other Clinical Secondary Endpoints

The times from randomization to the first adjudicated and confirmed occurrence of the endpoints below (as defined in Appendix 4):

- 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.

7.1.2. Biomarker Efficacy Endpoints

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 will be evaluated as nominal change from baseline. The inflammatory parameter, hs-CRP, will be evaluated as the percent change from baseline.

The subject, 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.

7.1.2.1. Lipid Profile

Fasting lipid profile plasma samples will be collected at the pre-screening visit, Visit 3, 5 (the randomization visit), and every visit thereafter, except for EDC or EOS visits. 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. Lipid analyses will be performed by a central laboratory and include:

- 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);[43,66]
- VLDL-C (calculated as triglycerides x 0.2, when using mg/dL or triglycerides x 0.458, when using mmol/L);[43,66]
- RLP-C (calculated as total cholesterol – [HDL-C + LDL-C]).

7.1.2.2. Special Lipid and Efficacy Assessments

At the screening visit hs-CRP, Lp(a), and a urinary microalbuminuria assessment may be evaluated, in subjects without a prior qualifying CV event or those subjects who had a CV event more than 5 years prior to screening. Apo B and apo A-I will not be collected at the screening visit.

Special lipid and efficacy assessments will be analyzed by a central laboratory or assessed as calculated parameters based on analyses of lipid profile measurements. Special lipid and efficacy blood samples will be collected, and stored for later analysis, by the central laboratory or values will be calculated for them, for Visits 5, 8, and 11, only. These assessments include:

- Apo-A-I;
- Apo-B;

- Lp(a);
- hs-CRP.

7.2. Safety

7.2.1. Laboratory

Laboratory tests for safety will be performed at times defined in the Schedule of Activities of this protocol. Subject eligibility based on these tests will be determined at screening.

Every effort should be made to collect laboratory test samples at the investigator's study site where the subject was consented, for sending to the central laboratory for analysis. However, in the event that the subject is travelling long distance for an extended period of time, the subject must be made aware that a laboratory test sample can be collected at a local laboratory chosen by the investigator or at a local investigator study site, that is also participating in the study, that is located in the area where the subject is travelling. The study site should consult with the study management team on how to proceed with this process. Laboratory test measurements are performed by the central laboratory and laboratory reports are communicated to the original investigator. No other study visit procedures will be conducted at these visits other than laboratory test collections.

Laboratory test collection that occurs at a local laboratory and or at another investigator study site will require the original investigator follow up with the subject for any safety AE/SAEs. Investigators who have subjects that will have laboratory test collection at a local laboratory and or at another investigator study site should communicate to the appropriate study management team regarding any subjects that will be travelling and will be gone for an extended period of time so that they can work with the investigator on the logistics.

7.2.1.1. Local Laboratory Tests

Urine dipstick assessments and urine pregnancy tests should be performed locally at times defined in the Schedule of Activities and Section 6 of this protocol. A serum pregnancy test is always submitted for analysis to the central laboratory, whenever a urine pregnancy test is performed.

7.2.1.2. Central Laboratory Tests

A central laboratory will be used to analyze hematology and blood chemistry tests (as listed in the table below) to ensure accuracy and consistency in test results. Serum pregnancy tests are performed centrally as specified in the Schedule of Activities. The central laboratory will transmit all results for protocol tests, scheduled and unscheduled, to the sponsor for inclusion in the clinical data base.

The following laboratory tests will be performed at times defined in the Schedule of Activities and Section 6 of this protocol. Additional tests not listed here may be performed as needed, with the approval of the clinical study team.

Table 2. Laboratory Tests

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 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.

7.2.1.2.1. Pregnancy Testing (Local and Central Laboratory)

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. For female subjects of childbearing potential, serum and urine pregnancy tests, with sensitivity of at least 25 mIU/mL, will be performed. The urine pregnancy test is conducted with the test kit provided by the central laboratory in accordance with instructions provided in its package insert.

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 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.

7.2.2. 12-Lead Electrocardiogram

A 12-lead electrocardiogram (ECG) will be obtained at Visit 5, and annually thereafter. ECGs will be locally assessed and interpreted and stored at the study site and a copy will be stored centrally. ECGs may be recorded, at scheduled or unscheduled visits, for safety purposes, if needed. Clinically significant ECG abnormalities at any visit will be recorded in the CRF.

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.

7.2.3. Examinations

7.2.3.1. Vital Signs

Temperature, PR, and BP will be measured at visits specified in the Schedule of Activities of this protocol. Additional measurements of PR and BP rate will be permitted, as necessary, to ensure appropriate collection of safety data.

Sitting BP should be measured with the subject's arm supported at the level of the heart, and recorded to the nearest mm Hg after approximately 5 minutes of rest. The same arm (preferably the dominant arm) should be used throughout the study. The same size BP cuff, which has been properly sized and calibrated, should be used to measure BP each time. The use of automated devices for measuring PR and BP is preferred, although, when done manually, PR should be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, PR and BP should be obtained prior to the nominal time of the blood collection.

Baseline BP is defined as the mean of the average systolic and diastolic BP measures at the Randomization visit and will serve as the comparator for average values obtained at later visits. 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 CRF and their average will serve as the value for that visit.

7.2.3.2. Physical Exam

Physical exam will be performed at baseline (Visit 5), annually, and at EDC and/or EOS. Abnormal changes from baseline, deemed clinically significant by the Investigator should be recorded as AEs.

7.2.3.2.1. Weight, Height, and Waist Circumference

Height will be measured without shoes at the baseline visit (Visit 5).

Body weight will be measured at the baseline visit (Visit 5), annually, and at EDC and/or EOS. Body weight will be measured in indoor clothing without shoes.

Waist circumference will be measured at baseline (Visit 5) and at EDC and/or EOS. To measure waist circumference, place a tape measure around the subject's bare abdomen just above the subject's hip bone (at the level of the subject's navel). Be sure that the tape is snug, but does not compress the subject's skin, and is parallel to the floor. Have the subject relax, exhale, and measure the subject's waist.

7.2.3.3. Neurological Exam

A basic neurological panel consists of clinical tests of selected cranial nerves, sensation, coordination, and peripheral reflexes and will be performed at baseline (Visit 5), annually, and at EDC and/or EOS, as part of the physical exam. These tests can be performed by individuals with basic medical training and do not require specialized equipment. Abnormal changes from baseline, deemed clinically significant by the Investigator should be recorded as AEs.

7.2.3.4. Cognitive Testing

Cognitive testing will be performed at baseline (Visit 5), annually, and at EDC and/or EOS visits at a subset of designated study sites in approximately 500 subjects (250/treatment group). This number of subjects is based on feasibility of sites with the appropriate staff and workspace to administer the testing accurately, which have the trained personnel and facilities to perform the tests.

The cognitive testing battery will comprise the following assessments:

- Wechsler Adult Intelligence Scale (WAIS-III) - Digit Span (Forward and Backward)[55,56]

  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.

- Wechsler Adult Intelligence Scale (WAIS-III) - Digit Symbol-Coding [55,56]

  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.

- Trail Making Test (Parts A and B)[57]

  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 or pencil from the page.

- Hopkins Verbal Learning Test (HVLT)[65,66]

  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. Test administration time is about seven minutes for the Immediate Recall test and three minutes for the Delayed Recall and Recognition tests.

7.2.4. Injection Site Reactions

In case of acute injection site reactions, the Investigator should institute treatment measures deemed medically appropriate such as topical therapy at the injection site. Such events and treatments are to be captured and reported as AEs. The Investigator should provide a clear description of the observed or reported AE including location and severity. All concomitant treatments used to treat injection site reactions should be recorded and captured in the CRF, together with the AE of injection site reactions. AEs should be reported as serious per the criteria in Section 8.6 of this protocol.

7.2.5. Creatine Kinase (CK) / Symptomatic Myopathy Monitoring

If at any clinic visit after screening, a subject experiences unexplained (ie, not associated temporally with recent trauma, intra muscular injections, heavy exercise or physically strenuous activity) CK values >5x ULN, then the subject must return to the clinic for repeat CK testing preferably within 48 hours of when results are made available to the Investigator. At the time of repeat testing, CK isozymes (to assess CK-MM and CK-MB fractions) and a serum creatinine will be obtained, as well as a urine dipstick. If the repeat testing confirms CK values >5x ULN, and the CK elevation is associated with muscle pain, muscle tenderness and/or muscle weakness, or new onset renal dysfunction, then the subject must be discontinued from study treatment and asked to complete the remainder of the scheduled visits without receiving bococizumab or placebo. If completing the remainder of the trial without study treatment is not possible, end of study evaluations must be performed.

The Sponsor must be notified of any CK >5x ULN within 24 hours. If the subject's CK value is >5x ULN on repeat testing, without muscle pain, muscle tenderness, and/or muscle weakness, or new onset renal dysfunction, the subject may continue on study therapy if approved by Pfizer's Medical Monitor, who may request additional assessments. At the time of repeat testing, CK isozymes (to assess CK-MM and CK-MB fractions) and a serum creatinine will be obtained. The subject's CK levels should continue to be monitored, pending resolution of the CK elevation.

Prior to obtaining blood for a scheduled 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.

7.2.6. LDL-C monitoring

7.2.6.1. LDL-C <25 mg/dL (0.65 mmol/L)

Some subjects may have LDL-C measurements below 25 mg/dL (0.65 mmol/L). An independent safety review of AEs, and laboratory results will be conducted by the data monitoring committee (DMC) for all subjects presenting with LDL-C <25 mg/dL (0.65 mmol/L).

7.2.6.2. Subjects with a History of LDL-C ≤10 mg/dL (0.26 mmol/L)

Subjects who have had dosing of IP modified by the IRT system to Q4wks (Section 5.4.1.1), will need to have their visit frequency changed to obtain a direct LDL-C level every 8 weeks (Q8wks). The first visit of increased frequency should take place 6 weeks after the visit at which the subject was informed of the change in IP dose frequency. This will permit the DMC to perform an independent safety review, in an ongoing fashion so as to ascertain if there are any potential safety issues, consequent to the modification of IP dosing. Since all subjects with a dose frequency modification (both those on placebo and those receiving bococizumab) will have more frequent direct LDL-C monitoring, the blinding of the study should be preserved.

7.2.7. Immunogenicity

7.2.7.1. Anti-drug Antibodies

Blood samples will be collected and assayed for development of ADAs to bococizumab. This monitoring will take place at regular intervals as described in the Schedule of Activities. 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 at the same time as the rescheduled lipid sample collection. ADA, PK, and PCSK9 samples will be collected at EDC and EOS visits.

ADA samples will be analyzed using a tiered testing strategy. All ADA samples that are positive in a screening assay, will be confirmed for antibody specificity. Confirmed positive samples will be characterized further for titer and neutralizing antibody response, if appropriate.

Blood samples for anti-bococizumab antibody analysis (4 ml to provide approximately 1.5 ml of plasma),will be collected into appropriately labeled tubes containing K_2EDTA.

Samples for anti-bococizumab antibody will be analyzed using validated analytical methods in compliance with Pfizer standard operating procedures.

As part of understanding the immunogenicity of the study drug, samples may be used for evaluation of the bioanalytical method. These data will be used for internal (ie, Pfizer) exploratory purposes and will not be included in the clinical report.

7.2.7.2. Hypersensitivity Types 1 and 3 Reactions

Type 1 hypersensitivity or allergic (eg, shortness of breath, urticaria, anaphylaxis, angioedema) reactions are theoretically possible in response to any injected protein. Immune complex mediated Type 3 hypersensitivity reactions are similar to the adverse events (AEs) of Type 1 reactions but are likely to be delayed from the time of injection and may include symptoms such as rash, urticaria, polyarthritis, myalgias, polysynovitis, fever, and, if severe, glomerulonephritis.

In the case of a hypersensitivity reaction, the subject will be treated symptomatically with supportive care, further monitoring, and treatment with anti-histamines and/or corticosteroids. Study injections may be stopped and the subject will be followed until the end of the study. At the time of any hypersensitivity reaction an ADA, PK, and PCSK9 specimen should be collected, and another sample collected at the next visit, as per the Schedule of Activities.

If a subject reports an injection site reaction that has not resolved by the end of the third day, after dosing, an unscheduled visit should be performed, to collect an ADA, PK, and PCSK9 sample.

7.3. Health-Related Quality of Life and Depression Assessment

7.3.1. EQ-5D Health Questionnaire

A health-related quality of life assessment, the EQ-5D Health Questionnaire, is administered at Visits 5 (baseline), 8, 9, 11, 14, 17, 20, and at early discontinuation from study or end of study visit (Appendix 6).

The EQ-5D is a generic measure of health-related quality of life.[44] 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 health outcomes assessment survey (EQ-5D) evaluates the subject's own perceptions. In order to gain the most objective results possible, subjects should complete the EQ-5D prior to performing any other study-related procedure for the visit and prior to any study-specific discussion of how they are feeling. The investigator must not influence the subject's assessments. Every effort should be made to maintain an unbiased assessment. All subject self-assessments should be reviewed for completeness while the subject is still present for the study visit.

7.3.2. Patient Health Questionnaire Depression Module

Depression is an affective disorder that sometimes occurs in patients with CV disease. The assessment of depression in patients with CV disease is recommended since it may impact the quality of life and adherence to medical treatment.[62] The Patient Health Questionnaire (PHQ) depression assessment is a validated tool to assess the presence of depression and its severity. It will be used to evaluate subjects for clinical evidence of depression in this study.

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.[63] 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.

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 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.

7.4. Pharmacokinetics

7.4.1. Plasma for Analysis of Bococizumab and 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 response of bococizumab in this study population. In addition, baseline PCSK9 samples collected on Visits 3 and 5 will be analyzed in a randomly selected subset of subjects (N=1,200).

Blood samples (4 mL) to provide a minimum of 1.5 mL of plasma for pharmacokinetic analysis will be collected into appropriately labeled tubes containing K_2EDTA at times specified above.

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

Detailed instructions for the preparation and shipment of the samples may be found in the Laboratory Manual supplied by the Central Laboratory.

As part of understanding the pharmacokinetics/pharmacodynamics of the IP, samples may be used for evaluation of the bioanalytical methods. These data will be used for internal (ie, Pfizer) exploratory purposes and will not be included in the clinical report.

7.5. Banked Biospecimens

7.5.1. Markers of Drug Response

Studying the variation in genetic markers and other biomarkers may help to explain some of the variability in response seen with some drugs among different individuals. This is referred to as pharmacogenomic/biomarker research. Comparing the deoxyribonucleic acid (DNA), ribonucleic acid (RNA), protein, and metabolite variation patterns of subjects who respond well and those who respond poorly to treatment may help to better define the most appropriate group of patients in which to target a given treatment. Collecting biospecimens for exploratory pharmacogenomic/biomarker analyses and retaining them in the Pfizer BioBank makes it possible to better understand the drug's mechanism of action and to seek explanations for differences in, for example, exposure, efficacy, tolerability, or safety not anticipated prior to the beginning of the study. Providing these biospecimens is a required study activity for study sites and subjects, unless prohibited as such by local regulations or ethics committee decision.

To protect subjects' confidentiality, the banked biospecimens and data generated from them will be coded with the subject's study identification (ID) number. Samples will be kept in a facility accessible only by badge-swipe. Data will be stored on password-protected computer systems. The key between the code and the subject's personal identifiers will be held at the study site; the researchers using the biospecimens and data generated from them will not have access to the key nor any personally identifying information. Biospecimens will only be used for the purposes described here and in the informed consent document/subject information sheet; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored indefinitely to allow for future research on the topics described here, including research conducted during the lengthy drug development process and also post-marketing research. Subjects can withdraw their consent for the use of their biospecimens at any time by making a request to the investigator, in which event any remaining biospecimen will be destroyed; data already generated from the biospecimens will continue to be stored to protect the integrity of existing analyses. It is very unlikely that results generated from the biospecimens will have any clinical, diagnostic, or therapeutic implications for the individual

study participants. Subjects are notified in the informed consent document/subject information sheet that their results will not be given to them, unless required by local laws or regulations, in which case results will be returned via the investigator. Results will not be provided to family members or other physicians; nor will they be recorded in the subject's medical record. There is no intention to contact subjects after completion of the clinical study.

The following biospecimens will be retained for potential exploratory pharmacogenomic/biomarker analyses related to drug response, unless prohibited by local regulations or ethics committee decision. For example, putative safety biomarkers, drug metabolizing enzyme genes, drug transport protein genes, or genes or biomarkers thought to be related to the mechanism of drug action may be examined. The biospecimens include:

- **Prep D1 (K2 edetic acid (ethylenediaminetetraacetic acid) (EDTA) whole blood collection optimized for DNA analysis):** a 4 ml blood biospecimen will be collected at the baseline visit (Visit 5);

- **Prep B1 (K_2 EDTA plasma collection optimized for biomarker/proteomic/metabonomic analysis)**: a 10 mL blood biospecimen will be collected at baseline (Visit 5) and at the Week 52 visit (Visit 11).

The Banked Biospecimens will be collected from all subjects **unless prohibited by local regulations or ethics committee decision.** Detailed collection, processing, storage and shipment instructions are provided in the central laboratory manual.

It is possible that the use of these biospecimens may result in commercially viable products. Subjects will be advised in the informed consent document/subject information sheet that they will not be compensated in this event.

7.5.2. Additional Research

Unless prohibited by local regulations, subjects will be asked to indicate on the consent form whether they will allow the Banked Biospecimens to also be used for the following research:

- Investigations of the disease under study in the clinical trial, and related conditions;

- Biospecimens may be used as controls. This includes use in case-control studies of diseases for which Pfizer is researching drug therapies; use in characterizing the natural variation amongst people in genes, RNA, proteins, and metabolites; and use in developing new technologies related to Pharmacogenomics/biomarkers.

Subjects need not provide additional biospecimens for the uses described in this section; the biospecimen specified in Markers of Drug Response Section will be used. Subjects may still participate in the clinical trial if they elect not to allow their Banked Biospecimens to be used for the additional purposes described in this section.

7.6. Triggered Requirements

Condition	Action
Reduction of IP Dosing Frequency	
If a subject has IP dosing reduced to Q4wks	The subject will have direct LDL-C measurements approximately Q8 wks, for the duration of the study.
Management of Hypertriglyceridemia	
If the fasting triglyceride result is ≥600 mg/dL (6.78 mmol/L) and <800 mg/dL (9.03 mmol/L) one occasion; and it is determined that the subject was NOT fasting a minimum of 10 hours	The subject does NOT need to have an unscheduled visit for a repeat triglyceride assessment, and should return to the study site at the next scheduled visit time. The investigator should reinforce the importance of dietary compliance and fasting for 10 hours, prior to laboratory testing.
If the fasting triglyceride result is ≥600 mg/dL (6.78 mmol/L) and <800 mg/dL (9.03 mmol/L) on one occasion; and it is determined that the subject was fasting a minimum of 10 hours	The subject should have an unscheduled visit for a repeat triglyceride assessment, to confirm the elevation. The investigator should reinforce the importance of dietary compliance and refer the subject for the treatment of hypertriglyceridemia and/or prescribe therapy in accordance with accepted local treatment guidelines.
If the triglyceride result is ≥800 mg/dL (9.03 mmol/L), and it was determined that the subject was fasting a minimum of 10 hours	The investigator should reinforce the importance of dietary compliance. The subject must be prescribed additional therapy to manage hypertriglyceridemia. More specifically, fibrates or niacin or fish oil, in accordance with clinical practice. If the subject is diabetic glycemic control should be optimized.
Symptomatic Myopathy Monitoring/CK	
If at any study visit after screening, a subject experiences unexplained (ie, not associated temporally with recent trauma, intra muscular injections, heavy exercise or physically strenuous activity) CK values >5x ULN, If completing the remainder of the trial without study treatment is not possible, end of study evaluations must be performed.	The subject must return to the clinical research site for repeat CK testing preferably within 48 hours of when results are made available to the Investigator. Continued follow up for the lab abnormality should be conducted in accordance with the Adverse Events section of the protocol (Section 8) and Appendix 7. At the time of repeat testing, a CK isozyme assessment (to assess CK MM and MB fractions) should be performed, a urine dipstick should be performed, and a serum creatinine specimen should also be obtained. If the repeat testing confirms CK values >5x ULN, and the CK elevation is associated with muscle pain, muscle tenderness and/or muscle weakness, or new onset renal dysfunction, then the subject must be discontinued from study treatment and asked to

Condition	Action
	complete the remainder of the scheduled visits without receiving bococizumab or placebo. If completing the remainder of the trial without study treatment is not possible, end of study evaluations must be performed.
If a subject has a CK >5x ULN,	The Sponsor must be notified of any CK >5x ULN within 24 hours. Continued follow up for the lab abnormality should be conducted in accordance with the Adverse Events section of the protocol (Section 8) and Appendix 7. If the subject's CK value is >5x ULN on repeat testing, without muscle pain, muscle tenderness, and/or muscle weakness, or new onset renal dysfunction, the subject may continue on study therapy if approved by Pfizer's Medical Monitor or designated representative, who may request additional assessments. At the time of repeat testing, CK isozymes (to assess CK-MM and CK-MB fractions), a urine dipstick, and a serum creatinine will be obtained. The subject's CK levels should continue to be monitored, pending resolution of the CK elevation.

7.7. Health Care Resource Utilization Assessments

At each visit after Visit 5 (Randomization) an assessment will be made of HCRU. Specifically, subjects will be asked if they have utilized health care resources. Should health care resources have been utilized, the investigator will obtain a release of medical records, so that HCRU data can be obtained and extracted for completion of the HCRU CRF. It is quite possible that this HCRU data will identify AEs and or SAEs which will also require appropriate safety reporting (Section 8.14).

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.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious adverse event (SAE) requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the Sponsor, any non-serious adverse event that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 40 calendar days after the last administration of the investigational product. This period includes the period between pre-screening (the time of pre-screening informed consent) and randomization, as well as the run-in visits, when the subject is receiving placebo injections. Serious adverse events occurring to a subject after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all serious adverse events that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the Sponsor.

- AEs (serious and non-serious) should be recorded on the case report form (CRF) from the time the subject has signed the informed consent document through the last subject visit.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.4. Medication Errors

Medication errors may result, in this study, from the administration of the wrong product by the wrong subject, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error CRF, which is a specific version of the AE page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the investigational product;

- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is captured on the medication error version of the adverse event (AE) page and, if applicable, any associated AE(s) are captured on an AE CRF page.

A single missed dose is not automatically considered a medication error. In the event of a medication dosing error, the sponsor should be notified immediately. If a single dose is outside of the injection window and there are at least 7 days separation between this dose and the nearest dose (previous and/or subsequent), this would not be considered a medication error. If the subject repeats this out of window administration again in the study, it would still not be recorded as a medication error as long as the out of window administrations are not consecutive. If the subject repeats their out of window administration consecutively or the minimum time (7 days) between doses is not maintained, this will be considered a medication error. Subjects should return to their original dosing schedule.

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.6. Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Medical device complaints may meet the SAE reporting requirement criteria (see the section on Medical Device Complaint Reporting Requirements). An incident is any malfunction (ie, the failure of a device to meet its performance specifications or to perform as intended; performance specifications include all claims made in the labeling for the device) that, directly or indirectly, might lead to or might have led to the death of a subject, or user, or of other persons, or to a serious deterioration in their state of health.

A serious injury that can cause a serious deterioration in state of health can include:

- a life-threatening illness, even if temporary in nature;
- a permanent impairment of a body function or permanent damage to a body structure;
- a condition necessitating medical or surgical intervention to prevent the above 2 bulleted items;

Examples: clinically relevant increase in the duration of a surgical procedure, a condition that requires hospitalization or significant prolongation of existing hospitalization;

- any indirect harm as a consequence of an incorrect diagnostic or in vitro diagnostic device test results when used within the manufacturer's instructions for use;
- fetal distress, fetal death, or any congenital abnormality or birth defects.

8.6.1. Disease-Related Efficacy Endpoints

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) (as shown in Appendix 9):

- 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).

8.6.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransaminase (AST) and/or alanine aminotransaminase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (X ULN) concurrent with a total bilirubin values ≥2 X ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 X ULN or not available;
- For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the upper limit of normal, the following threshold values should be used in the definition mentioned above:
    - For subjects with pre-existing AST or ALT baseline values above the normal range: AST or ALT ≥2 times the baseline values and ≥3 X ULN, **or** ≥8 X ULN (whichever is smaller).
- Concurrent with
    - For subjects with pre-existing values of total bilirubin above the normal range: Total bilirubin levels increased from baseline by an amount of at least one time the upper limit of normal **or** if the values reaches ≥3 times the upper limit of normal (whichever is smaller).

The subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment.

In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/ International Normalized Ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as SAEs (Section 8.6).

Training and a flowchart is provided to the study sites, to explain the reporting process for potential drug induced liver injury events (see Appendix 8).

8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Pre-planned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.8. Severity Assessment

If required on the AE CRFs, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.9. Causality Assessment

The investigator’s assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE requirements if applicable. An investigator’s causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts

(evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor (see the Section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to the Pfizer SAE Triage Group, on an SAE report form and Exposure During Pregnancy (EDP) supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the

terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.11. Occupational Exposure

An occupational exposure occurs when during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an adverse event.

An occupational exposure is reported to the Pfizer SAE Triage Group within 24 hours of the investigator's awareness, using the SAE Report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a CRF, however a copy of the completed SAE Report form is maintained in the investigator site file.

8.12. Withdrawal Due to Adverse Events (See Also the Section on Subject Withdrawal)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.13. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs.

8.14. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14.1. Serious Adverse Event Reporting Requirements

All SAEs will be reported on the AE eCRF (marked as serious) and on the Clinical Trial SAE report form (available in Firecrest) to be submitted to the Pfizer SAE Triage Group, within 24 hours of investigator's awareness. The form must be completed fully, including an assessment of SAE causality on the submitted forms (see Section 8.9). The Pfizer SAE Triage Group will identify potential disease-related efficacy endpoint SAEs as defined in Section 8.6.1. The identified potential disease-related efficacy endpoints will not be reported into the Pfizer DSU unless the investigator believes there is a causal relationship between study drug and a potential disease-related efficacy endpoint. Other SAEs that are not potential disease-related efficacy endpoints will be reported to the DSU, by the Pfizer SAE Triage Group.

In particular, if the SAE is fatal or life-threatening, notification to the Pfizer SAE Triage Group must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy, exposure via breastfeeding and occupational exposure cases.

If a potential disease-related efficacy endpoint SAE is subsequently adjudicated not to be an endpoint, the site will be contacted by the Adjudication Committee and asked to submit an updated SAE form. The form should be revised to show the awareness date (the date of notification by the Adjudication Committee). This form should be submitted to the Pfizer SAE Triage Group within 24 hours of the notification from the Adjudication Committee. This process is shown in Appendix 9.

SAEs must be reported for all subjects (including screen failures) from the time of signing informed consent up to and including 40 days after discontinuing study drug, with this period, including events occurring between pre-screening (the time of pre-screening informed consent) and randomization.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames for reporting specified above. Follow up information for previously forwarded SAE reports, should be reported directly to the DSU within 24 hours of investigator awareness. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the

case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event to the Pfizer SAE Triage Group within 24 hours after learning of it and document the time of his or her first awareness of the SAE.

8.14.2. Non-Serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.14.3. Medical Device Complaint Reporting Requirements

All medical device complaints, regardless of whether the medical device complaint is associated with an AE, will be collected on the applicable pages within the CRF. This includes potential incidents or malfunctions associated with the use of a medical device product. An incident or malfunction is an event that might have led to death or serious deterioration in health, or if it occurred again might have led to death or serious deterioration in health.

Pfizer is to be notified of all medical device complaints within 24 hours of the investigator's awareness of the event.

8.14.4. Sponsor's Reporting Requirements to Regulatory Authorities

Adverse event reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summaries and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.1. Sample Size Determination

A sample size estimate of 11,000 randomized subjects (5,500 on bococizumab and 5,500 on placebo) has approximately 90% power to detect a 25% reduction in the risk of experiencing the primary endpoint, by means of a two-sided α=0.05 log rank test. The required number of subjects with an adjudicated and confirmed event is 508. The sample size calculation is

based on an annual event rate of 2.7% and a premature study discontinuation rate of 1% per year. The trial is intended to complete after approximately 508 subjects have accrued an adjudicated and confirmed primary endpoint event (as defined in Section 2.2.1) or 12 months following the date that the last subject is randomized, whichever occurs later. Assuming that the trial will recruit in 2.5 years, with approximately 50% of the subjects in the last six months, the study will finish in another approximately 1.4 years for a trial duration of approximately 3.9 years.

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.

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.

These power and trial duration calculations were done with the software package EaST® (version 6.3.1).

9.1.1. Cognitive Testing Sample Size

One of the objectives for this trial is to describe the safety of bococizumab and placebo with respect to assessments of cognitive testing. Cognitive testing will be performed at baseline (Visit 5), annually, and at the EDC and EOS visits at a subset of designated study sites in approximately 500 subjects (250/treatment group). This number of subjects is based on feasibility of sites with the appropriate staff and workspace to administer the testing accurately.

Assuming 80% of the 500 subjects will have cognitive testing performed at Visit 11 (Week 52) and 70% at Visit 14 (Week 104), it is expected that 400 subjects (200/group) will have cognitive testing at Week 52 and 350 subjects (175/group) at Week 104. Precision estimates are defined as the half-width of the 95% confidence interval for these assumed sample sizes at Week 52 and Week 104 for each cognitive test and are displayed in the table below.

Table 3. Precision Estimates for Cognitive Assessments

Cognitive Test	Visit	N/group	SD*	Precision
Digit Span (Forward)	Week 52	200	2	±0.39
	Week 104	175	2	±0.42
Digit Span (Backward)	Week 52	200	2	±0.39
	Week 104	175	2	±0.42
Digit Symbol Substitution Test	Week 52	200	9	±1.76
	Week 104	175	9	±1.89
Trail Making A	Week 52	200	22	±4.31
	Week 104	175	22	±4.61
Trail Making B	Week 52	200	40	±7.84
	Week 104	175	40	±8.38
HVLT Learning	Week 52	200	4	±0.78
	Week 104	175	4	±0.84
HVLT Delayed Recall	Week 52	200	2	±0.39
	Week 104	175	2	±0.42

* Based on data for cognitively normal subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study except for HVLT which is based on data for placebo subjects from Pfizer Study A4091004

9.1.2. Primary Endpoint Placebo Event Rate Estimate

Given the power and the alpha level, the expected duration of the trial will be driven by the assumed rate of accrual of adjudicated and confirmed primary endpoint events in the placebo group, the assumed hazard ratio, the subject accrual rate and the premature study discontinuation rate. To produce an estimate of the primary endpoint event rate in the placebo group, meta-analyses, published and unpublished, were considered and a review of lipid lowering clinical trial literature was conducted (Section 9.1.3). These trials vary considerably with respect to their temporal execution, background cardioprotective medications, and differences in enrichment of various risk factors, any of which may impact CV event rates. Furthermore, the component of the primary endpoint for the present study, hospitalization for unstable angina needing urgent revascularization, did not appear to be a predefined component of the trials that were reviewed, some of which had endpoint components comprising hospitalization for unstable angina, irrespective of the need for revascularization, and for other clinical trials, revascularization rates were reported separately, as a secondary endpoint.

Given the uncertainty of the primary endpoint event rate in the placebo group, the current estimates of trial duration and event accrual will assume a placebo event rate of 2.7%/year, which is the lower bound of the 80% prediction interval for a baseline LDL-C of 100 mg/dL (2.6 mmol/L) from an unpublished meta-analysis.

9.1.3. Representative Analyses of Event Rates

The Cholesterol Treatment Trialists' Collaboration (CTTC) meta-analysis showed an average major vascular event rate of 4.5%/year, for trials that compared more intensive to less intensive statin therapy (Table 4).[45] These event rates are expected to be somewhat higher

than what would be expected for this study, for which only unscheduled urgent revascularizations, rather than any revascularizations serve as an element of the primary endpoint.

Table 4. CTTC Statin Lipid Lowering Trials and Event* Rate Estimates, %/Year

CTTC trial meta-analysis	Statin more intensive	Statin less intensive
Trial name		
PROVE-IT[46]	11.3	13.1
A to Z[47]	4.0	5.4
TNT[48]	5.2	6.3
IDEAL[49]	3.6	3.8
SEARCH[50]	7.2	8.1
Mean	4.5	5.3

*Major vascular events CHD death, non-fatal MI, any revascularization, any stroke

The Cholesterol Treatment Trialists' Collaboration (CTTC) meta-analysis also evaluated event rates by the baseline level of LDL (Table 5). The analysis did not demonstrate a trend by baseline LDL-C level (Trend $\chi^2 = 2.04$, $p = 0.2$).[45]

Table 5. CTTC Statin Lipid Lowering Trial Event Rates (%/year) by LDL Level

mg/dL	mmol/L	Statin more intensive	Statin less intensive
<77	<2.0	4.6	5.2
≥77 to <97	≥2.0 to <2.5	4.2	4.8
≥97 to <116	≥2.5 to <3.0	4.5	5.0
≥116 to <135	≥3.0 to <3.5	5.7	7.8
≥135	≥3.5	4.5	5.3

The statin treatment control arm event rate of two recent trials assessing the efficacy and safety of treatments increasing levels of HDL-C were also informative and would be considered near, contemporaneous, with expected event rates for the present trial. The AIM-HIGH study of subjects at risk of CVD with low levels of HDL-C, with a baseline LDL-C of 74 mg/dL (1.9 mmol/L) taking simvastatin, had a somewhat broader primary endpoint than the present study (death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, hospitalization for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization). The investigators reported an event rate of 16% over a mean of 3 years, or an approximate rate of 5.4%/year.

The dal-OUTCOMES assessment of dalcetrapib in subjects with recent acute coronary syndrome had a primary endpoint which was a composite of death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, unstable angina, or cardiac arrest with resuscitation.[52] The mean LDL-C level reported in that study was 76 mg/dL (2.0 mmol/L) and the investigators reported a primary endpoint incidence of 9.1% (95% CI 8.4-9.9) or approximately 3%/year.

An independent, unpublished meta-analysis of CV event rates, was performed by Quantitative Solutions, Inc. It evaluated the occurrence of CV events observed in a large number of lipid lowering studies. The analysis included a simulation of a Phase 3 outcomes trial similar to the current study design and assumed a population comprising 60% CHD subjects and 40% with diabetes, an HDL-C of 47 mg/dL and a body mass index (BMI) of 29 kg/m^2. The analysis demonstrated a 4.5 year cumulative incidence of 8.3% (1.8%/year) for major cardiovascular events (CV death, non-fatal MI, and non-fatal stroke) and 14.5% (3.3%/year) for any CV event (major CV events as described, and coronary revascularization).[53]

An evaluation of whether or not the level of baseline LDL-C contributed to the event rate estimates (with 80% prediction interval [PI]) suggested a trend toward a modestly higher rate with increasing levels of baseline LDL-C, but there was considerable variation in the estimates (Table 6).[53]

Table 6. Estimates of Expected CV Event Rates by Baseline LDL-C

Baseline LDL mg/dL	Baseline LDL mmol/L	CV events with End Organ Injury [80% PI]	Any CV event [80% PI]
80	2.1	1.9 [1.4-2.7]	3.3 [2.4-4.5]
90	2.3	2.0 [1.4-2.8]	3.5 [2.5-4.8]
100	2.6	2.2 [1.5-3.0]	3.8 [2.7-5.1]
110	2.8	2.3 [1.6-3.2]	4.0 [2.9-5.4]
120	3.1	2.4 [1.7-3.4]	4.3 [3.1-5.7]

PI = Prediction Interval

9.2. Efficacy Analysis

Efficacy analyses, unless otherwise indicated, will be performed according to the intention-to-treat (ITT) principle. The Full Analysis Set (FAS) includes all subjects who were randomized and will be the primary analysis set for the analysis of efficacy data 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. For time-to-event analyses of clinical efficacy endpoints, all data through the efficacy cutoff date will be included, unless specified otherwise. For all other efficacy analyses, all data will be included.

9.2.1. 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 4). 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 efficacy cutoff date, or on the date of last contact, whichever is earlier. The efficacy cutoff date is defined as the estimated

date that the criteria in Section 3 for ending the study, excluding continuing the study for at least 12 months after the last randomization, will be met. This date will be determined during the conduct of the study, prior to unblinding. 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 onset date of the last AE, or the randomization date, whichever occurs last. 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 an interim analysis for clinical benefit (See Section 9.5) and DMC reviews of all-cause death (see Section 9.6), resulting in a two-sided alpha of 0.04898. A Cox proportional hazards model will be fit with treatment group as a covariate and geographic region and complete statin intolerance as a 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 model will be assessed with an Arjas plot.[78] Kaplan-Meier estimates of time to first major cardiovascular event will be plotted.

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 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% confidence interval (CI) will be presented. Kaplan-Meier estimates of time to premature discontinuation from the study will be plotted.

The impact of informative censoring on the primary analysis will be evaluated through multiple imputations. Imputation will only be done for subjects who withdrew consent to be followed prior to the efficacy cutoff date and did not have a primary endpoint event. Several imputation models for informative censoring will be used. Each model will incorporate possible explanatory variables for premature study discontinuation. In a conservative approach, the imputation model for subjects in both treatment groups will be based only on data from placebo subjects. In one approach, the imputation model will incorporate reasons for premature study discontinuation. In a second approach, the imputation model will incorporate the incidence of targeted medical events associated with the mechanism of action of bococizumab.

In a supplemental analysis, the log rank test and Cox proportional hazards model analysis for the primary endpoint will be repeated incorporating all adjudicated and confirmed events, including events after the efficacy cutoff date.

In a second supplemental analysis, time to recurrent primary endpoint events will be analyzed using the Wei-Lin-Weissfeld methodology with treatment group as a covariate and geographic region and complete statin intolerance as stratification factors.[58] If the model fitting fails to converge, complete statin intolerance will be removed as a stratification factor. The common hazard ratio 95% confidence interval, and p-value will be presented.

An additional supplemental analysis of the primary endpoint will assess the efficacy of bococizumab for subjects who adhere to treatment. Only subjects who have been treated for at least 26 weeks will be included. Adherence to treatment will be defined as attaining an LDL-C level at or below 40 mg/dL at Visit 11 (Week 52). Treatment-adherent bococizumab subjects, non-treatment-adherent bococizumab subjects and placebo subjects will be compared using the above Cox proportional hazards model with additional covariates including smoking status, age, BMI, and relevant baseline history.

9.2.1.1. Subgroup Analyses

Cox regression for the primary endpoint will be performed in a subset of subgroups of the FAS listed below. The subgroup analyses will be finalized in the SAP prior to final unblinding.

- Gender;
- Age (<65, 65-74, ≥75);
- Race;
- Ethnicity;
- Geographic region;
- Statin intolerance;
- BMI; <25 kg/m2, ≥25 kg/m2– <30 kg/m2, ≥30 kg/m2);
- Smoking status;
- Baseline history of:
    - Atherosclerotic/cardiovascular event;
    - Hypertension;
    - MI;
    - Coronary heart disease;
    - Diabetes;
    - Diabetes and atherosclerotic/cardiovascular event;
    - Coronary revascularization;
    - Peripheral artery revascularization;

- heFH/LDL-C ≥190 mg/dL (4.9 mmol/L) historically or at pre-screening;
- Peripheral vascular disease;
- CHF;
- Microalbuminuria;
- eGFR (≥30 ml/min/1.73m2 - <60 ml/min/1.73m2 [moderate renal impairment], ≥60 ml/min/1.73m2- <90 ml/min/1.73m2 [mild renal impairment], ≥90 ml/min/1.73m2 [no renal impairment]) (as calculated by MDRD equation);
- Any renal impairment and history of an atherosclerotic/cardiovascular event;
- Baseline LDL-C (<130 mg/dL, ≥ 130 mg/dL-<160 mg/dL, ≥160 mg/dL);
- Baseline triglycerides (<200 mg/dL, ≥200 mg/dL);
- Baseline hs-CRP (<2.0 mg/L, ≥2.0 mg/L);
- Baseline Lp(a) (<50 mg/dL, ≥50 mg/dL);
- Additional background lipid lowering treatments;
- Time from atherosclerotic/cardiovascular event (≤1 year, >1 year).

Geographic region and complete statin intolerance will be stratification factors in the Cox regressions, as appropriate. If model fitting fails to converge, complete statin intolerance will be removed as a stratification factor. The hazard ratios and 95% confidence intervals will be reported and plotted. For each categorical variable used to define subgroups, an additional Cox proportional hazards model will be fit. This Cox model will also include the categorical variable and an interaction between the categorical variable and treatment group. The interaction p-value will be reported.

In addition, the primary endpoint will be summarized by the number of dose adjustments. The subjects randomized to bococizumab with 0, 1 and 2 dose adjustments will be tabulated with all placebo subjects; subgroups will not be taken of the placebo subjects.

9.2.2. Analysis of Secondary Endpoints

The experimentwise Type 1 error rate, after a single Bonferroni adjustment for DMC reviews of all-cause death (see Section 9.6), will be controlled by using a gatekeeping procedure followed by the a fixed sequence testing procedure. Key secondary endpoints will be formally tested only if the null hypothesis for the primary analysis is rejected. The fixed sequence testing procedure will be applied to the key secondary endpoints with a two-sided α=0.04898 using the sequence indicated in Section 2.2.2. All other statistical tests for

secondary endpoints will be performed at the two-sided α=0.05 level; no further corrections will be made for multiple endpoints.

9.2.2.1. Secondary Endpoints for Clinical Outcomes

The secondary endpoints for clinical outcomes include the times from randomization to the first occurrence of the adjudicated and confirmed clinical endpoints described below (Section 9.2.2.1.1 and Section 9.2.2.1.2). 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 with a two-sided α=0.04898 will be used for the log rank test of each endpoint. The sequence indicated in Section 2.2.2 will be used. 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 95% confidence intervals will be reported. For each endpoint, Kaplan-Meier estimates of time to first event will be plotted.

For each of the key secondary endpoints and for all-cause death, the log rank test and Cox proportional hazards model analysis will be repeated incorporating all adjudicated and confirmed events, including events after the efficacy cutoff date.

Times to recurrent events for each of the key secondary endpoints and the remaining composite endpoint will be analyzed using the Wei-Lin-Weissfeld methodology with treatment group as a covariate and geographic region and complete statin intolerance as stratification factors. If a model fitting fails to converge, complete statin intolerance will be removed as a stratification factor. The common hazard ratios, 95% confidence interval, and p-values will be presented.

In addition, an adherent subject analysis will be performed for all-cause death and for the composite endpoint of CV death, non-fatal MI and non-fatal stroke using the same methodology as for the primary endpoint (Section 9.2.1).

9.2.2.1.1. Key Secondary Endpoints

The key secondary endpoints (as defined in Appendix 4) 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.

9.2.2.1.2. Other Clinical Secondary Endpoints

Other clinical secondary endpoints (as defined in Appendix 4) are the times from randomization to the 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.

9.2.2.2. Secondary Endpoints for Circulating Biomarkers

Percent changes from baseline in all lipid endpoints and hs-CRP and nominal change 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). Baseline will be calculated as the mean of the last two non-missing values prior to and including the randomization date.

Restricted Maximum Likelihood (REML) estimation will be used, and the default covariance structure will be unstructured. If the model fitting 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. 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 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.

For Lp(a), triglycerides and hs-CRP, the same model will be fit in the same manner for log-transformed nominal changes from baseline. 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 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 95% confidence intervals along with untransformed p-values. The transformed estimated mean percent changes and corresponding transformed 95% confidence intervals will be plotted.

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 a factors. Least squares means with corresponding 95% confidence intervals, least squares mean differences and corresponding 95% confidence intervals, and p-values will be presented.

Secondary endpoints for circulating biomarkers are:

- The percent and nominal change from baseline at Week 14 (Visit 8) and percent change from baseline to the last available post-baseline observation in LDL-C (direct measurement);
- The percent change from baseline to Week 14 (Visit 8) in
    - Non-HDL-C;
    - VLDL-C;
    - RLP-C;
    - Lp(a);
    - Apo-B;
    - HDL-C;
    - apo-A-I;

- Total cholesterol;
- Triglycerides.

- The percent change from baseline to Week 14 (Visit 8) in hs-CRP.

Friedewald LDL-C will be summarized by treatment group and visit according to sponsor standards.

9.3. Analysis of Other Endpoints

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

9.3.1. Health –Related Quality of Life and Health Care Resource Use

Observed values and changes from baseline in the health index score and the health state score and the observed value of individual EQ-5D items will be summarized according to the sponsor standards.

Health care resource utilization will be summarized by treatment group according to sponsor standards. Additional analyses, including comparisons of the bococizumab treatment group to the placebo treatment group, will be prespecified in a separate analysis plan.

9.3.2. Analysis of Pharmacokinetic and Pharmacodynamic Endpoints

If data permit, the following analyses may be performed for plasma bococizumab concentration data and PCSK9 concentration data:

1. A listing of all plasma bococizumab concentrations by subject at nominal time post dose. This listing will also include actual times post dose.

2. A descriptive summary of plasma bococizumab concentrations. Summary statistics of arithmetic mean, geometric mean, % coefficient of variation, standard deviation, median, minimum, and maximum will be tabulated by visit.

3. A listing of all plasma PCSK9 concentrations by subject at nominal time post dose. This listing will also include actual times post dose.

4. Descriptive summaries for observed PCSK9 concentrations, absolute and percentage change from baseline in PCSK9 concentrations. Summary statistics of arithmetic mean, % coefficient of variation, standard deviation, median, minimum and maximum will be tabulated by visit.

5. Baseline PCSK9 concentration will be defined as the mean of the last two non-missing values prior to and including randomization.

Details on the PK/PCSK9 analyses may be found in the Statistical Analysis Plan.

In addition, PK/PD (LDL-C and PCSK9) data from this study may be combined with data from other studies for population PK/PD analysis.

9.4. Safety Analysis

Safety will be assessed through adverse events (including Type 1 and 3 hypersensitivity reactions and injection site reactions), 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.

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, AEs leading to temporary discontinuation, and SAEs will be tabulated by treatment group. Out of concern for appropriate reporting of adverse events associated with the prefilled syringe, adverse events and SAEs will be reported separately during the screening period and after the first dose of randomized study medication, without any requirement that the intensity increase after the first dose of study medication. AEs leading to discontinuation from treatment and leading to temporary discontinuation will only be summarized after the first dose of study medication. Summaries will also be provided by severity and relationship to study therapy. In addition, a 3-tier approach will be used. Tier 1 AEs are AEs of special clinical interest, including Type 1 and Type 3 hypersensitivity reactions and injection site reactions, and will be specified in the Safety Risk Plan. For these events, the number and percentage of subjects with AEs with onset after first dose of study medication, the risk difference versus placebo, the associated 95% confidence interval, and p-value will be provided. 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 provided. The confidence intervals are for estimation purposes only. All events are Tier 3 events and will be summarized as described above.

Observed values and changes from baseline in systolic BP, diastolic BP, PR, weight, and waist circumference will be tabulated by visit according to sponsor standards. Mean changes from baseline will be plotted longitudinally according to sponsor standards. Observations of potential clinical concern at any time during the study for these parameters will be tabulated according to sponsor standards. Height and temperature will be listed.

Observed values and changes from baseline in hematology, blood chemistry, and quantitative urinalysis parameters will be tabulated by visit according to sponsor standards. Mean changes from baseline will be plotted longitudinally for selected laboratory parameters according to sponsor standards. 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 according to sponsor standards. In addition, the number and percentage of subjects with positive ADAs and neutralizing ADAs will be tabulated for bococizumab-treated subjects.

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.

Physical examination findings will be listed. Neurological exam findings will be summarized according to sponsor standards.

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 treatment group and visit and interaction between treatment group and baseline value. Baseline value will be the last non-missing value on or before the day of randomization. REML estimation will be used and the default covariance structure will be unstructured. 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.

The PHQ-2 score and PHQ-9 score will be summarized by treatment group at baseline according to sponsor standards.

Time-to-event analyses of all-cause death will be repeated in the SAS. Adjudicated and confirmed causes of death will be tabulated by treatment group.

AEs with onset after first dose of study medication will be tabulated for subjects in subgroups defined by age (<65, 65-74, ≥75), gender, number of dose adjustments and having a post-baseline LDL-C ≤25 mg/dL at the end of a dosing interval. For the number of dose adjustments, the subjects receiving bococizumab with 0, 1 and 2 dose adjustments will be tabulated along with all placebo subjects; subgroups will not be taken of the placebo subjects. Similarly, subjects receiving bococizumab having a post-baseline LDL-C ≤25 mg/dL and not having a post-baseline LDL-C ≤25 mg/dL will be tabulated along with all placebo subjects.

Adverse events with onset after the first dose of study medication, Tier 1 AEs, SAEs and selected lab parameters will be summarized by treatment group according to sponsor standards for the adherent subject treatment groups defined in Section 9.2.1.

9.5. Interim Analyses

An interim analysis for clinical benefit will be performed by a group external to the sponsor and reviewed by the DMC when two conditions are met:

1. An adjudicated and confirmed primary endpoint event has occurred in 75% of the required number (508) of subjects to complete the trial and

2. 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 (288) of subjects.

The interim analysis 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 both at most 0.001.

The following additional guidelines will be provided to the DMC as additional considerations for stopping the trial early:

- Consistency across geographic regions and subgroups.

- A positive trend for key and non-key secondary endpoints, including all-cause mortality.

- No excess non-cardiovascular mortality.

- No potential safety issues have emerged for which the additional safety information from B1481038 would be critical.

The decision to stop or continue the study 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.

To protect the experimentwise Type 1 error, the Heybittle-Peto method will be used with alpha = 0.001. The adjustment to the alpha for the final analysis will be 0.00002 (East, Version 6.3.1).

Although a two-sided alpha is used for consistency with the DMC reviews of all-cause death (see Section 9.6), this interim analysis is only for clinical benefit, so no futility bound will be used.

As the Sponsor will remain blinded to results and the choices for the information fraction (75%) and the alpha level (0.001) are sufficiently conservative, the bias introduced by the interim analysis is expected to be negligible.[77]

The analysis methodology used for the interim analysis will be the same as for the final analysis, except that the primary analysis done for the interim analysis will be done with an alpha of 0.001 and, if that analysis is positive favoring bococizumab, the key secondary endpoints will be tested using the fixed sequence testing procedure with alpha=0.001.

Prior to the completion of this study, additional analyses of time to 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. 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. More information about DMC analyses is in Section 9.6.

As there is no possibility of this 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 additional adjustment to the experimentwise Type 1 error will be made.

9.6. Data Monitoring Committee

This study will use an external 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. 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 in Appendix 5. 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 in Appendix 5.

In addition, the DMC will review the interim analysis for clinical benefit described in Section 9.5 and provide the recommendation for stopping or continuing the study.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits, during study conduct, to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the study site may be subject to review by the IRB)/IEC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the study site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source

documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's subject's chart. In these cases data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator's site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to International Conference on Harmonisation (ICH), local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/IEC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 and 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data is compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify study subjects. The study site will maintain a confidential list of subjects who participated in the study linking their numerical code to the subject's actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject personal data consistent with applicable privacy laws.

The informed consent/assent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent/assent documents used during the informed consent process must be reviewed by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject, or his or her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a subject's her legally acceptable representative, the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject's decisional capacity is so limited he/she cannot reasonably be consulted, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, then the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his/her own consent, the source documents must record why the subject did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, parent, spouse) and that the subject's assent was obtained, or waived. If assent is obtained verbally it must be documented in the source documents.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative, when applicable, before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

12.4. Subject Recruitment

Advertisements approved by ethics committees and investigator databases may be used as recruitment procedures.

Pfizer will have an opportunity to review and approve the content of any study recruitment materials directed to potential study subjects before such materials are used.

12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of Trial in a Member State of the European Union is defined as the time at which it is deemed that sufficient subjects have been recruited and completed the study as stated in the regulatory application (ie, Clinical Trial Application [CTA]) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in All Other Participating Countries

End of Trial in all other participating countries is defined as Last Subject Last Visit (LSLV). LSLV in all other participating countries is defined as the date the investigator reviews the last subject's final safety data and determines that no further evaluation is required for the subject to complete the trial.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of bococizumab at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and

the hospital pharmacy (if applicable) within 30 days of the notification. Final study visits should occur within 30 days of subject contact. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies in patients that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

Primary Completion Date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated.

EudraCT

Pfizer posts EU Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the principal investigator of the results of the study based on information collected or generated by principal investigator, whether or not the results are favorable to the Pfizer product.

However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "Publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the Study is part of a multi-centre study, Investigator agrees that the first publication is to be a joint publication covering all study sites, and that any subsequent publications by the principal investigator will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the Study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - “Ethical Considerations in the Conduct and Reporting of Research” of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any Attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

16. REFERENCES

1. Wood D, Mendis S Ebrahim S et al. Research priorities: prevention and control of cardiovascular diseases, with a focus on low and middle-income countries. Prioritized Research Agenda for Prevention and Control of Noncommunicable diseases: Paper 1: Geneva, World Health Organization, 2011.

2. Ballantyne C, Arroll B, Shepherd J. Lipids and CVD management: towards a global consensus. Eur Heart J 2005;26:2224-2231.

3. World Health Organization (WHO), The Atlas of Heart Disease and Stroke. Mackay J, Mensah G, with Mendis S and Greenlund K, editors. World Health Organization, 2004.

4. Global Atlas on Cardiovascular Disease Prevention and Control. Mendis S, Puska P and Norrving B editors. World Health Organization, Geneva 2011.

5. European Association for Cardiovascular Prevention & Rehabilitation, Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, Agewall S, Alegria E, Chapman MJ, Durrington P, Erdine S, Halcox J, Hobbs R, Kjekshus J, Filardi PP, Riccardi G, Storey RF, Wood D; ESC Committee for Practice Guidelines (CPG) 2008-2010 and 2010-2012 Committees. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) Eur Heart J. 2011 Jul;32(14):1769-818. Epub 2011 Jun 28.

6. National Cholesterol Education Program Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002;106:3143-3421.

7. Revkin JH, Shear CL, Pouleur HG, Ryder SW, Orloff DG. Biomarkers in the prevention and treatment of atherosclerosis: need, validation, and future. Pharamacol Rev. 2007;59(1):40-53.

8. Glagov S, Weisenberg E, Zarins CK, et al. Compensatory enlargement of human atherosclerotic coronary arteries. N Engl J Med. 1987;316: 1371-1375Moreno PR, Falk E, Palacios IF, et al. Macrophage infiltration in acute coronary syndromes. Implications for plaque rupture. Circulation 1994; 90:775-778.

9. Moreno PR, Falk E, Palacios IF, et al. Macrophage infiltration in acute coronary syndromes. Implications for plaque rupture. Circulation 1994; 90:775-778.

10. Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, Badimon JJ, Stefanadis C, Moreno P, Pasterkamp G, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I Circulation 2003 Oct 7; 108(14):1664-72.

11. O'Keefe JH Jr, Cordain L, Harris WH, Moe RM, Vogel R. Optimal Low Density Lipoprotein is 50 70 mg/dL. Lower is better and physiologically normal. J Am Coll Cardiol 2004; 43(11):2142-2146.

12. Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, Paternak RC, Smith SC Jr, Stone NJ; for the Coordinating Committee of the National Cholesterol Education Program. Implications of recent clinical trials for the National Cholesterol Education Program Adult treatment Panel III guidelines [published correction appears in Circulation. 2004; 110:763]. Circulation 2004;110:227-239.

13. Smith SC Jr, Benjamin EJ, Bonow RO, Braun LT, Creager MA, Franklin BA, Gibbons RJ, Grundy SM, Hiratzka LF, Jones DW, Lloyd-Jones DM, Minissian M, Mosca L, Peterson ED, Sacco RL, Spertus J, Stein JH, Taubert KA; World Heart Federation and the Preventive Cardiovascular Nurses Association. AHA/ACCF Secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 Update: a guideline from the American Heart Association and American College of Cardiology Foundation. Circulation. 2011;124:2458-2473.

14. Basak A. Inhibitors of proprotein convertases. J. Mol Med. 2005;83:844 855.

15. Horton JD, Cohen JC and Hobbs HH. Molecular biology of PCSK9: its role in LDL metabolism. Trends in Biochemical Sciences 2007;32(2):71-77.

16. Lambert G. Unraveling the functional significance of PCSK9. Current Opinion in Lipidology 2007; Jun 18(3):304-3099.

17. Abifadel M, Varret M, Rabes JP, Allard D, Ouguerram K, Devillers M, Cruaud C, Benjannet S, Wickham L, Erlich D et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. Nat Genet 2003;34:154-156.

18. Berge KE, Ose L, and Leren TP. Missense mutations in the PCSK9 gene are associated with hypocholesterolemia and possibly increased response to statin therapy. Arterioscler. Thromb Vasc. Biol 2006;26:1094-1100.

19. Kotowski I. K., Pertsemlidis A, Luke A, Cooper RS, Vega GL, Cohen JC, and Hobbs HH. 2006. A spectrum of PCSK9 alleles contributes to plasma levels of low-density lipoprotein cholesterol. Am J Hum Genet 78: 410–422.

20. Cohen JC, Boerwinkle E, Mosley TH and Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N Engl J Med 2006;354:1264-1272.

21. Cohen J, Petsemlidis A, Kotowski IK, Graham R, Garcia CK and Hobbs HH. Low LDL cholesterol in individuals of African descent resulting from frequent nonsense mutations in PCSK9. Nat Genet 2005;37:161-165.

22. Zhao Z, Tuakli Wosornu Y, Lagace TA, Kinch L, Grishin NV, Horton JD, Cohen JC, and Hobbs HH. Molecular characterization of loss of function mutations in PCSK9 and identification of a compound heterozygote. Am J Hum Genet 2006;79:514-523.

23. Maxwell KN, Soccio RE, Duncan EM, Sehayek E and Breslow JL. Novel putative SREBP and LXR target genes identified by microarray analysis in liver of cholesterol fed mice. J Lipid Res 2003;44:2109-2119.

24. Horton JD, Shah NA, Warrington JA, Anderson NN, Park SW, Brown MS and Goldstein JL. Combined analysis of oligonucleotide microarray data from transgenic and knockout mice identifies direct SREBP target genes. Proc. Natl Acad. Sci. 2003;100:12027-12032.

25. Hua X, Yokoyama C, Wu J, Briggs M, Broen M, Goldstein J and Wang X. SREBP 2, a second basic helix loop helix leucine zipper protein that stimulates transcription by binding to a sterol regulatory element. Proc. Natl. Acad. Sci. USA 1993;90:11603 11607.

26. Sheng Z, Otani H, Brown M, and Goldstein J. Independent regulation of sterol regulatory element binding proteins 1 and 2 in hamster liver. Proc Natl Acad Sci USA, 1995;92:935-938.

27. Rashid S, et al. Decreased plasma cholesterol and hypersensitivity to statins in mice lacking PCSK9. Proc Natl Acad Sci USA, 2005;102:5374-5379.

28. Dubuc G et al. Statins upregulate PCSK9, the gene encoding the proprotein convertase neural apoptosis regulated convertase 1 implicated in familial hypercholesterolemia. Arterioscler Thromb Vasc Biol 2004;24:1454-1459.

29. Lambert G, Sjouke B, Choque B, Kastelein JJ, Hovingh GK. The PCSK9 decade. J Lipid Res. 2012 Jul 17. [epub ahead of print, doi: 10.1194/jlr.R026658].

30. Maxwell KN, Breslow JL. Antibodies to PCSK9 : A Superior Way to Lower LDL Cholesterol? Circ Res. 2012;111:274-277.

31. Tall AR. Protease Variants, LDL, and Coronary Heart Disease. N Engl J Med 2006;354 (12):1310-12.

32. Dias CS, Shaywitz AJ, Wasserman SM, Smith BP, Gao B, Stolman DS, Crispino CP, Smirnakis KV, Emery MG, Colbert A, Gibbs JP, Retter MW, Cooke BP, Uy ST, Matson M, Stein EA. Effects of AMG 145 on Low-Density Lipoprotein Cholesterol Levels: Results From 2 Randomized, Double-Blind, Placebo-Controlled, Ascending-Dose Phase 1 Studies in Healthy Volunteers and Hypercholesterolemic Subjects on Statins. J Am Coll Cardiol. 2012 Nov 6;60(19):1888-98.

33. McKenney JM, Koren MJ, Kereiakes DJ, Hanotin C, Ferrand AC, Stein EA. Safety and efficacy of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease, SAR236553/REGN727, in patients with primary hypercholesterolemia receiving ongoing stable atorvastatin therapy. Am Coll Cardiol. 2012 Jun 19;59(25):2344-53.

34. Stein EA, Gipe D, Bergeron J, Gaudet D, Weiss R, Dufour R, Wu R, Pordy R Effect of a monoclonal antibody to PCSK9, REGN727/SAR236553, to reduce low-density lipoprotein cholesterol in patients with heterozygous familial hypercholesterolaemia on stable statin dose with or without ezetimibe therapy: a phase 2 randomised controlled trial. Lancet. 2012 Jul 7;380(9836):29-36. Epub 2012 May 26.

35. Stein EA, Mellis S, Yancopoulos GD, Stahl N, Logan D, Smith WB, Lisbon E, Gutierrez M, Webb C, Wu R, Du Y, Kranz T, Gasparino E, Swergold GD. Effect of a monoclonal antibody to PCSK9 on LDL cholesterol. N Engl J Med. 2012;366:1108 – 1118.

36. Roth EM, McKenney JM, Hanotin C, Asset G, Stein EA. Atorvastatin with or without an antibody to PCSK9 in primary hypercholesterolemia. N Engl J Med 2012 Nov 15;367(20):1891-900.

37. Koren MJ, Scott R, Kim JB, Knusel B, Liu T, Lei L, Bolognese M, Wasserman SM. Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 as monotherapy in patients with hypercholesterolaemia (MENDEL): a randomized, double-blind, placebo-controlled, study. Lancet. 2012 Dec 8;380(9858):1995-2006.

38. Giugliano RP, Desai NR, Kohli P, Rogers WJ, Somaratne R, Huang F, Liu T, Mohanavelu S, Hoffman EB, McDonald ST, Abrahamsen TE, Wasserman SM, Scott R, Sabatine MS; LAPLACE-TIMI 57 Investigators. Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57): a randomized, placebo-controlled, dose-ranging phase 2 study. Lancet. 2012 Dec 8;380(9858):2007-2017.

39. Liang H, Chaparro-Riggers J, Strop P, Gent T. Suttone JE, Tsai D, Bai L, Abdiche Y, Dilley J, Yu J, Wu S, Chin SM, Lee NA, Rossi A, Lin JC, Rajpal A, Pons J, Shelton DL. Proprotein convertase subtilisin/kexin type 9 antagonism reduces low-density lipoprotein cholesterol in statin-treated hypercholesterolemic nonhuman primates. J Pharmacol Exp Ther. 2012 Feb;340(2):228-236.

40. Chaparro-Riggers J, Liang H, DeVay RM, Bai L, Sutton JE, Chen W, Geng T, Lindquist K, Casas MG, Boustany LM, Brown CL, Chabot J, Gomes B, Garzone P, Rossi A, Strop P, Shelton D, Pons J, Rajpal A. Increasing serum half-life and extending cholesterol lowering in vivo by engineering antibody with pH-sensitive binding to PCSK9. J Biol Chem. 2012 Mar 30;287(14):11090-11097.

41. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD; the Writing Group on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. Third universal definition of myocardial infarction. European Heart Journal. 2012; 33:2551-2567.

42. Hicks KA, Tcheng JE, Bozkurt B, Chaitman BR, Cutlip DE, Farb A, Fonarow GC, Jacips JP, Jaff MR, Lichtman JH, Limacher MC, Mahaffey KW, Mehran R, Nissen SE, Smith EE, Targum SL. 2014 ACC/AHA key data elements and definitions for cardiovascular endpoint events in clinical trials: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (writing Committee to Develop Cardiovascular Endpoints Data Standards). Circulation. 2015;132(4):302-361.

43. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972; 18(6):499-502.

44. EuroQol Group, EQ-5D-3L User Guide, Version 4.0, April 2011, Marten Meesweg 107, 3068 AV Rotterdam, The Netherlands.

45. Cholesterol Treatment Trialists' Collaboration. Efficacy and safety of more intensive lipid lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376:1670-1680.

46. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med. 2004; 350:1495–504.

47. de Lemos JA, Blazing MA, Wiviott SD, et al. Early intensive *vs* a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. JAMA. 2004;292:1307–16.

48. LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 2005;352:1425–35.

49. Pedersen TR, Faergeman O, Kastelein JJ, et al. High-dose atorvastatin *vs* usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. JAMA. 2005;294:2437–45.

50. Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12, 064 survivors of myocardial infarction: a double-blind randomised trial. Lancet. 2010; 376(9753):1658-69.

51. The AIM-HIGH Investigators. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Eng J Med. 2011;365:2255-2267.

52. Schwartz GG, Olsson AG, Abt M, Ballantyne CM, Barter PJ, et al, for the dal-OUTCOMES Investigators. Effects of dalcetrapib in patients with a recent acute coronary syndrome. N Eng J Med. 2012;367:2089-2099.

53. Mandema J. personal communication. Quantitative Solutions, 845 Oak Grove Avenue, Menlo Park, California, USA.

54. DeMott K, Nherera L, Shaw EJ, Minhas R, Humphries SE, Kathoria M, Ritchie G, Nunes V, Davies D, Lee P, McDowell I, Neil A, Qureshi N, Rowlands P, Seed M, Stracey H, Thorogood M, Watson M. Clinical Guidelines and Evidence Review for Familial hypercholesterolaemia: the identification and management of adults and children with familial hypercholesterolaemia. 2008. London: National Collaborating Centre for Primary Care and Royal College of General Practitioners.

55. Wechsler D. Wechsler Adult Intelligence Scale Manual. 1955. New York: Psychological Corporation.

56. Wechsler D. Wechsler Adult Intelligence Scale-3rd Edition (WAIS-3®). 1997. San Antonio, TX: Harcourt Assessment.

57. Reitan RM. (1958) Validity of the Trail Making test as an indicator of organic brain damage. Percept Mot Skills. 1958;8:271-276.

58. Wei LJ, Lin DY, Weissfeld L. Regression analysis of multivariate incomplete failure time data by modeling marginal distributions. Journal of the American Statistical Association. 1989;84:1065-1073.

59. Perk J, De Backer G, Ghoke H, Graham I, et. al. on Behalf of the Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). Eur Heart J. 2012;33(13):1615-1701.

60. Expert Dyslipidemia Panel of the International Atherosclerosis Society Panel Members. An International Atherosclerosis Society Position Paper: global recommendations for the management of dyslipidemia--full report. J Clin Lipidol. 2014;8(1):29-60.

61. Advisory Committee on Immunization Practices. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States. Morbidity Mortality Weekly Report. 2005;55(RR-16):1-32.

62. Lichtman JH, Bigger JT Jr, Blumenthal JA, et al. Depression and coronary heart disease: recommendations for screening, referral and treatment: a science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Psychiatric Association. Circulation 2008;118:1768-1775.

63. Kroenke K, Spitzer RL, Williams JB. The Patient Health Questionnaire-2: validity of a two-item depression screener. Med care. 2003;41(11)1284-1292.

64. Brandt J. The Hopkins Verbal Learning Test: development of a new memory test with six equivalent forms. Clin Neuropsychol. 1991;5(2):125-142.

65. Shapiro AM, Benedict RH, Schretien D. Brandt J. Construct and concurrent validity of the Hopkins Verbal Learning Test-revised. Clin. Neuropsychol. 1999;13(3)348-358.

66. DeLong DM, DeLong ER, Wood PD, Lippel K, Rifkind BM. A comparison of methods for the estimation of plasma low- and very low-density lipoprotein cholesterol. The Lipid Research Clinics Prevalence Study. JAMA. 1986 Nov 7;256(17):2372-7.

67. Raal F, Scott R, Somaratne R, et al. Low-density lipoprotein cholesterol-lowering effects of AMG 145, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease in patients with heterozygous familial hypercholesterolemia. The reduction of LDL-c with PCSK9 inhibition in heterozygous familial hypercholesterolemia disorder (RUTHERFORD) randomized trial. Circulation. 2012;126:2408-17.

68. Sullivan D, Olsson AG, Scott R, et al. Effect of monoclonal antibody to PCSK9 on low-density lipoprotein cholesterol levels in statin-intolerant patients. The GAUSS randomized trial. JAMA. 2012;308:2497-506.

69. Roth EM, McKenney JM, Hanotin C, et al. Atorvastatin with or without an antibody to PCSK9 in primary hypercholesterolemia. N Engl J Med. 2012;367:1891-900.

70. Koren MJ, Lundqvist P, Bolognese M, et al. Anti-PCSK9 monotherapy for hypercholesterolemia; the MENDEL-2 randomized, controlled phase III clinical trial of evolocumab. J Am Coll Cardiol. 2014;63:2531-40.

71. Blom DJ, Hala T, Bolognese M, et al. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. N Engl J Med. 2014;370:1809-19.

72. Schwartz GG, Bessac L, Berden LG, et al. Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes: rationale and design of the ODYSSEY Outcomes trial. Am Heart J. 2014;168:682-9.

73. Robinson JG, Nedergaard BS, Rogers WJ, et al. Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. JAMA. 2014;311:1870-8.

74. Ballantyne CM, Neutel J, Cropp A, et al. Results of bococizumab, a monoclonal antibody against proprotein convertase subtilisin/kexin type 9, from a randomized, placebo-controlled, dose-ranging study in statin-treated subjects with hypercholesterolemia. Am J Cardiol. 2015;115(9):1212-21.

75. Sabatine MS, Giugliano RP, Wiviott SD, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015;372:1500-9.

76. Robinson JG, Farnier M, Krempf M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015;372:1488-99.

77. Freidlin B and Korn EL. Stopping clinical trials early for benefit: impact on estimation. Clin Trials. 2009;6(2):119-125.

78. Arjas E. A Graphical Method for Assessing Goodness of Fit in Cox's Proportional Hazards Model. Journal of the American Statistical Association. 1988;83,(401):204-212.

79. Cook TD, Benner RJ, Fisher MR. "The WIZARD trial as a case study of flexible clinical trial design," *Drug Information Journal,* 2006;40: 345-53.

Appendix 1. Abbreviations

Ab	Antibody
ABI	Ankle brachial index
Abs	Absolute
ACCF	American College of Cardiology Foundation
Apo	Apolipoprotein
ADA	Anti-drug antibodies
ADAs	Anti-drug antibodies
ADNI	Alzheimer's Disease Neuroimaging Initiative
AHA	American Heart Association
AE	Adverse event
ALT	Alanine aminotransaminase
AntiHBc	Hepatitis B core antigen antibody
Anti-HBs	Hepatitis B surface antigen antibody
AST	Aspartate aminotransaminase
BMI	Body Mass Index
BP	Blood pressure
C	Centigrade
CABG	Coronary artery bypass graft surgery
CCU	Cardiac care unit
CETP	Cholesteryl ester transfer protein
CFB	Change from baseline
CHD	Coronary heart disease
CHF	Congestive heart failure
CI	Confidence interval
CK	Creatine kinase (also known as CPK, creatine phosphokinase)
CKD	Chronic kidney disease
CK-MB	Creatine kinase heart isoenzyme
CK-MM	Creatine kinase muscle isoenzyme
Con Med	Concomitant medication
CPK	Creatine phosphokinase (also known as CK, creatine kinase)
CRF	Case report form
CSA	Clinical Study Agreement
CTA	Clinical trial application
CTTC	The Cholesterol Treatment Trialists' Collaboration
CVD	Cardiovascular disease
CV	Cardiovascular
DAI	Dosing and administration instructions
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DSM	Diagnostic and statistical manual of mental disorders
DSU	Drug Safety Unit
DU	Dispensible unit
EASD	European Association for the Study of Diabetes
ECG	Electrocardiogram

ED80	80% of the maximal response
EDC	Early discontinuation of study drug
EDP	Exposure during pregnancy
ELISA	Enzyme-linked immunosorbent assay
EOS	End of study
ESC/EAS	European Society of Cardiology/European Society of Atherosclerosis
EQ-5D	EuroQol 5-Dimensions Health State Profile
EU	European Union
FAS	Full analysis set
Fc	Fragment crystallizable
FDA	Food and Drug Administration
FDAAA	US Food and Drug Administration Amendments Act of 2007
FH	Familial hypercholesterolemia
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
eGFR	Estimated glomerular filtration rate
HbA1c	Glycated hemoglobin
HBsAg	Hepatitis B surface antigen
hCG	Human Chorionic Gonadotropin
HCRU	Health Care Resource Utilization
HDL	High density lipoprotein
HDL-C	High density lipoprotein cholesterol
heFH	Heterozygous familial hypercholesterolemia
HIV	Human immunodeficiency virus
HMG-CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A
HR	Hazard ratio
hs-CRP	High sensitivity C-reactive protein
HVLT	Hopkins Verbal Learning Test
IA	Interim analysis
IEC	Independent Ethics committee
ICD	Informed consent document
ID	Identification
IDL-C	Intermediate density lipoprotein cholesterol
ICH	International Conference on Harmonization
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IM	Intramuscular
IND	Investigational new drug
INR	International normalized ratio
IRB	Institutional review board
IRT	Interactive response technologies
ITT	Intent to treat
IUD	Intrauterine device
IVR	Interactive voice response
IWR	Interactive web response
K_2EDTA	Potassium ethylenediaminetetraacetic acid

LDH	Lactate Dehydrogenase
LDL	Low density lipoprotein
LDL-C	Low density lipoprotein cholesterol
LDLR	Low density lipoprotein receptor
LFTs	Liver function tests
Lp(a)	Lipoprotein (a)
LPD	Local Product Document
LSLV	Last subject last visit
LVEF	Left ventricular ejection fraction
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MICU	Medical intensive care unit
mg	milligrams
MI	Myocardial infarction
mL	millilter
mm Hg	millimeters of mercury
MMRM	Mixed models repeated measures
mRNA	Messenger ribonucleic acid
NCEP ATPIII	National Cholesterol Education Program Adult Treatment Panel III
NICU	Neurology intensive care unit
NYHA	New York Heart Association
ODIS	Off drug in study
PCI	Percutaneous coronary intervention
PCD	Primary completion date
PCP	Primary care physician
PCR	Polymerase chain reaction
PCSK9	Proprotein convertase subtilisin kexin type 9
PD	Pharmacodynamic
PHQ	Patient Health Questionnaire
PI	Predictive Index
PK	Pharmacokinetic
PR	Pulse rate
RC	Risk condition
REML	Restricted Maximum Likelihood
RF	Risk factor
RLP	Remnant lipoprotein
RNA	Ribonucleic acid
RR	Relative risk
Q2wks	Every 2 weeks
Q4wks	Every 4 weeks
QOL	Quality of life
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety Analysis Set
SC	Subcutaneous
SICU	Surgical intensive care unit

SPC	Summary of Product Characteristics
SREBP 2	Sterol regulatory element binding protein 2
SRSD	Single Reference Safety Document
TC	Total cholesterol
TG	Triglycerides
TIA	Transient ischemic attack
TICU	Thoracic intensive care unit
TMT	Trail Making Test
ULN	Upper limit of normal
US	United States
USA	United States of America
USPI	United States Package Insert
VLDL	Very low density lipoprotein
VLDL-C	Very low density lipoprotein cholesterol
VAS	Visual Analogue Scale
WAIS	Wechsler Adult Intelligence Scale
WCBP	Women of childbearing potential

Appendix 2. Criteria for Diagnosis of Heterozygous Familial Hypercholesterolemia

For the purposes of this study, the diagnosis of heFH should be based on historically having met the Simon Broome criteria (off or on treatment) as defined below (revised to add measures of cholesterol levels in mg/dL).[54]

A diagnosis of definite Familial Hypercholesterolemia (FH) requires:

Cholesterol above 290 mg/dL (7.5 mmol/l) or LDL cholesterol above 189 mg/dL (4.9 mmol/l) in an adult.

PLUS

Tendon xanthomas in patient or a 1st degree relative (parent, sibling, child), or in a 2nd degree relative (grandparent, uncle, aunt).

OR

DNA-based evidence of an LDL receptor mutation, familial defective apoB-100, or a PCSK9 mutation.

A diagnosis of possible FH requires:

Cholesterol above 290 mg/dL (7.5 mmol/l) or LDL cholesterol above 189 mg/dL (4.9 mmol/l) in an adult.

PLUS

Family history of myocardial infarction (MI): Before 50 years in a 2nd degree relative or below age 60 in a 1st degree relative.

OR

Family history of raised total cholesterol: Above 290 mg/dL (7.5 mmol/l) in adult 1st or 2nd degree relative or above 259 mg/dL (6.7 mmol/l) in a child or sibling aged under 16 years.

Appendix 3. Hepatitis B Assessment

Interpretation of hepatitis B serology results.

Serologic Marker				
Hepatitis B Surface Antigen (HBsAg)	Hepatitis B Core Antibody (Anti-HBc)	Hepatitis B Surface Antibody (Anti-HBs)	Interpretation	Inclusion
–	–	–	Never infected	Permitted
+	–	–	Early infection or post vaccination	Not permitted
+	+	–	Acute infection	Not permitted
–	+	–	Acute resolving infection	Not permitted
–	+	+	Recovered from past infection and immune	Permitted
+	+	–	Chronic infection	Not permitted
–	+	–	Exposed and susceptible	Not permitted
–	–	+	immune	Permitted

Key
– : negative serology
+ : positive serology

Appendix 4. Clinical 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 stenosis [Type 4c]), or Type 5 (MI related to CABG), consistent with the draft endpoint definitions of the Standardized Data Collection for Cardiovascular Trials Initiative.[41, 42]

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. This 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.[42]

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.[42] 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 5. Data Monitoring Committee Stopping Rules for Periodic Reviews

The Data Monitoring Committee (DMC) will use all available evidence and its collective judgment in making a recommendation to (1) stop or modify any of the ongoing studies in the Bococizumab Phase 3 Clinical Development Program for safety or to (2) make a recommendation to stop for early benefit on all-cause death in either of the CV outcomes studies. These statistical considerations are not a substitute for the committee's medical, scientific, or statistical expertise.

Major CV events for safety

At each periodic review, a flag based on $p \leq 0.001$ for harm will be used to assess major CV events in bococizumab versus placebo. This flag would signal further examination of all available data by the committee with consideration of altering the conduct or terminating any of the ongoing studies in the bococizumab Phase 3 Clinical Development Program. This flag would be applied to chi-square tests for each study; a Cochran-Mantel-Haenszel (CMH) general association test across all studies; and log-rank tests for the CV outcomes studies, performed separately and in a pooled test with stratification by study.

All-cause death for safety

At each periodic review, a flag based on $p \leq 0.01$ for harm will be used to assess all-cause death in bococizumab versus placebo. This flag would signal further examination of all available data by the committee with consideration of altering the conduct or terminating any of the ongoing studies in the bococizumab Phase 3 Clinical Development Program. This flag would be applied to chi-square tests for each study; a Cochran-Mantel-Haenszel (CMH) general association test across all studies; and log-rank tests for the CV outcomes studies, performed separately and in a pooled test with stratification by study.

All-cause death for benefit in each CV outcomes study

Each CV outcomes study is designed to provide evidence in a specific population that LDL-C lowering with bococizumab compared to placebo will reduce the occurrence of the primary endpoint of major CV outcomes (a composite endpoint of cardiovascular death, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina needing urgent revascularization).

The minutes of the End of Phase 2 Meeting with the United States Food and Drug Administration 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.

There will be no interim monitoring for the purposes of stopping early for efficacy for the primary endpoint in either CV outcomes study. However, the DMC will consider evidence

for overwhelming benefit for all-cause death (one of the non-key secondary endpoints) in each CV outcomes study as a potential reason to recommend early termination for efficacy.

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 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. 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 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 $\boldsymbol{\alpha(t) = 0.001 * t}$ with final alpha $\boldsymbol{\alpha(1) = 0.001}$. 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 $\boldsymbol{\alpha(t)}$ will be calculated based on an information fraction $\boldsymbol{t}$ equal to the aggregate number of observed *adjudicated 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).[79]

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 meetings or teleconferences). 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 (eg, 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%

Planned interim safety analysis of the Cardiovascular Outcome Studies' primary endpoint

Prior to the regulatory filing for hyperlipidemia and mixed dyslipidemia indications, a single planned interim safety analysis of the primary endpoint for the Cardiovascular Outcome Studies will be included in the committee report for review at a schedule meeting. This analysis will include Major Cardiovascular Events from each of the studies in the bococizumab Phase 3 Clinical Development Program. The DMC's recommendation with respect to the cardiovascular outcome studies, based on this analysis as well as all available safety information, will be included in the regulatory filing.

For all randomized subjects in each study in the bococizumab Phase 3 Clinical Development Program, the time to the first adjudicated and confirmed occurrence of the a major CV event will be analyzed using a log rank test stratified by protocol and geographic region within a protocol. A major CV event is defined as a composite endpoint which includes cardiovascular (CV) death, non-fatal MI, non-fatal stroke, and hospitalization for unstable angina needing urgent revascularization. Subjects who do not experience any of the components of the primary endpoint will be censored on the earlier of the date of death or the date of data transfer for this analysis. A flag based on $p<0.001$ for harm of bococizumab would signal further examination of all available data by the DMC and consideration of recommendation not to continue the Cardiovascular Outcome Studies.

Appendix 6. EQ-5D Health Questionnaire

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (eg, work, study, housework, family or leisure activities)

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

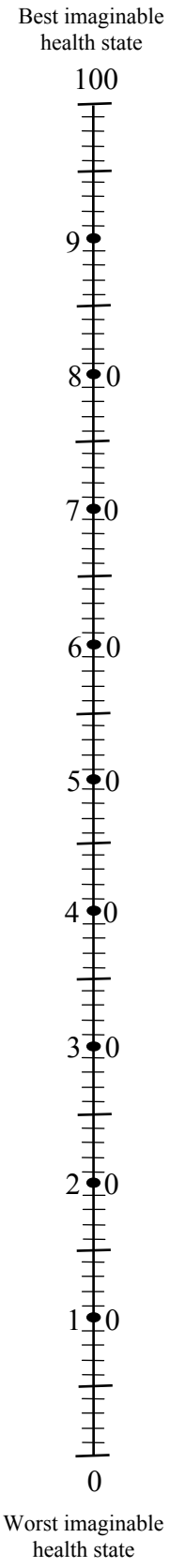
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

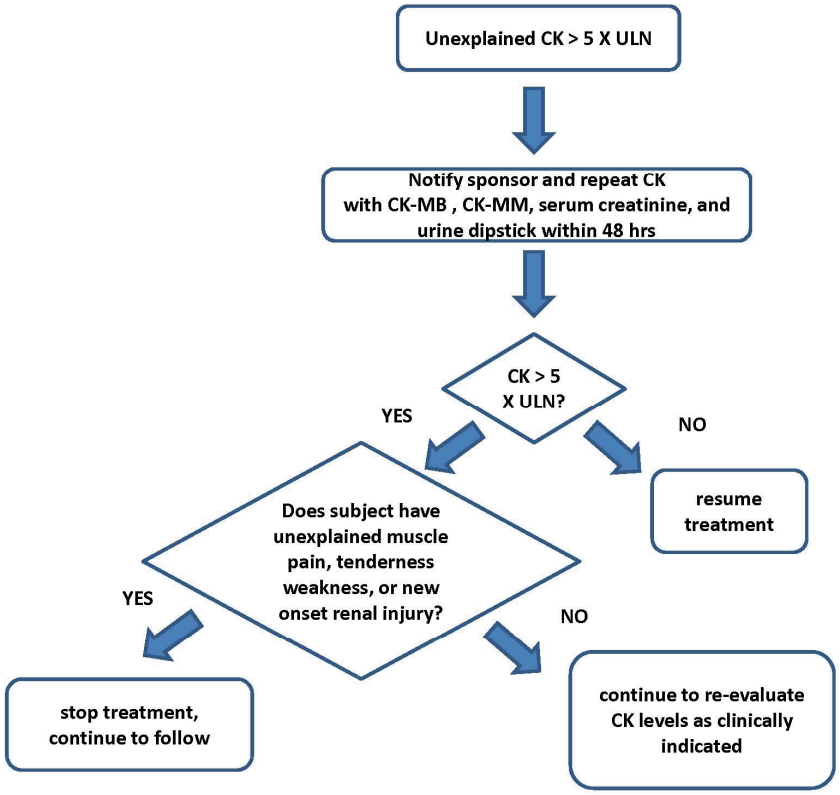
We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



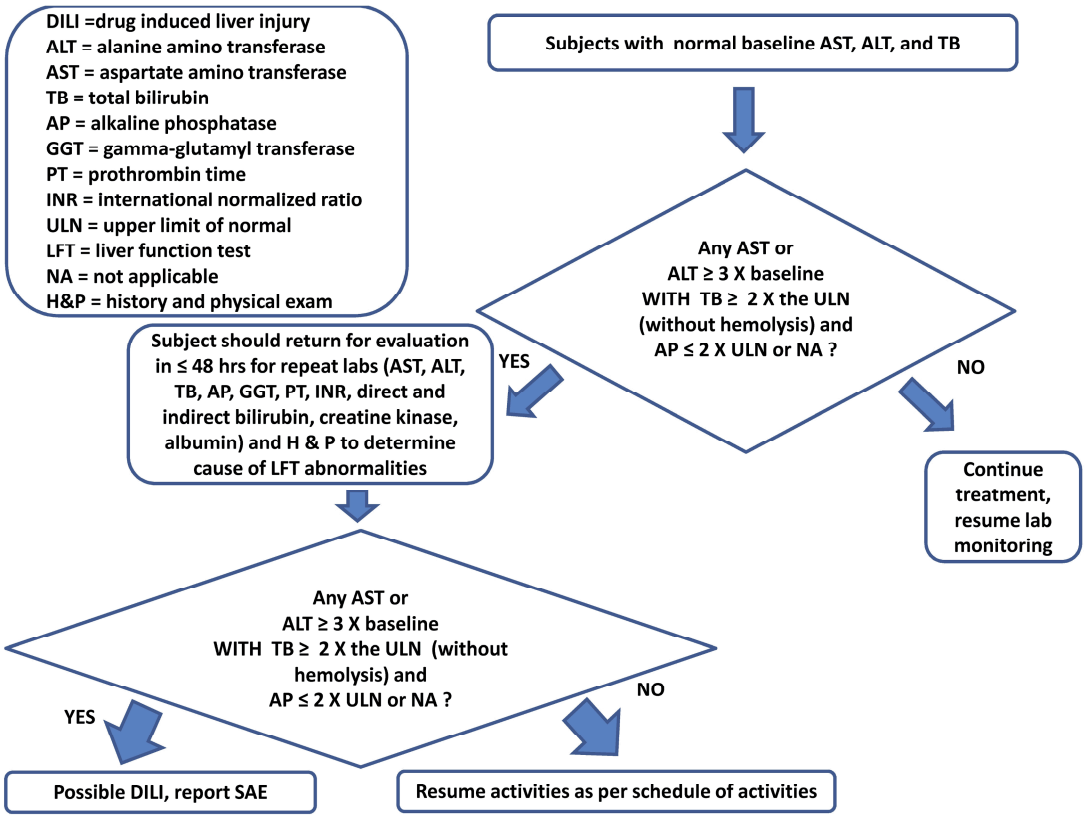
Appendix 7. Safety Algorithm: Myopathy

The following process illustrates the decision tree for evaluating potential myopathy related AEs and/or CK elevations.

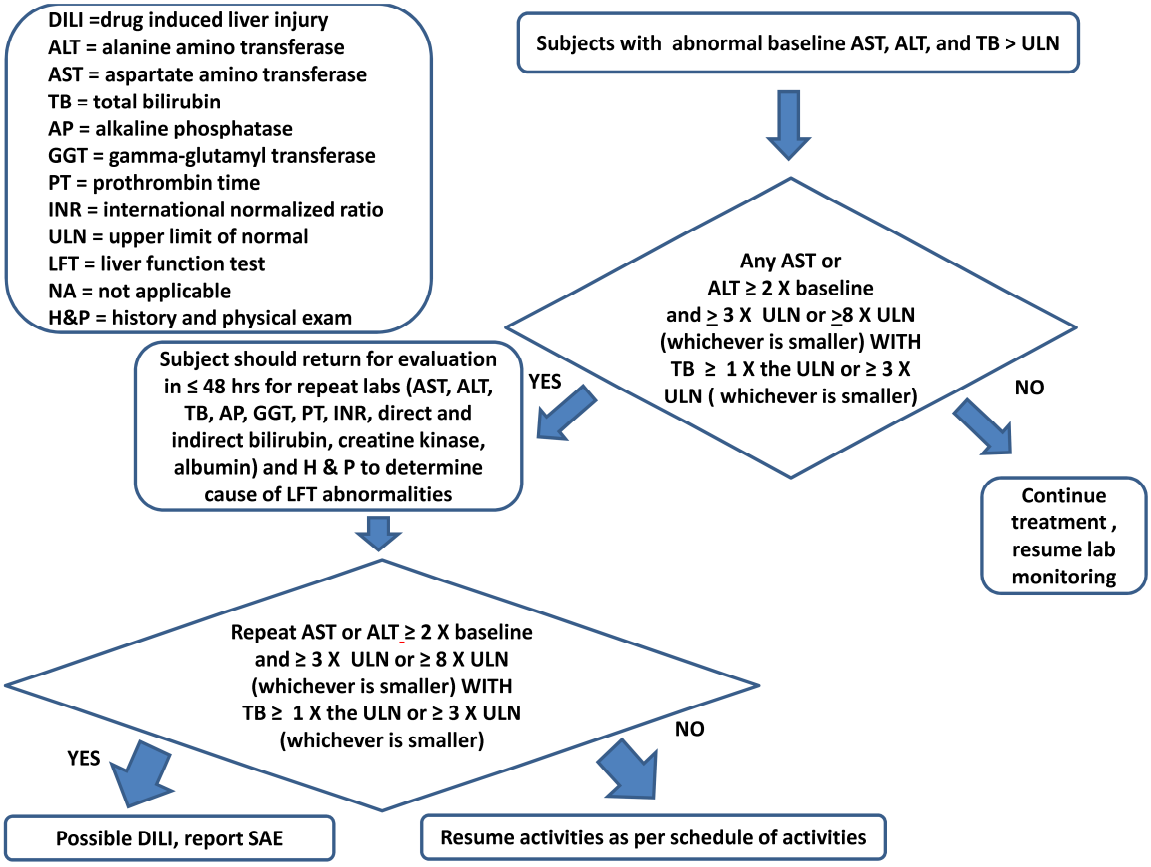


Appendix 8. Potential Drug Induced Liver Injury Assessment

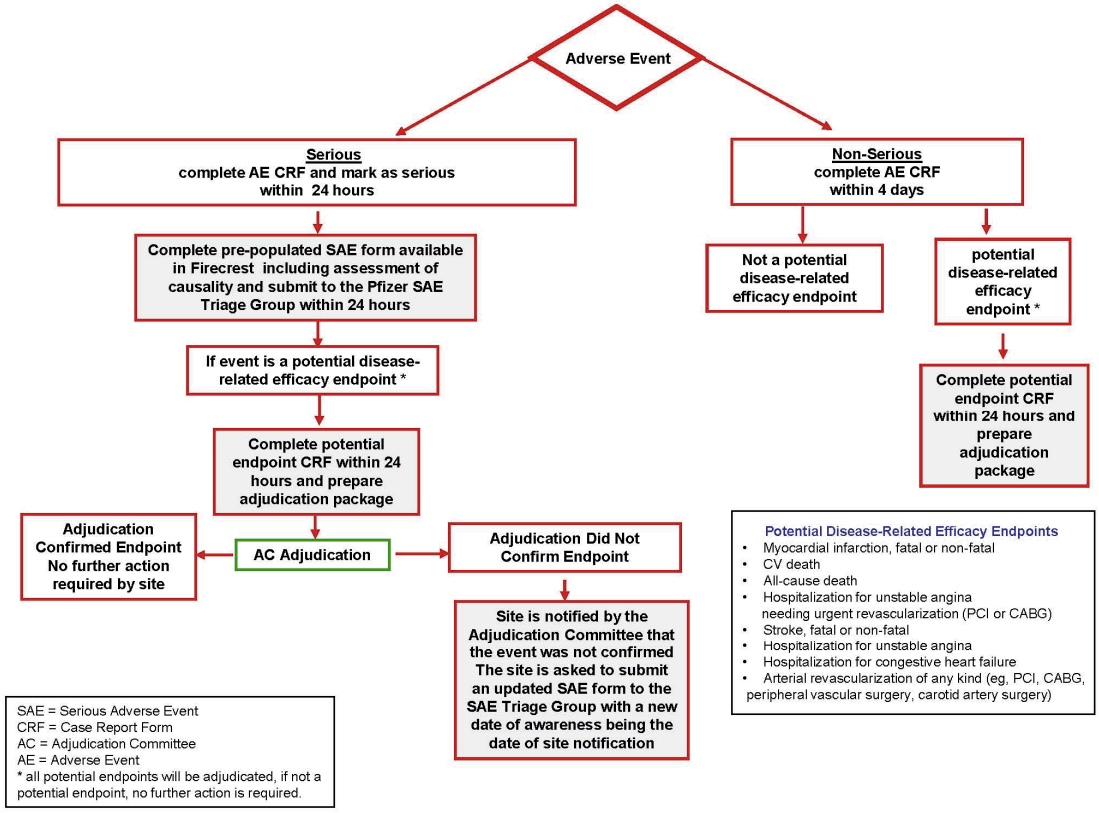
Appendix 8.1. Liver Function Assessment in Subjects With Normal Baseline Liver Function



Appendix 8.2. Liver Function Assessment in Subjects with Abnormal Baseline Liver Function

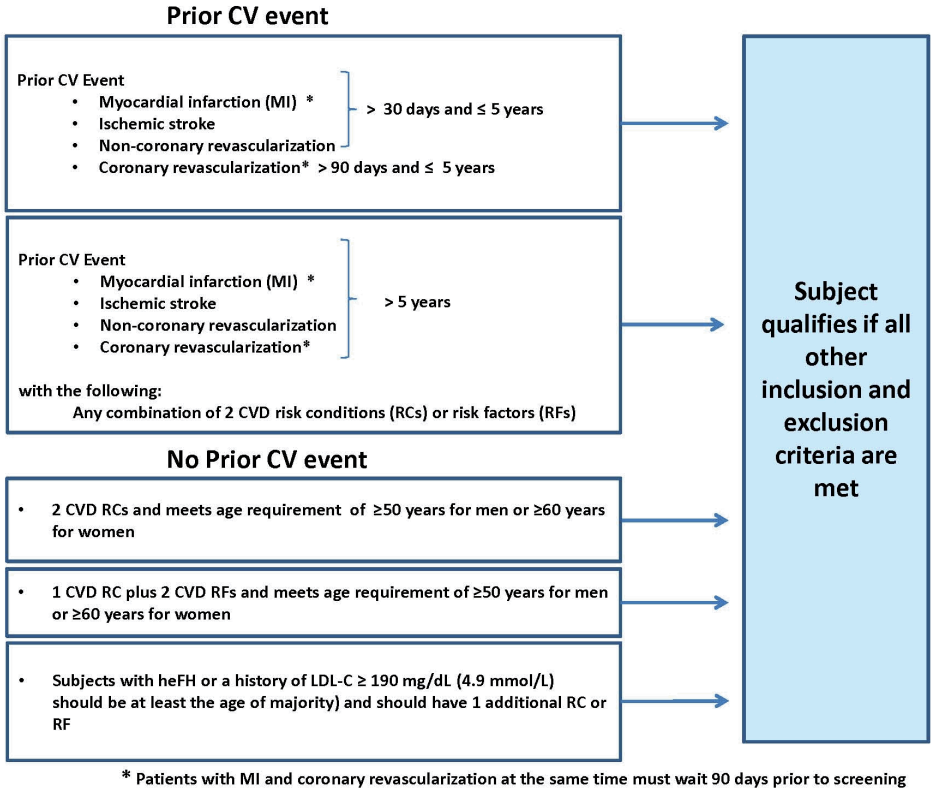


Appendix 9. Adverse Event and Potential Outcome Event Flowchart



Appendix 10. Categories of Cardiovascular Risk

Appendix 10.1. Flow Chart



* Patients with MI and coronary revascularization at the same time must wait 90 days prior to screening

Appendix 10.2. Cardiovascular Disease Risk Conditions and Risk Factors

CVD Risk Conditions (RCs)	CVD Risk Factors (RFs)
• Peripheral vascular disease: ankle brachial index <0.85; limb peripheral artery stenosis >50%; limb amputation due to vascular disease; carotid artery stenosis > 50%; carotid artery plaque area > 119 mm^2 or equivalent plaque volume	• Imaging evidence of significant coronary artery disease: ○ coronary artery stenosis of >50% narrowing in at least 2 major coronary arteries ○ coronary calcium score of ≥300 Agatston units or ≥ 75th percentile for age, sex and ethnicity
• Diabetes Type I or Type II as defined by local diabetes guidelines	• Smoking (cigarette, current, >30 days and any number)
• Chronic kidney disease: eGFR ≥30 and ≤ 60 mL/min/1.73m^2 (Modification of Diet in Renal Disease)	• Low HDL-C <40 mg/dL (<1.03 mmol/L)
• Conditions of elevated LDL-C and no prior CV event ○ Heterozygous familial hypercholesterolemia: Simon Broome Criteria ○ History of LDL-C ≥ 190 mg/dL (4.9 mmol/L)	• Elevated hs-CRP (>2.0 mg/L within 1 year of screening date)
	• Microalbuminuria (a spot urine albumin-to-creatinine ratio>30 mg/g at screening)
	• Lipoprotein (a) cholesterol ≥ 50 mg/dL