



AMENDED CLINICAL TRIAL PROTOCOL NO. 3

COMPOUND: Alirocumab (SAR236553/REGN727)

A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Alirocumab in Patients with Hypercholesterolemia Not Adequately Controlled with Non-statin Lipid Modifying Therapy or the Lowest Strength of Statin

STUDY NUMBER: EFC14305

STUDY NAME: ODYSSEY NIPPON

VERSION DATE / STATUS: 26-Apr-2017 / Approved

NCT02584504

Protocol Amendment 3	Version number: 1 (electronic 1.0)	Date : 26-Apr-2017
Amended Clinical Trial Protocol 2	Version number: 1 (electronic 1.0)	Date : 15-Mar-2016
Protocol Amendment 2	Version number: 1 (electronic 1.0)	Date : 15-Mar-2016
Amended Clinical Trial Protocol 1	Version number: 1 (electronic 1.0)	Date : 15-Sep-2015
Protocol Amendment 1	Version number: 1 (electronic 1.0)	Date : 15-Sep-2015
Clinical Trial Protocol	Version number: 1 (electronic 1.0)	Date : 03-Jul-2015
Version Number: 1	EudraCT	Not applicable
	IND Number(s)	Not applicable
	WHO universal trial number:	U1111-1170-7697
Date: 26-Apr-2017	Total number of pages:	142

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CLINICAL TRIAL SUMMARY

COMPOUND: Alirocumab (SAR 236553/REG727)	STUDY No: EFC14305 (Odyssey NIPPON)
TITLE	A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Alirocumab in Patients with Hypercholesterolemia Not Adequately Controlled with Non-statin Lipid Modifying Therapy or the Lowest Strength of Statin
INVESTIGATOR/TRIAL LOCATION	Japan, Multi-center
PHASE OF DEVELOPMENT	Phase 3
STUDY OBJECTIVE(S)	<p>Primary Objective</p> <ul style="list-style-type: none"> To demonstrate the reduction of low density lipoprotein cholesterol (LDL-C) by alirocumab 150 mg every 4 weeks (Q4W) or 150 mg every 2 weeks (Q2W) regimen as add on therapy to non-statin lipid modifying therapy (LMT) including diet therapy alone or the lowest strength of statin in comparison with placebo after 12 weeks of treatment in patients with hypercholesterolemia. <p>Secondary Objectives</p> <ul style="list-style-type: none"> To evaluate the effect of two treatment regimens of alirocumab on other lipid parameters: Apolipoprotein B (Apo-B), non-high-density lipoprotein cholesterol (non HDL-C), total cholesterol (TC), lipoprotein (a) (Lp [a]), high density lipoprotein cholesterol (HDL-C), triglyceride (TG), apolipoprotein A-1 (Apo A-1). To evaluate the safety and tolerability of alirocumab 150 mg Q4W and 150 mg Q2W. To evaluate the development of anti- alirocumab antibodies To evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) profile of alirocumab 150 mg Q4W and 150 mg Q2W. To evaluate the long-term safety in patients receiving open-label alirocumab 150 mg Q4W and 150 mg Q2W.
STUDY DESIGN	<p>This is a randomized, double-blind, placebo-controlled, parallel-group, balanced (1:1:1, alirocumab 150 mg Q4W: alirocumab 150 mg Q2W: placebo), multi-center phase 3 study. Randomization will be stratified according to background statin therapy (Yes/No). "No statin background" will be also stratified according to background fibrate/ezetimibe therapy (Yes/No), where Yes represents fibrate or ezetimibe, and No represents diet therapy alone.</p> <p>The study consists of:</p> <ul style="list-style-type: none"> A run-in period of 4 weeks. Patients will be treated with stable non-statin LMTs or stable daily atorvastatin 5 mg. Patients who will have already been treated with stable non-statin LMTs or stable daily atorvastatin 5 mg for at least 4 weeks will be able to skip this period. A screening period of up to 3 weeks.

	<ul style="list-style-type: none">• A double-blind treatment period (DBTP) of 12 weeks. Patients will receive double-blind treatment as follows:<ul style="list-style-type: none">- alirocumab 150 mg Q4W alternating with placebo Q4WOR- alirocumab 150 mg Q2WOR- placebo for alirocumab Q2W• An open-label treatment period (OLTP) of 52 weeks. All patients will receive alirocumab 150 mg Q4W from the start of OLTP.• At Week 24, the up-titration to alirocumab 150 mg Q2W will be conducted through Interactive Web Response System (IWRS) only under the following circumstances:<ul style="list-style-type: none">- In patients with heFH or in patients with non-FH with documented coronary heart disease (CHD), LDL-C is ≥ 100 mg/dL (2.59 mmol/L) at Week 20.- In patients with non-FH classified as primary prevention category III, LDL-C is ≥ 120 mg/dL (3.10 mmol/L) at Week 20 <p>The lipid results will be masked from randomization to Week 12 in order to keep the double-blind manner of DBTP. No attempts should be made by the investigator or patient to routinely have the patient's lipid values independently evaluated during DBTP. Lipid values will be communicated to the investigators from Week 24.</p> <p>Patients should be on a stable diet therapy (Japan Atherosclerosis Society [JAS] Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2012 diet or equivalent) throughout the entire study duration.</p> <p>Regarding fibrates, only fenofibrate or bezafibrate are allowed during the study.</p> <p>Background LMTs should remain stable (including dose) throughout the entire study duration.</p> <p>Modification of the background LMT is allowed only under the following circumstances:</p> <ul style="list-style-type: none">• Exceptional circumstances per the Investigator's judgment.• If patient meets the pre-specified TG alert [TG\geq500 mg/dL (5.65 mmol/L)], lab alerts will be sent and repeat testing should be done as soon as possible. Then diet will have to be reinforced. If necessary, LMTs (newly added or dose modifications) might be considered based on the best clinical judgement of the investigators. <p>All injections will be conducted by site staffs, patients, or another designated person (such as a spouse, relative, etc.) if patients cannot conduct the injection.</p> <ul style="list-style-type: none">• Injection training is planned at Week -1 with a placebo for alirocumab in cases that injections will be conducted by patients or another designated person from Week 0.
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	<ul style="list-style-type: none"> From Week 0 to Week 10, all injections will be conducted at the study site. From Week 12, all injections could be conducted by patients or another designated person at home if patients agree.
<p>STUDY POPULATION</p> <p>Main selection criteria</p>	<p>Main Inclusion criteria</p> <p>I 01. Patients with hypercholesterolemia[§] (heFH* or non-FH), receiving non statin LMTs** or the lowest strength of statin***.</p> <p>* Diagnosis of heFH must be made either by genotyping or by clinical criteria before randomization. For those patients not genotyped, the clinical diagnosis may be based on JAS Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2012. If the clinical criteria is not met but heFH is strongly suspected by investigators, genotyping will be conducted during the screening period after signed written informed consent for obtaining genotype information.</p> <p>** Fibrate or ezetimibe, or diet therapy alone.</p> <p>*** Defined as atorvastatin 5 mg.</p> <p>§ Patients receiving monotherapy with 5 mg daily atorvastatin, fibrate, or ezetimibe are allowed to enter the study. It is noted that patients with any combined drug therapy, such as atorvastatin + fibrate, atorvastatin + ezetimibe, or fibrate + ezetimibe, are not allowed. Patients with diet therapy alone or diet therapy with drug monotherapy (atorvastatin, fibrate, or ezetimibe) are allowed to enter the study.</p> <ul style="list-style-type: none"> In patients with heFH, patients with or without a history of documented coronary heart disease (CHD). In patients with non-FH, patients must have a history of documented CHD; otherwise patients have a history of documented diseases or other risk factors classified as primary prevention category III. <p>A) Definitions for CHD (includes one or more of the following):</p> <ul style="list-style-type: none"> Myocardial infarction. Unstable angina. Coronary revascularization procedure (e.g., percutaneous coronary intervention [PCI] or coronary artery bypass graft surgery [CABG]). Clinically significant CHD diagnosed by invasive or non-invasive testing (such as coronary angiography, stress test using treadmill, stress echocardiography or nuclear imaging). <p>B) Definitions for documented diseases or other risk factors classified as primary prevention category III:</p> <ul style="list-style-type: none"> Ischemic stroke (excluding cardiogenic cerebro-embolism and/or TIA). Peripheral arterial disease (PAD). Diabetes. Chronic kidney disease (CKD): Other risk factors.

	<ul style="list-style-type: none"> - A 10-year fatal CHD risk SCORE $\geq 2\%$. - A 10-year fatal CHD risk SCORE $\geq 0.5\%$ and $< 2\%$, and have 1 or more of the following criteria: <ol style="list-style-type: none"> a) Hypo HDL-C (< 40 mg/dL). b) Family history of premature coronary artery disease (first-degree relative and male: < 55 year-old, female: < 65 year-old). c) Impaired glucose tolerance (defined as a fasting blood glucose [Fasting blood glucose, FBG] < 126 mg/dL [< 7.0 mmol/L], and a two- hour post glucose challenge value: 140-199 mg/dL [7.8-11.1 mmol/L] [Oral glucose tolerance test, OGTT]). <p>I 02. Hypercholesterolemia (heFH or non-FH) patients with one or more following risk factors that can explain why statin is not appropriate or why the lowest strength statin dose should not be increased.</p> <ul style="list-style-type: none"> • History of side effects caused by statin (Hypersensitivity, elevated serum ALT, AST, γGT, ALP, and/or LDH levels, statin-induced liver dysfunction, abnormal values in CPK, Skeletal muscle-related symptoms, etc.) • CYP3A4 inhibitor (fibrate, immunosuppressant, azole antifungal agents or erythromycin) • Hepatic dysfunction or abnormal liver function (except fatty liver and/or confirmed other types of liver disease, history of hepatic dysfunction related to other causes) • Renal Impairment or abnormal renal function (except history of renal impairment with defined cause) • Hypothyroidism • Impaired glucose tolerance as defined previously or impaired fasting glycaemia (FBG 110-125 mg/dL [6.1 – 6.9 mmol/L]) • Diabetic nephropathy • Elderly with $BMI < 18.5$ kg/m² • Other documented factors medically judged by investigators why statin is not appropriate or why statin dose cannot be increased from the lowest strength for the patients other than the factors described above. <p>I 03. Signed written informed consent</p> <p>Main Exclusion criteria</p> <ul style="list-style-type: none"> • LDL-C < 100 mg/dL (< 2.59 mmol/L) at the screening visit (Week -3) in patients with heFH or in patients with non-FH who have a history of documented CHD. • LDL-C < 120 mg/dL (< 3.10 mmol/L) at the screening visit (Week -3) in patients with non-FH patients who have a history of documented diseases or other risk factors classified as primary prevention category III. • Not on a stable dose of LMTs (including diet therapy alone) in the run-in period or the screening period. • Use of statins other than atorvastatin 5 mg daily in the run-in period
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	<p>or the screening period.</p> <ul style="list-style-type: none"> • Use of fibrates, other than fenofibrate or bezafibrate in the run-in period or the screening period. • Use of nicotinic acid or bile acid-binding sequestrants or probucol or EPA (ethyl icosapentate) or red yeast rice products in the run-in period or the screening period. • Fasting serum TG >400 mg/dL (>4.52 mmol/L) at the screening period. • Systolic BP >160 mmHg or diastolic BP >100 mmHg at the run-in visit (Week -7) or the screening visit (Week -3) or the randomization visit (Week 0).
Total expected number of patients	<p>Approximately 159 randomized patients (53:53:53, alirocumab 150 mg Q4W: 150 mg Q2W: placebo).</p> <p>█ [REDACTED]</p> <p>█ [REDACTED]</p>
Expected number of sites	█ [REDACTED]
Investigational medicinal product(s) Formulation	<p>Alirocumab:</p> <p>Sterile alirocumab drug product supplied at a concentration of 150 mg/mL in histidine, pH 6.0, polysorbate 20, and sucrose with 1 mL volume in an autoinjector.</p> <p>Placebo:</p> <p>Sterile solution consisting of histidine, pH 6.0, polysorbate 20, and sucrose with 1 mL volume in an autoinjector.</p>
Route(s) of administration	Subcutaneous (SC) injections in the abdomen, thigh or outer area of upper arm.
Dose regimen	<p>Double-blind treatment period:</p> <p>Alirocumab 150 mg Q4W alternating with placebo Q4W OR Alirocumab 150 mg Q2W OR Placebo for Alirocumab Q2W</p> <p>Open-label treatment period:</p> <p>Alirocumab 150 mg Q4W OR Alirocumab 150 mg Q4W up to Week 24 followed by alirocumab 150 mg Q2W.</p>
Injection for training	Placebo for alirocumab
Non-Investigational product Formulation	<ul style="list-style-type: none"> • Statin (atorvastatin, 5mg daily) • Cholesterol absorption inhibitor (ezetimibe) • Fibrate (fenofibrate, bezafibrate, but not other fibrates)
Route(s) of administration	Oral administration

Dose Regimen	Dose regimen approved in Japan
ENDPOINT(S)	<p>Primary Efficacy Endpoint</p> <ul style="list-style-type: none"> The percent change in calculated LDL-C from baseline to Week 12 in the intent-to-treat (ITT) population, using all LDL-C values regardless of adherence to treatment (ITT estimand). <p>Key Secondary Efficacy Endpoints</p> <ul style="list-style-type: none"> The percent change in calculated LDL-C from baseline to Week 12 in the modified ITT (mITT) population, using all LDL-C values during the efficacy double-blind treatment period (on-treatment estimand). The percent change in calculated LDL-C from baseline to average Week 10-12 (ITT and on-treatment estimands). The percent change in Apo-B from baseline to Week 12 (ITT and on treatment estimands). The percent change in non-HDL-C from baseline to Week 12 (ITT and on-treatment estimands). The percent change in TC from baseline to Week 12 (ITT estimand). The proportion of patients reaching LDL-C goal at Week 12, i.e., calculated LDL-C <100 mg/dL (2.59 mmol/L) for heFH or non-FH patients who have a history of documented CHD patients, or LDL-C <120 mg/dL (3.10 mmol/L) for non-FH patients who have a history of documented diseases or other risk factors classified as primary prevention category III (ITT and on-treatment estimands). The percent change in Lp(a) from baseline to Week 12 (ITT estimand). The percent change in HDL-C from baseline to Week 12 (ITT estimand). The percent change in fasting TG from baseline to Week 12 (ITT estimand). The percent change in and Apo A-1 from baseline to Week 12 (ITT estimand). <p>Other Secondary Efficacy Endpoints</p> <ul style="list-style-type: none"> The proportion of patients with calculated LDL-C <100 mg/dL (2.59 mmol/L) at Week 12 (ITT estimand). The proportion of patients with calculated LDL-C <120 mg/dL (3.10 mmol/L) at Week 12 (ITT estimand). The proportion of patients with calculated LDL-C < 70 mg/dL (1.81 mmol/L) at Week 12 (ITT estimand). The absolute change in LDL-C from baseline to Week 12 (ITT estimand). The change in Apo-B/Apo A-1 ratio from baseline to Week 12 (ITT estimand). The proportion of patients with Apo-B <80 mg/dL (0.8 g/L) at Week 12 (ITT estimand). The proportion of patients with non HDL-C <130 mg/dL (3.37 mmol/L) at Week 12 (ITT estimand).

	<ul style="list-style-type: none"> The proportion of patients achieving at least 50% reduction in LDL-C at Week 12 (ITT estimand). The percent change in TC, Lp(a) from baseline to Week 12 (on treatment estimand) <p>Safety Endpoints</p> <ul style="list-style-type: none"> Safety parameters (adverse events [including adjudicated cardiovascular events], laboratory data, and vital signs) assessed throughout the study. <p>Other Endpoints</p> <ul style="list-style-type: none"> Anti-alirocumab antibodies assessed throughout the study. Proportion of patients who are up-titrated to alirocumab 150 mg Q2W during the OLTP. <p>Pharmacokinetics and pharmacodynamics:</p> <ul style="list-style-type: none"> Serum alirocumab concentrations. Serum total and free PCSK9 concentrations.
<p>ASSESSMENT SCHEDULE</p>	<p>Patient assessments in the run-in period: On-site visits: Week -7 (run-in visit).</p> <p>Patient assessments in the screening period: On-site visits: Week -3 (screening visit), Week -1 (injection training visit).</p> <p>Patient assessments in the double-blind treatment period (DBTP): On-site visits: Week 0 (randomization visit), Week 2, Week 4, Week 6, Week 8, Week 10, and Week 12 (end of DBTP).</p> <p>Patient assessments during the open-label treatment period (OLTP):</p> <ul style="list-style-type: none"> On-site visits: Week 12 (start of OLTP), Week 20, Week 24, Week 36, Week 48, and Week 64 (end of OLTP). Phone call visits: Week 16, Week 28, Week 32, Week 40, Week 44, Week 52, Week 56, and Week 60.
<p>STATISTICAL CONSIDERATIONS</p>	<p>Sample size determination:</p> <p>The study is expected to enroll approximately 159 patients.</p> <p>Two pairwise comparisons will be performed (alirocumab 150 mg Q4W versus placebo and alirocumab 150 mg Q2W vs placebo). In order to handle multiple comparisons Bonferroni adjustment will be used, i.e., the alpha level for each comparison is 0.025 to obtain an overall study alpha level of 0.05.</p> <p>A sample size of 38 patients in the ITT population (19 in alirocumab group and 19 in placebo group) will have 90% power to detect a difference of 30% in mean percent change in calculated LDL-C in any pairwise comparison with a 0.025 two-sided significance level and assuming a common standard deviation of 25%. As a result, the total sample size will be 57 patients (19 in each of the two alirocumab arms and 19 in the placebo arm).</p> <p>The sample size was also considered in order to obtain long-term safety data. A sample size of 159 patients (randomization ratio 1:1:1, i.e., 53 in alirocumab 150 mg Q4W, 53 in alirocumab 150 mg Q2W, and 53 in placebo) will allow having long term open-label safety data. With this sample size, 100 patients</p>

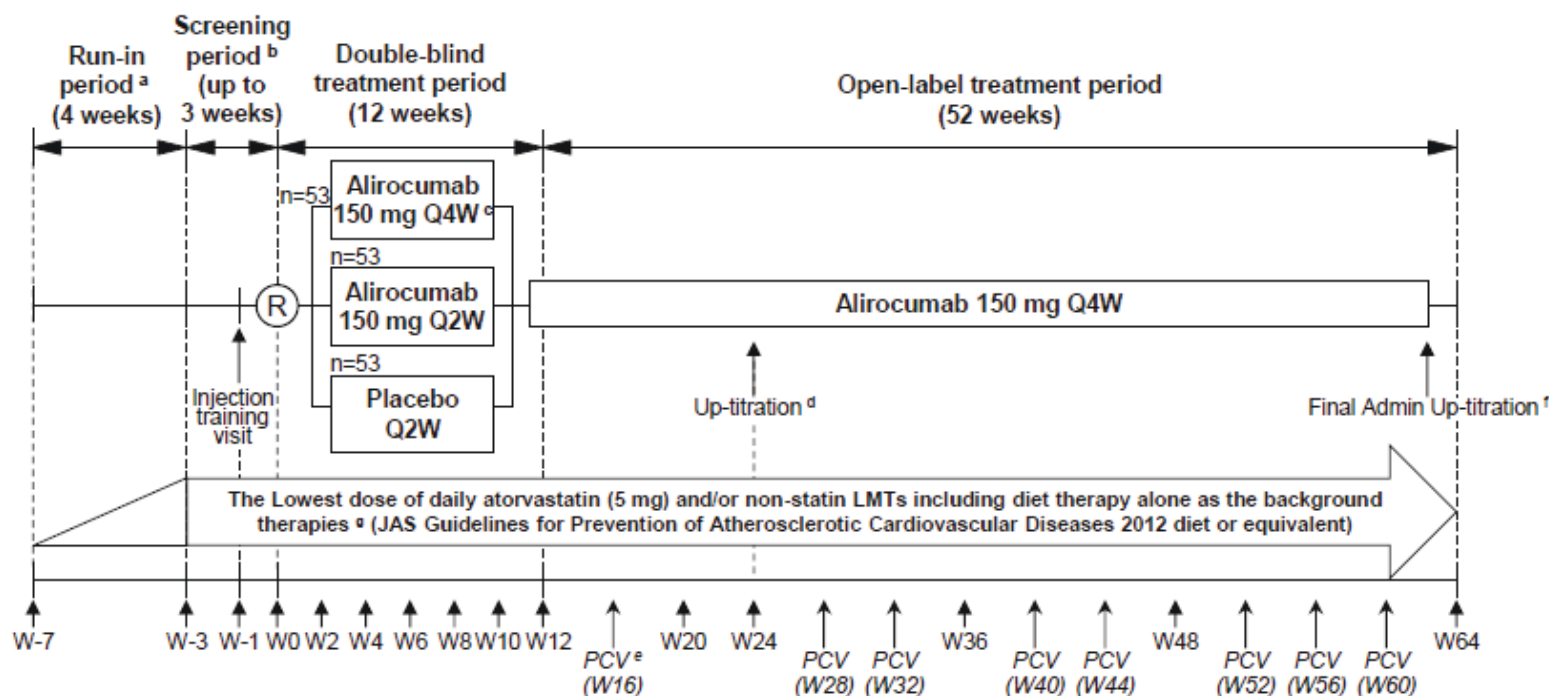
	<p>are expected to be exposed to alirocumab for a minimum of 12 months providing that the proportion of drop out in the entire study duration (from randomization to Week 64) is 36%, which is obtained using exponential distribution with the same hazard as that of 30% dropout rate within 12 months. Moreover, with 100 patients treated with alirocumab for at least 12 months, AEs with a rate ≥ 0.03 will be detected with 95% probability.</p> <p>Therefore, 159 patients (53 in alirocumab 150 mg Q4W, 53 in alirocumab 150 mg Q2W, and 53 in placebo) will be needed to evaluate both efficacy and safety.</p> <p>Analysis populations:</p> <p>Randomized population includes any patients who have been allocated to a randomized treatment regardless of whether the treatment kit was used or not.</p> <p>The primary efficacy analysis population will be the intent to treat (ITT) population, defined as the randomized population who has an evaluable primary endpoint. The primary efficacy endpoint is evaluable when both following conditions are met:</p> <ul style="list-style-type: none">• Availability of at least one value for calculated LDL-C before first dose of double-blind investigational medicinal product (IMP) (i.e., baseline).• Availability of at least one value for calculated LDL-C within one of the following analysis windows: Week 4, Week 8, Week 10 and Week 12. <p>The mITT population is defined as the randomized population who took at least one dose or part of dose of the double-blind IMP injection and had an evaluable primary efficacy endpoint during the efficacy double-blind treatment period. The primary efficacy endpoint will be considered evaluable when both of the following conditions are met:</p> <ul style="list-style-type: none">• Availability of at least 1 value for calculated LDL-C before the first dose of double-blind IMP (i.e., baseline).• Availability of at least 1 value for calculated LDL-C within one of the following analysis window: Week 4, Week 8, Week 10 and Week 12 during the efficacy double-blind treatment period. <p>The efficacy double-blind treatment period will be defined as:</p> <ul style="list-style-type: none">• The time period from the first double-blind IMP injection up to 21 days after the last double-blind IMP injection (i.e., up to Week 12). <p>Patients in the ITT or mITT populations will be analyzed according to the treatment group allocated by randomization.</p> <p>The safety population consists of the randomized population who actually received at least one dose or partial dose of IMP. The safety population will be analyzed according to the treatment actually received.</p> <p>Primary analysis:</p> <p>The primary efficacy endpoints, percent change in calculated LDL-C from baseline to Week 12 will be analyzed in the ITT population using mixed-effect model with repeated measures (MMRM) approach. All post-baseline data available within Week 4, Week 8, Week 10, and Week 12 analysis windows will be used (on treatment and off-treatment through Week 12) and missing data will be accounted for by the MMRM model.</p> <p>The model will include the fixed categorical effects of treatment group</p>
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	<p>(placebo, alirocumab 150 mg Q4W, alirocumab 150 mg Q2W), time point (Week 4, Week 8, Week 10, and Week 12), stratification factor of statin (Yes/No), treatment-by-time point interaction and statin-by time point interaction, as well as the continuous fixed covariates of baseline calculated LDL-C value, and baseline value-by-time point interaction.</p> <p>This model is used to provide baseline adjusted least square means (LS means) estimates at Week 12 for each treatment group with their corresponding standard errors. Each alirocumab group will be compared to placebo group (at significance level of 2.5%) using appropriate contrasts, and the 97.5% confidence interval (CI) of the difference will be provided.</p> <p>Subgroup analyses will be performed in order to assess the consistency of the treatment effect within stratification factor of statin (Yes/No).</p> <p>Analysis of key secondary efficacy endpoints:</p> <p>Continuous secondary endpoints anticipated to have a normal distribution (i.e., lipids other than Lp[a] and TG), will be analyzed using the same MMRM model as for the primary endpoint with the continuous fixed covariates of corresponding baseline value and baseline value-by-time point interaction.</p> <p>Continuous secondary endpoints anticipated to have a non-normal distribution (i.e., Lp[a] and TG) will be analyzed using multiple imputation approach for handling of missing values followed by robust regression.</p> <p>Binary secondary endpoints will be analyzed using multiple imputation approach for handling of missing values followed by logistic regression. In the data dependent case that the logistic regression method is not applicable (e.g., the response rate is zero in 1 treatment arm and thus the maximum likelihood estimate may not exist), the Last Observation Carried Forward (LOCF) approach would be used for handling of missing values and a stratified exact conditional logistic regression would be performed to compare treatment effects.</p> <p>Multiplicity adjustment:</p> <p>A hierarchical procedure will be used for each pairwise comparison to control the type I error and to handle multiple endpoints. If the primary endpoint analysis is significant at the 2.5% alpha level, the key secondary efficacy endpoints will be tested sequentially at the 0.025 level, using the order defined in section "Key secondary efficacy endpoints". Hierarchical procedure for comparisons of alirocumab 150 mg Q4W versus placebo and alirocumab 150 mg Q2W versus placebo will be processed separately. The other secondary efficacy endpoints not included into key secondary endpoints will be analyzed for exploratory purpose only.</p> <p>No further adjustment will be made for multiple analyses (i.e., first and second analyses) described below, since the primary efficacy endpoint and the key secondary efficacy endpoints up to Week 12 will have been conducted at the time of first analysis only. Analyses conducted in the OLTP are exploratory only.</p> <p>Safety Analysis:</p> <p>Safety analysis (Adverse events [including adjudicated cardiovascular events], laboratory, ECG, and vital signs) will be descriptive, based on the safety population. The safety analysis will focus on the Treatment Emergent Adverse Events (TEAE) period defined as</p> <ul style="list-style-type: none">• TEAE period for DBTP<ul style="list-style-type: none">- The time from the first dose of double-blind IMP to the last
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	<p>dose of double-blind IMP + 70 days (10 weeks) or the first dose of open-label IMP injection.</p> <ul style="list-style-type: none"> • TEAE period for long-term safety (DBTP and OLTP) <ul style="list-style-type: none"> - For 150 Q4W group and 150 Q2W group: The time from the first dose of double-blind IMP to the last dose of IMP (double-blind or open-label) + 70 days (10 weeks) - For placebo group: The time from the first dose of open-label IMP to the last dose of open-label IMP + 70 days (10 weeks) <p>Safety analyses will be conducted using data of the DBTP. Besides, safety analyses using data of the DBTP and the OLTP (from the first double-blind IMP injection for alirocumab 150 mg Q4W group and alirocumab 150 mg Q2W group, and from the first open-label IMP injection for placebo group) will be conducted to evaluate long-term safety.</p> <p>Timing of analyses:</p> <p>Two analyses will be conducted:</p> <ul style="list-style-type: none"> • First step: Efficacy and safety analyses using data up to 24 weeks after randomization (including 12 weeks double-blind) <p>The first analysis will be conducted when all patients have been randomized and have at least all their data up to Week 24 (including 12 weeks DBTP and 12 weeks OLTP) collected and validated, and will consist in the final analysis of the primary and secondary efficacy endpoints up to Week 12. [REDACTED]</p> <p>[REDACTED] The safety analysis will be performed on all safety data up to Week 24 collected and validated.</p> <ul style="list-style-type: none"> • Second step: Long-term safety and efficacy exploratory analysis <p>The second analysis will be conducted at the end of the study with all data including the data of the OLTP, and will consist in the final analysis of the safety endpoints and exploratory efficacy assessment during the OLTP.</p>
<p>DURATION OF STUDY PERIOD (per patient)</p>	<p>Approximately 71 weeks (run-in period: 4 weeks, screening: 3 weeks, DBTP: 12 weeks, OLTP: 52 weeks).</p>

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



- a: As a general rule, patients start the Run-in period to reach at stable daily dose of atorvastatin 5 mg or non-statin LMTs.
- b: When patients have received atorvastatin 5 mg/day or non-statin LMTs at stable daily dose for at least 4 weeks, they can skip the Run-in period and start the study from the Screening period.
- c: In order to keep the double-blind manner, injections of placebo will be conducted at W2, W6 and W10.
- d: Up-titration to Alirocumab 150 mg Q2W at W24 is done only if LDL-C is ≥ 100 mg/dL or ≥ 120 mg/dL at W20 depending on risk category.
- e: Phone Call Visit (PCV).
- f: Last administration of up-titrated Alirocumab 150 mg Q2W at W62.
- g: The permitted atorvastatin at a dose of 5 mg daily, non-statin LMTs, or diet therapy should remain stable (including dose) throughout the study duration barring exceptional circumstances.

1.2 STUDY FLOW CHART

	Run-in period	Screening period		Double-blind treatment period (DBTP)						
Day (D) / Week (W) / Month (M)	W-7 (D-49-to D-22)	W-3 (D-21 to D-8)	W-1 (D-7)	W0 (D1)	W2 (D15)	W4 (D29)	W6 (D43)	W8 (D57)	W10 (D71)	W12 ^a (D85) End of DBTP
Visit Number	1	2	3	4	5	6	7	8	9	10
Visit Window (Days) ^k			±6		±7	±7	±7	±7	±3	±3
Design:										
On-site visit	X	X	X	X	X	X	X	X	X	X
Phone call visit										
Informed consent/ Patient demography	X	X ^b								
Inclusion/Exclusion criteria	X	X		X						
Medical / family / surgical history, alcohol habits, smoking habits	X	X								
Prior medication history	X	X								
Physical examination	X	X		X						X
Body weight		X		X						X
Measured height		X								
Randomization				X						
IWRS contact	X	X	X	X	X	X	X	X	X	X
IMP dispensation				X	X	X	X	X	X	
Injection training			X ^c							
Treatment:										
IMP administration				X	X	X	X	X	X	
Review of diet	X	X		X						X
Compliance check of IMP and NIMP				X	X	X	X	X	X	
Concomitant medication	X	X		X	X	X	X	X	X	X

Day (D) / Week (W) / Month (M)	Run-in period	Screening period		Double-blind treatment period (DBTP)						
	W-7 (D-49-to D-22)	W-3 (D-21 to D-8)	W-1 (D-7)	W0 (D1)	W2 (D15)	W4 (D29)	W6 (D43)	W8 (D57)	W10 (D71)	W12 ^a (D85) End of DBTP
Visit Number	1	2	3	4	5	6	7	8	9	10
Visit Window (Days) ^k			±6		±7	±7	±7	±7	±3	±3
<u>Vital signs:</u>										
Heart rate, blood pressure	X	X	X	X	X	X	X	X	X	X
<u>Safety:</u>										
AE / SAE recording	X	X	X	X	X	X	X	X	X	X
12-lead ECG		X								X
<u>Laboratory Testing - Efficacy</u>										
TC, calculated LDL-C, HDL-C, TG, non-HDL-C		X		X		X		X	X	X
Apo-B, Apo A-1, Apo-B/Apo A-1 ratio, Lp(a)				X				X	X	X
<u>Laboratory Testing - Safety</u>										
Hematology and chemistry ^d		X		X						X
Creatine phosphokinase (CPK)		X		X						X
Liver panel ^e		X		X		X		X		X
Hepatitis B surface antigen		X								
Hepatitis C antibody ^f		X								
Serum pregnancy test ^g		X								
Urine pregnancy test ^g				X						X
Urinalysis (dipstick and microscopy) ^h		X		X						X
<u>Laboratory Testing - Other</u>										
HbA _{1c}		X								X
Thyroid-stimulating hormone (TSH)		X								
Anti-alirocumab antibodies ⁱ				X		X				X

Day (D) / Week (W) / Month (M)	Run-in period	Screening period		Double-blind treatment period (DBTP)						
	W-7 (D-49-to D-22)	W-3 (D-21 to D-8)	W-1 (D-7)	W0 (D1)	W2 (D15)	W4 (D29)	W6 (D43)	W8 (D57)	W10 (D71)	W12 ^a (D85) End of DBTP
Visit Number	1	2	3	4	5	6	7	8	9	10
Visit Window (Days) ^k			±6		±7	±7	±7	±7	±3	±3
Serum alirocumab concentration ⁱ				X		X		X	X	X
[REDACTED]				X						X
[REDACTED]										
[REDACTED]				X						
[REDACTED]				X						

a Patients who prematurely discontinue study treatment (regardless of reason) will have an unscheduled visit with assessments originally planned at the end of study visit (Week 64, it should take place within 5 days of treatment discontinuation, if possible). The patients will also continue the study and assessments originally planned until the end of DBTP visit (Week 12, V10), and they will be followed up until recovery or stabilization of any AE to be followed up as specified in this protocol. If patients prematurely discontinue the study treatment and deny the study continuation, the patients will have an unscheduled visit with assessments originally planned at the end of study visit (Week 64, it should take place within 5 days of treatment discontinuation, if possible) and also the patients will be followed up until recovery or stabilization of any AE to be followed up as specified in this protocol.

b Informed consent and patient demography will be obtained at Week -3 for the patients who start the study from the Screening period.

c In case injection is conducted by patients, Injection training at screening period visit Week -1 is performed with placebo. Investigators will have the option of providing a second injection training prior to randomization visit for patients who require additional injection training.

d Hematology includes: complete blood cell count (CBC) including hematocrit, red blood cell distribution width (RDW), reticulocyte count, hemoglobin, red blood cell count, white blood cell count with differential count and platelets. Chemistry includes: glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, eGFR, uric acid, lactate dehydrogenase (LDH), total protein, albumin, haptoglobin and γGT. (Reticulocyte count and haptoglobin are measured only when hemoglobin is decrease with ≥1.5g/dL from the baseline).

e Liver panel: ALT, AST, alkaline phosphatase (ALP), and total bilirubin.

f If positive, then confirmed by Hepatitis C Virus (HCV) polymerase chain reaction (PCR).

g Women of child bearing potential (WOCBP) only.

h Urinalysis will be performed at the Central Laboratory. Dipstick will be assessed for pH, specific gravity, and for the presence of blood, protein, glucose, ketones, nitrites, leukocyte esterase, urobilinogen, bilirubin and microscopic examination.

i Blood samples for anti-alirocumab antibodies and alirocumab concentration have to be taken before the IMP administration. Total and free PCSK9 concentrations will be measured from the same PK sample.

j [REDACTED]

k In the event an injection is delayed by more than 7 days or is completely missed, the patient should return to the original schedule of the IMP administration without administering the delayed injection. If the delay is less than or equal to 7 days from the missed date, the patient should administer the delayed injection and then resume the original dosing schedule of the IMP administration. At least 7 days must be needed between the IMP injections.

	Open Label Treatment Period (OLTP)									
Day (D) / Week (W) / Month (M)	W12 (D85) Start of OLTP	W16 (D113)	W20 (D141)	W24 (D169)	W28 (D197) W32 (D225)	W36 (D253)	W40 (D281) W44 (D309)	W48 (D337)	W52 (D365) W56 (D393) W60 (D421)	W64 ^a (D449) End of OLTP
Visit Number	10	11	12	13	14,15	16	17,18	19	20,21,22	23
Visit Window (Days) ^l	±3	±7	±7	±3	±7	±3	±7	±3	±7	±5
Design:										
On-site visit	X		X	X		X		X		X
Phone call visit		X			X		X		X	
Physical examination	X			X		X		X		X
Body weight	X			X		X				X
IWRS contact	X			X		X		X		X
IMP dispensation	X			X		X		X		
Treatment:										
IMP administration	X	X	X	X ^m	X	X	X	X	X ^a	
Compliance check of IMP	X	X	X	X	X	X	X	X	X	X ^k
Review of diet ⁿ	X			X		X		X		X
Concomitant medication	X	X	X	X	X	X	X	X	X	X
Vital signs:										
Heart rate, blood pressure	X		X	X		X		X		X
Safety:										
AE / SAE recording	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X			X						X
Laboratory Testing - Efficacy										
TC,calculated LDL-C, HDL-C, TG, non-HDL-C	X ^c		X ^c	X		X		X		X
Apo-B, Apo A-1, Apo-B/Apo A-1 ratio, Lp(a)	X			X		X				X

	Open Label Treatment Period (OLTP)									
Day (D) / Week (W) / Month (M)	W12 (D85) Start of OLTP	W16 (D113)	W20 (D141)	W24 (D169)	W28 (D197) W32 (D225)	W36 (D253)	W40 (D281) W44 (D309)	W48 (D337)	W52 (D365) W56 (D393) W60 (D421)	W64 ^a (D449) End of OLTP
Visit Number	10	11	12	13	14,15	16	17,18	19	20,21,22	23
Visit Window (Days) ^l	±3	±7	±7	±3	±7	±3	±7	±3	±7	±5
Laboratory Testing - Safety										
Hematology and chemistry ^d	X			X		X		X		X
CPK	X			X		X		X		X
Liver panel ^e	X			X		X		X		X
Hepatitis C antibody ^f										X
Urine pregnancy test ^g	X			X		X		X		X
Urinalysis (dipstick and microscopy) ^h	X			X						X
Laboratory Testing - Other										
HbA _{1c}	X			X		X		X		X
Anti-alirocumab antibodies ⁱ	X			X		X		X		X ^j

-
- a* Patients, who prematurely discontinue study treatment (regardless of the reasons) during OLTP, will have an unscheduled visit with assessments originally planned at the end of study visit (Week 64, it should take place within 5 days of treatment discontinuation, if possible). The patient will be followed up until recovery or stabilization of any AE to be followed up as specified in this protocol.
- b* The last IMP administration for the patients with up-titration to alirocumab 150 mg Q2W will be done at Week 62.
- c* Lipid values at Week 12 (Visit 10) will be blinded in order to keep the double-blind manner of DBTP. Lipid values will be communicated to investigators from Week 24 (Visit 13).
- d* Hematology includes: CBC including hematocrit, RDW, reticulocyte count, hemoglobin, red blood cell count, white blood cell count with differential count and platelets. Chemistry includes: glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, eGFR, uric acid, LDH, total protein, albumin, haptoglobin and γ GT (Reticulocyte count and haptoglobin are measured only when hemoglobin is decrease with $\geq 1.5\text{g/dL}$ from the baseline).
- e* Liver panel: ALT, AST, ALP, and total bilirubin.
- f* If positive, then confirmed by HCV polymerase chain reaction.
- g* WOCBP only.
- h* Urinalysis will be performed at the Central Laboratory. Dipstick will be assessed for pH, specific gravity, and for the presence of blood, protein, glucose, ketones, nitrites, leukocyte esterase, urobilinogen and bilirubin.
- i* Blood samples for anti-alirocumab antibodies have to be taken before the IMP administration.
- j* [REDACTED]
- k* Compliance check of IMP at Week 64 will be done only for the patients with up-titration to alirocumab 150 mg Q2W in order to check the compliance of IMP administration at Week 62.
- l* In the event an injection is delayed by more than 7 days or is completely missed, the patient should return to the original schedule of the IMP administration without administering the delayed injection. If the delay is less than or equal to 7 days from the missed date, the patient should administer the delayed injection and then resume the original dosing schedule of the IMP administration. At least 7 days must be needed between the IMP injections.
- m* At week 24, the up-titration to alirocumab 150 mg Q2W will be conducted through Interactive Web Response System (IWRS) based on LDL-C values at Week 20 (Refer [Section 6.1](#))
- n* Patients should be on a diet following Japan Atherosclerosis Society Guideline or equivalent.

2 TABLE OF CONTENTS

1	FLOW CHARTS	13
1.1	GRAPHICAL STUDY DESIGN	13
1.2	STUDY FLOW CHART	14
2	TABLE OF CONTENTS	20
3	LIST OF ABBREVIATIONS	26
4	INTRODUCTION AND RATIONALE	29
5	STUDY OBJECTIVES	38
5.1	PRIMARY	38
5.2	SECONDARY	38
6	STUDY DESIGN	39
6.1	DESCRIPTION OF THE PROTOCOL.....	39
6.2	DURATION OF STUDY PARTICIPATION	41
6.2.1	Duration of study participation for each patient	41
6.2.2	Determination of end of clinical trial (all patients)	41
6.3	TWO-STEP ANALYSIS	41
6.4	STUDY COMMITTEES	42
7	SELECTION OF PATIENTS	43
7.1	INCLUSION CRITERIA.....	43
7.2	EXCLUSION CRITERIA	45
7.2.1	Exclusion criteria related to study methodology	45
7.2.2	Exclusion criteria related to the active comparator and/or mandatory background therapies.....	48
7.2.3	Exclusion criteria related to the current knowledge of Sanofi compound	48
7.2.4	Additional exclusion criteria during or at the end of screening or run-in phase before randomization.....	49
8	STUDY TREATMENTS	50
8.1	INVESTIGATIONAL MEDICINAL PRODUCT(S)	50

8.1.1	Route and method of administration	50
8.1.2	Timing of administration	51
8.2	NONINVESTIGATIONAL MEDICINAL PRODUCT(S)	52
8.3	BLINDING PROCEDURES	52
8.3.1	Methods of blinding	52
8.3.1.1	Lipid parameters	53
8.3.1.2	Anti-alirocumab antibodies	53
8.3.1.3	Pharmacokinetics measurements, total and free PCSK9 concentrations	54
8.3.1.4	Committee	54
8.3.2	Randomization code breaking during the study	54
8.4	METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP	55
8.5	PACKAGING AND LABELING	55
8.6	STORAGE CONDITIONS AND SHELF LIFE	56
8.7	RESPONSIBILITIES	56
8.7.1	Treatment accountability and compliance	57
8.7.2	Return and/or destruction of treatments	57
8.8	CONCOMITANT MEDICATION	57
8.8.1	Management of background lipid modifying therapy	58
8.8.2	Contraception	58
8.8.3	Prohibited concomitant medications	58
9	ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT	59
9.1	EFFICACY ENDPOINT	59
9.1.1	Primary efficacy endpoint	59
9.1.2	Secondary endpoints	59
9.1.2.1	Key secondary efficacy endpoints	59
9.1.2.2	Other Secondary Efficacy Endpoints	60
9.1.3	Efficacy assessment method	60
9.1.3.1	Lipid parameters	60
9.2	SAFETY ENDPOINTS	61
9.2.1	Adverse events	61
9.2.2	Laboratory safety variables,	63
9.2.3	Vital signs	63
9.2.4	Electrocardiogram variables	63
9.3	OTHER ENDPOINTS	63

9.3.1	Anti-alirocumab antibodies assessments.....	63
9.3.1.1	Sampling time	63
9.3.1.2	Sample procedure.....	64
9.3.1.3	Bioanalytical method.....	64
9.3.2	Hemoglobin A _{1c} (HbA _{1c})	64
9.3.3	Pharmacokinetics.....	64
9.3.3.1	Sampling time	64
9.3.3.2	Pharmacokinetics handling procedure.....	65
9.3.3.3	Bioanalytical method.....	65
9.3.4	Pharmacogenetic assessment.....	65
9.3.4.1	Optional stored DNA sample	66
9.3.5	Proportion of patients who are up-titration to alirocumab 150 mg Q2W.....	67
9.4	FUTURE USE OF SAMPLES	67
9.5	APPROPRIATENESS OF MEASUREMENTS	67
9.6	ASSESSMENT SCHEDULE.....	67
10	STUDY PROCEDURES	69
10.1	VISIT SCHEDULE.....	72
10.1.1	Run-in period.....	72
10.1.2	Screening period	73
10.1.3	Double-blind treatment period (Study Site Visits).....	75
10.1.3.1	Randomization visit (Visit 4 / Week 0 /Day 1).....	75
10.1.3.2	Visit 5 / Week 2 (Day 15 ± 7)	77
10.1.3.3	Visit 6 / Week 4 (Day 29 ± 7)	77
10.1.3.4	Visit 7 / Week 6 (Day 43 ± 7)	78
10.1.3.5	Visits 8 / Week 8 (Day 57 ± 7)	78
10.1.3.6	Visit 9 / Week 10 (Day 71 ± 3)	79
10.1.3.7	Visit 10 / Week 12 (Day 85 ± 3): End of DBTP and Start of OLTP.....	80
10.1.4	Open-label treatment period (Study Site Visits or Phone Call Visits).....	81
10.1.4.1	Visit 10 / Week 12 (Day 85 ± 3): End of DBTP and Start of OLTP.....	81
10.1.4.2	Visit 11 / Week 16 (Day 113 ± 7)	82
10.1.4.3	Visit 12 / Week 20 (Day 141 ± 7)	82
10.1.4.4	Visit 13 / Week 24 (Day 169 ± 3)	83
10.1.4.5	Visits 14 and 15 / Weeks 28 (Day 197 ± 7) and 32 (Day 225 ± 7)	85
10.1.4.6	Visit 16 / Week 36 (Day 253 ± 3)	85
10.1.4.7	Visits 17 and 18 / Weeks 40 (Day 281 ± 7) and Week 44 (Day 309 ± 7)	86
10.1.4.8	Visit 19 / Week 48 (Day 337 ± 3)	86
10.1.4.9	Visits 20, 21, and 22 / Weeks 52 (Day 365 ± 7), Week 56 (Day 393 ± 7), and Week 60 (Day 421 ± 7)	87
10.1.4.10	Visit 23 / Week 64 (Day 449 ± 5) / End of OLTP	88
10.2	DEFINITION OF SOURCE DATA.....	89

10.3	HANDLING OF PATIENT TEMPORARY OR PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION	90
10.3.1	Temporary treatment discontinuation with investigational medicinal product(s)	90
10.3.2	Permanent treatment discontinuation with investigational medicinal product(s)	90
10.3.3	List of criteria for permanent treatment discontinuation	90
10.3.4	Handling of patients after permanent treatment discontinuation	91
10.3.5	Procedure and consequence for patient withdrawal from study	91
10.4	OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING	92
10.4.1	Definitions of adverse events	92
10.4.1.1	Adverse event	92
10.4.1.2	Serious adverse event	92
10.4.1.3	Adverse event of special interest (AESI)	93
10.4.2	General guidelines for reporting adverse events	93
10.4.3	Instructions for reporting serious adverse events	94
10.4.4	Guideline for reporting adverse events of special interest	95
10.4.4.1	Reporting of adverse events of special interest (AESI) with immediate notification	95
10.4.4.2	Reporting of adverse events of special interest without immediate notification	96
10.4.5	Guidelines for management of specific laboratory abnormalities	97
10.4.5.1	Hemoglobin decrease	97
10.4.6	Summary of adverse event reporting instructions	98
10.5	OBLIGATIONS OF THE SPONSOR	98
10.6	SAFETY INSTRUCTIONS	99
10.6.1	Local tolerability (Local Injection Site Reactions)	99
10.6.2	Allergic adverse events	99
10.6.2.1	Allergic adverse events with cutaneous involvement	99
10.6.2.2	Acute allergic reactions of IMP injection	100
10.6.3	Cardiovascular events and all deaths	100
10.6.4	Laboratory alert related to two consecutive calculated LDL-C <25 mg/dL (0.65 mmol/L)	101
10.7	ADVERSE EVENTS MONITORING	102
11	STATISTICAL CONSIDERATIONS	103
11.1	DETERMINATION OF SAMPLE SIZE	103
11.2	DISPOSITION OF PATIENTS	103
11.3	ANALYSIS POPULATIONS	104
11.3.1	Efficacy populations	104
11.3.1.1	Intent-to-treat (ITT) population	104
11.3.1.2	Modified intent-to-treat (mITT) population	104
11.3.2	Safety population	105

11.3.3	Other analysis population	105
11.4	STATISTICAL METHODS	105
11.4.1	Extent of study treatment exposure and compliance	105
11.4.1.1	Extent of investigational medicinal product exposure	106
11.4.1.2	Compliance	106
11.4.2	Analyses of efficacy endpoints.....	106
11.4.2.1	Analysis of primary efficacy endpoint(s)	106
11.4.2.2	Analyses of secondary efficacy endpoints	107
11.4.2.3	Multiplicity considerations	108
11.4.3	Analyses of safety data.....	109
11.4.3.1	Adverse events	110
11.4.3.2	Laboratory data and vital signs	111
11.4.3.3	Analyses of other endpoints.....	111
11.4.4	Analyses of pharmacokinetic and pharmacodynamic variables	112
11.5	TIMING OF ANALYSES	112
11.5.1	First step: Efficacy and safety analyses using data up to 24 weeks after randomization (including 12 weeks double-blind).....	112
11.5.2	Second step: Long-term safety and efficacy exploratory analysis.....	112
12	ETHICAL AND REGULATORY CONSIDERATIONS.....	113
12.1	ETHICAL AND REGULATORY STANDARDS	113
12.2	INFORMED CONSENT	113
12.3	INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)	114
13	STUDY MONITORING.....	115
13.1	RESPONSIBILITIES OF THE INVESTIGATOR(S).....	115
13.2	RESPONSIBILITIES OF THE SPONSOR.....	115
13.3	SOURCE DOCUMENT REQUIREMENTS.....	116
13.4	USE AND COMPLETION OF CASE REPORT FORMS (CRFS) AND ADDITIONAL REQUEST	116
13.5	USE OF COMPUTERIZED SYSTEMS.....	116
14	ADDITIONAL REQUIREMENTS.....	117
14.1	CURRICULUM VITAE.....	117
14.2	RECORD RETENTION IN STUDY SITES	117
14.3	CONFIDENTIALITY	117

14.4	PROPERTY RIGHTS.....	118
14.5	DATA PROTECTION.....	118
14.6	INSURANCE COMPENSATION.....	118
14.7	SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES	119
14.8	PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE.....	119
14.8.1	By the Sponsor.....	119
14.8.2	By the Investigator	120
14.9	CLINICAL TRIAL RESULTS	120
14.10	PUBLICATIONS AND COMMUNICATIONS	120
15	CLINICAL TRIAL PROTOCOL AMENDMENTS	121
16	BIBLIOGRAPHIC REFERENCES.....	122
17	APPENDICES.....	126
	APPENDIX A. DIAGNOSTIC CRITERIA FOR THE CLINICAL DIAGNOSIS OF HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA (HEFH) [JAPAN ATHEROSCLEROSIS SOCIETY (JAS) GUIDELINES FOR PREVENTION OF ATHEROSCLEROTIC CARDIOVASCULAR DISEASES 2012].....	127
	APPENDIX B. SUMMARY OF DIET FOR PREVENTION OF ATHEROSCLEROTIC CARDIOVASCULAR DISEASE (JAS GUIDELINES FOR PREVENTION OF ATHEROSCLEROTIC CARDIOVASCULAR DISEASE 2012).....	128
	APPENDIX C. THE STAGES OF HEART FAILURE – NYHA CLASSIFICATION	129
	APPENDIX D. SUMMARY OF ADVERSE EVENT REPORTING INSTRUCTIONS	130
	APPENDIX E. GENERAL GUIDANCE FOR THE FOLLOW-UP OF LABORATORY ABNORMALITIES BY SANOFI.....	132
	APPENDIX F. GUIDELINES FOR HEMOGLOBIN (HB) DECREASE ≥ 1.5 G/DL	137
	APPENDIX G. DNA STORAGE SAMPLES	138
	APPENDIX H. ASSESSMENT OF LOCAL INJECTION SITE REACTIONS.....	140
	APPENDIX I. MONITORING PLAN FOR CALCULATED LDL-C < 25 MG/DL (0.65 MMOL/L)	141

3 LIST OF ABBREVIATIONS

AE:	Adverse event
AESI:	Adverse event of special interest
ALT:	Alanine transaminase
Apo:	Apolipoprotein
AST:	Aspartate aminotransferase
AUC:	Area under the curve
BMI:	Body Mass Index
BP:	Blood pressure
CABG:	Coronary artery bypass graft surgery
CBC:	Complete blood cell count
CEC:	Clinical events committee
CHD:	Coronary heart disease
CI:	Confidence interval
CKD:	Chronic kidney disease
CPK:	Creatine phosphokinase
CRF:	Case report form
CSR:	Clinical study report
CV:	Cardiovascular
CVD:	Cardiovascular disease
DBTP:	Double-blinded treatment period
DMC:	Data monitoring committee
DNA:	Deoxynucleic acid
DRF:	Discrepancy resolution form
ECG:	Electrocardiogram
e-CRF:	Electronic case report form
eGFR:	Estimated glomerular filtration rate
ELISA:	Enzyme-linked immunosorbent assay
EPA:	Ethyl icosapentate
FBG:	Fasting blood glucose
FH:	Familial hypercholesterolemia
GCP:	Good clinical practice
GT:	Glutamyl transferase
Hb:	hemoglobin
HbA1c:	Hemoglobin A1c
hCG:	Human chorionic gonadotropin
HCV:	Hepatitis C virus
HDL-C:	High-density lipoprotein cholesterol
heFH:	Heterozygous FH
HIV:	Human immunodeficiency virus
HLGT:	High level group term
HLT:	High level term

HR:	Heart rate
IB:	Investigator's brochure
ICF:	Informed consent form
ICH:	International conference on harmonisation of technical requirement for registration of pharmaceuticals for human use
IEC:	Independent ethics committee
IMP:	Investigational medicinal product
IRB:	Institutional review board
ITT:	Intent-to-treat
IVRS:	Interactive voice response system
IWRS:	Interactive web response system
JAS:	Japan Atherosclerosis Society
LDH:	Lactate dehydrogenase
LDL-C:	Low-density lipoprotein cholesterol
LDL-R:	Low-density lipoprotein-receptor
LLN:	Lower limit of normal range
LLQ:	Lower limit of quantification
LLT:	Lowest level term
LMT:	Lipoprotein modifying therapy
LOCF:	Last observation carried forward
Lp(a):	Lipoprotein (a)
MedDRA:	Medical Dictionary for Regulatory Activities
MI:	Myocardial infarction
MMRM:	Mixed-effect model with repeated measures
NIMP:	Non-investigational medicinal product
NYHA:	New York Heart Association
OGTT:	Oral glucose tolerant test
OLTP:	Open-label treatment period
PAD:	Peripheral arterial disease
PCI:	Percutaneous coronary intervention
PCR:	Polymerase chain reaction
PCSA:	Potentially clinically significant abnormality
PCSK9:	Proprotein convertase subtilisin kexin type 9
PD:	Pharmacodynamics
PK:	Pharmacokinetics
PT:	Preferred term
Q2W:	Every 2 weeks
Q4W:	Every 4 weeks
RDW:	Red blood cell distribution width
SAE:	Serious adverse event
SAP:	Statistical analysis plan
SC:	Subcutaneous
SE:	Standard error
SNP:	Single nucleotide polymorphism
SOC:	System organ class
TC:	Total cholesterol

TEAE: Treatment emergent adverse event
TG: Triglyceride
TIA: Transient ischemic attack
TSH: Thyroid-stimulating hormone
ULN: Upper limit of normal range
WOCBP: Woman of childbearing potential

4 INTRODUCTION AND RATIONALE

Alirocumab is a fully human monoclonal antibody that binds proprotein convertase subtilisin kexin type 9 (PCSK9). All relevant information concerning the compound is available in the latest version of the Investigator's Brochure (IB).

Alirocumab is also referred to as SAR236553 or REGN727. However, for this study protocol (EFC14305), it will be referred to as alirocumab.

Background on patient populations:

This study will include patients with hypercholesterolemia (heterozygous familial hypercholesterolemia [heFH] or nonfamilial hypercholesterolemia [non-FH]).

Hypercholesterolemia, particularly an increase in low-density lipoprotein cholesterol (LDL-C) levels, constitutes a major risk for the development of atherosclerosis and coronary heart disease (CHD) (1), the leading cause of death and disability in the Western world (2) and Japan (3). The LDL-C is identified as the primary target of cholesterol lowering therapy (4) and is accepted as a valid surrogate endpoint (5)(6). Numerous studies have demonstrated that reducing LDL-C levels mainly via 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG CoA) inhibition, reduces the risk of CHD, with a strong direct relationship between LDL-C levels and CHD events; for each 1 mmol/L (~40 mg/dL) reduction in LDL-C, cardiovascular disease (CVD) mortality and morbidity is lowered by 22% (7). Recent data suggest that the lower the LDL-C level, the greater the benefit in patients at high cardiovascular risk (7)(8)(9)(10)(11).

In the Japan Atherosclerosis Society (JAS) Guidelines (12), drug therapy in parallel with life style modification (e.g., diet and exercise) is required for dyslipidemia patients who are categorized in secondary prevention (non-familial hypercholesterolemia [FH] with history of documented CHD). The treatment goal for LDL-C in patients categorized in the secondary prevention is set as <100 mg/dL. Since heFH is high risk disease which is highly developing the CHD, the heFH can be considered as equivalent as the secondary prevention. The treatment goal for LDL-C in heFH is set as <100 mg/dL as well. When the goal cannot be achieved in many heFH cases since the LDL-C level is relatively high, 50% reduction of LDL-C from baseline can be adopted for the alternative goal (13). For the patients who meet the primary prevention category III, they initiate the treatment with life style modification, but the drug therapy is considered from the early stage of treatment. The treatment goal for LDL-C is established as <120 mg/dL.

Current LDL-C-lowering medications include statins, cholesterol absorption inhibitors (i.e. ezetimibe), fibrates, niacin, and bile acid sequestrants; statins are the most commonly prescribed as they have shown a great ability to lower LDL-C and reduce CHD events. Since hypercholesterolemia is largely asymptomatic, side effects of pharmacologic agents used to manage it can undermine patient compliance. In several cohort studies, the reported rate of adherence to statin therapy at 1 year ranged from 26% to 85%, with a rapid decline in adherence rates typically observed within the first few months (14). While statins are proven to be well tolerated agents there is a subset of patients who are intolerant to statin therapy and/or who suffer

from side effects. The recently published survey, “Understanding Statin Use in America and Gaps in Education (USAGE)” assessed the attitudes, beliefs, practices, and behavior of current and former statin users (15). Muscle-related side effects were reported by 60% and 25% of former and current users, respectively, and the primary reason for discontinuation was side effects (62%). The incidence of severe myopathy is low, occurring in less than 0.1% of patients receiving statin monotherapy. Conversely, mild symptoms are far more frequent, in outpatients on statins complaining of muscle pain. However, due to a lack of consensus on the definition of muscle symptoms in statin-intolerant patients and a lack of agreed upon definition of statin intolerance, the true prevalence of statin intolerance is unknown (16). The majority of adverse effects reported to be associated with statins are musculoskeletal, hepatic, gastrointestinal, and psychiatric. The most prevalent adverse events are musculoskeletal in nature, and the spectrum of statin-associated myotoxicity ranges from the more common but less severe myalgia (5% to 10%) to the less common but more severe myopathy (0.1%) and its potentially fatal complication, rhabdomyolysis (0.01%). A retrospective cohort study in Japan representing a cohort of 35903 adult statin users suggested that statin use is generally well tolerated and safe, however, the risk of muscle toxicity related to the use of interacting drugs requires further exploration (17).

Three doses of atorvastatin (5, 10, 20 mg) caused statistically significant reductions from baseline in LDL-C (36%, 38%, and 50%, respectively) in Japan Cholesterol Lowering Atorvastatin Study (18). Although the starting dose of atorvastatin from package insert is 10 mg in Japan, there still are many patients receiving the lower dose, e.g., atorvastatin 5mg based on the results of the market research indicating that the doses of 10 mg, 5 mg and 20 mg of atorvastatin are used in 55%, 42% and 2% of patients, respectively. One of the reasons is likely due to physicians’ concerns regarding potential intolerance to the higher dose statin.

Fibrates or ezetimibe is one of treatment option for the hypercholesterolemic patients (19)(20). 8% and 4% of Japanese hypercholesterolemic patients are on fibrates and ezetimibe without statin, respectively (©2014 IMS Health. All rights reserved. Source: Calculated based on IMS Data NPA Oct–Dec 2013. Reprinted with permission). The LDL-C goal attainment may be lower given the mild to moderate effect of fibrate or ezetimibe on LDL-C lowering into consideration. Additionally the choice of lipid lowering therapy is limited because combination of fibrates and statins may increase the risk of rhabdomyolysis, and thus the combination is primarily contraindicated in Japan (20). Therefore, alternative treatment approach is deemed necessary in patients who are not adequately controlled with non-statin lipoprotein modifying therapies (LMTs) or the lowest strength of statin (e.g., atorvastatin 5 mg daily).

Introduction to proprotein convertase subtilisin kexin type 9 (PCSK9):

Proprotein convertase subtilisin kexin type 9 (PCSK9) belongs to the subtilisin family of serine proteases and is highly expressed in the liver. The PCSK9 is involved in regulating the levels of the low-density lipoprotein receptor (LDL-R) protein (21)(22). Once PCSK9 is secreted into plasma it directly binds to the LDL-R and promotes its intracellular degradation. The increased degradation of LDLRs leads to a reduced LDL-C removal, and therefore, higher LDL-C circulating levels. Experiments with mice have shown that increasing PCSK9 protein levels decreases levels of LDL-R protein in the liver while PCSK9 knockout mice have increased levels of LDL-R in the liver (23)(24). In humans, PCSK9 mutations have been identified: the gain of function mutations are rare and cause an autosomal dominant form of severe

hypercholesterolemia and premature CHD, whereas loss of-function mutations are more common and are associated with reduced plasma levels of LDL-C and protection from CHD (25)(26). One report from the Japanese population found the individual heterozygous for W428X mutation of PCSK9 had 70.4 mg/dL of plasma LDL-C, corresponding to a 44% decrease from the average LDL-C level in the untreated population (126.8 mg/dL). This observation is consistent with the finding that the two African-American nonsense mutations were associated with a 40% reduction in plasma LDL-C levels (27).

Therefore, blocking PCSK9 binding to the LDL-R can potentially benefit patients with hypercholesterolemia by decreasing their plasma LDL-C levels. In addition, PCSK9 messenger ribonucleic acid (mRNA) and protein levels are increased in response to statins, potentially attenuating their cholesterol-lowering effect (28).

Summary of main clinical studies with Alirocumab:

Japanese Phase 1 study (TDU12190)

The TDU12190 study investigated the safety, tolerability and pharmacokinetics/ pharmacodynamics (PK/PD) profile of a single ascending dose of subcutaneous (SC) alirocumab in Japanese healthy male volunteers with a LDL-C >100 mg/dL (>2.59 mmol/L) and for whom statin therapy was not indicated. A total of 32 subjects were enrolled at a single study site. Subjects in each dose cohort (100, 150, 250, or 300 mg) were randomized to receive a single dose of alirocumab (n = 6) or placebo (n = 2). The total observation period was 15 weeks (up to Day 106). All doses were well-tolerated. Very few treatment emergent adverse events (TEAEs) were reported with no evidence of dose relationship (1/8 subjects [12.5%] in placebo, and 1/6 subjects [16.7%] in 250 mg dose group). None of the TEAEs was reported in other treatment groups except 250 mg dose group. All TEAEs were unrelated to the treatment administered and of mild intensity, and no injection site reactions were reported. The administration of alirocumab significantly induced rapid and substantial reductions from baseline in LDL-C, approximately 40 to 60%. Regarding the PK profile, when comparing the lowest dose (100 mg) with the highest dose (300 mg), the exposure increased with estimates of 3.88 (90% CI = 2.90 to 5.20) for C_{max} and 5.55 (90% CI = 4.08 to 7.56) for area under the curve (AUC). When comparing the exposure of the 100 and 150 mg dose groups, point estimates of 0.87 for C_{max} (90% CI = 0.65 to 1.17) and 1.09 for AUC (90% CI = 0.80 to 1.48) were calculated. Geometric means of t_{1/2} ranged between 5.92 and 7.49 days. The PK of alirocumab in Caucasian subjects and in Japanese subjects was not dose proportional, the extent of the supra-dose proportionality being approximately similar between these 2 populations.

Oversea Phase 1 study of particular interest for the EFC 14305 study:

Data from study PKD12910 suggests a limited impact of background therapy with ezetimibe or fenofibrate on the duration of action of alirocumab (29). This study assessed PK and PD parameters in 72 healthy subjects receiving 150 mg alirocumab every 4 weeks (Q4W) in combination with ezetimibe, fenofibrate, or placebo ezetimibe for 120 days. Administration of alirocumab 150 mg Q4W either alone or on top of ezetimibe (10 mg/day) or fenofibrate

(160 mg/day) produced a decline in LDL-C reaching -47.4%, -56.6% and -54.3% in the alirocumab alone, ezetimibe and fenofibrate groups respectively 2 weeks after the 3rd administration of alirocumab, in comparison to pre-alirocumab baseline value. At 4 weeks after this 3rd administration, the reduction was of 47.0%, 49.6% and 43.1% in the alirocumab alone, ezetimibe and fenofibrate groups respectively. This suggests maintenance of the effect when alirocumab was administered alone, whereas a small change from the maximum effect was seen between 2 and 4 weeks post dose in both combination arms. Overall these data suggest that the alirocumab 150 mg Q4W can provide persistent and efficacious reductions in LDL-C over a 4-week dosing interval in patients as monotherapy or in patients receiving non-statin LMTs.

Phase 2 studies

Four Phase 2 studies (DFI11565, R727-CL-1003, DFI11566 and DFI12361 performed in Japanese patients) have been conducted in patients receiving a statin (with or without ezetimibe) as background therapy. Overall, a total of 349 (75 with DFI12361) patients were exposed to at least one dose of alirocumab in the 4 phase 2 studies. Generally, the efficacy and safety results in Japanese were similar with the results of overseas studies.

Efficacy results:

In both dose-finding studies, statistically significant decreases in percent change from baseline in LDL-C at 12 weeks were observed in all alirocumab groups compared to the placebo group. The greatest decrease was seen in the 150 mg Q2W group, with a mean decrease from baseline of up to 72.4%. (the least square [LS] mean difference versus placebo of -67.3% in DFI11565, -69.1% in DFI12361, -57.2% in R727-CL-1003; all $p < 0.0001$) (30). Decreases observed with the doses administered Q2W were maintained from the first injection throughout the study. Large decreases in LDL-C from baseline to 12 weeks were also observed with doses administered Q4W; however, the treatment effect was not fully maintained over a 4-week period (i.e., the time interval between the two injections) in all these statin-treated patients.

The same magnitude of effect was shown for the dose of 150 mg Q2W in the DFI11566 study, with a statistically significant decrease in LDL-C at 8 weeks in the alirocumab 150 mg + atorvastatin 80 mg group (median reduction of 70.6%) compared with the placebo + atorvastatin 80 mg group (median reduction of 26.9%). In all three studies, consistent results were seen for total cholesterol (TC), Apolipoprotein-B (Apo-B), non-high density lipoprotein cholesterol (non-HDL-C) and Apolipoprotein-B / Apolipoprotein-A-1 (Apo-B/ApoA-1) ratio. A favorable trend was also observed for HDL-C, ApoA-1, triglyceride (TG) and lipoprotein (a) [Lp(a)].

Safety results:

Alirocumab was well tolerated in all completed Phase 2 studies throughout the treatment period and for all treatment groups. Injection site reactions were reported in patients including placebo treated patients; the reporting of these events was greatest in the R727-CL-1003 study (40.3% in alirocumab-treated patients versus 12.6%, 9.3% and 3.3% in DFI11565, DFI12361 and DFI11566, respectively); however these events were generally transient. Rare cases of hypersensitivity reactions were reported. Among all serious adverse events (SAEs) reported for all alirocumab studies, only one case, leucocytoclastic vasculitis (angiitis), was reported as being

related to alirocumab (DFI11565 study). The patient developed one episode of diarrhea followed on the same evening by rash in arms, legs and abdomen 9 days after the first administration of alirocumab 300 mg Q4W. The diagnosis was confirmed by skin biopsy. The patient was discontinued from study drug but completed the study. The lesions resolved after a course of tapering steroid administration. No particular signal was noted for TEAEs related to musculoskeletal or connective tissue disorders as well as no elevations in liver enzymes. For detailed information, please refer to the IB (31).

Selection of dose/ dose regimen for overseas Phase 3 studies and Japanese EFC 13672 Study:

Based on the results of the dose finding studies carried out with statin as background therapy, the Q2W dosing regimen is appropriate to maintain constant LDL-C lowering throughout the interdosing interval in statin-treated patients, with the maximum efficacy at 12 weeks provided by the 150 mg Q2W dosing. A 75 mg Q2W dose was developed for patients who may not need the magnitude of effect observed with the 150 mg Q2W to achieve the target LDL-C goal, with up titration to 150 mg Q2W in patients not achieving their LDL-C goal. This represents an alternative dosing regimen in patients not achieving their LDL-C goal with 75 mg Q2W.

The same dose regimen with the initial dose of 75 mg is also being tested in a Japanese Phase 3 study (EFC 13672) given the existing data from Japanese and overseas studies and simulation that were done, LDL-C reduction is expected to be similar in Japanese and Caucasian.

Oversea Phase 3 studies

As of 31 December 2014, 12 Phase 3 studies were completed or had the first step analysis completed, with 10 evaluating alirocumab administered at Q2W regimen and 2 evaluating alirocumab administered at Q4W regimen. These studies evaluated heFH patients, patients with a range of cardiovascular (CV) risk but predominately high and very high risk, and patients not taking statins including statin intolerant patient.

Phase 3 studies that evaluated Q2W regimen – efficacy results:

Ten studies that were completed or had the first step analysis evaluating 75 mg Q2W (with possible up-titration to 150 mg Q2W at Week 12) and 150 mg Q2W as initiation dose regimen were performed. These studies demonstrated reductions in LDL-C from baseline to Week 24 ranging from 42.7% to 50.6%, and from 45.7% to 61.0%, respectively. Superiority in LDL-C reduction was demonstrated in all placebo-controlled studies with alirocumab administered as add-on to a maximally tolerated dose of statin. Superiority in LDL-C reduction was also demonstrated in all ezetimibe-controlled studies, with alirocumab being administered as add-on to statin, or to LMTs other than statin, or in monotherapy.

LDL-C reduction observed at Week 24 was maintained over time in all the studies including those up to 78 weeks. In all studies, the LDL-C reduction was observed at the first LDL-C measurement following the first alirocumab dose at Week 4.

Phase 3 studies that evaluated Q4W regimen – efficacy results:

Two studies EFC13786 and R727-CL-1308 (first-step analysis), have evaluated the 150 mg Q4W and 300 mg Q4W, respectively, as initiation dose regimen with a possible up-titration to 150 mg Q2W. For both studies, LDL-C reduction was observed at Week 4 was maintained over time up to Week 24. As with Q2W dosing, changes in Non-HDL-C, Apo B, and Total-C tended to correlate with LDL-C. The R727-CL-1308 study included patients with and without concomitant statin. In both of these populations, there were statistically significant effects in favor of alirocumab 300 mg Q4W with possible up-titration to 150 mg Q2W for both co-primary efficacy endpoints (percentage change in LDL-C from baseline to Week 24 and to averaged Weeks 21 - 24). For LDL-C reduction, the LS mean treatment difference for alirocumab versus placebo at Week 24 was -52.4% and -58.7% for the non-concomitant statin population and concomitant statin population, respectively. The results obtained at Week 12 were consistent with those at Week 24 for both populations, whereby the Week 12 effect assessed the sole contribution of 300 mg Q4W dose regimen.

The EFC13786 study included a vast majority of statin intolerant patients with many on background ezetimibe therapy. At Week 24, statistically significant LS mean treatment difference for alirocumab (150 mg Q4W with possible up-titration to 150 mg Q2W) versus placebo of -56.4% was achieved for LDL-C reduction. The results obtained at Week 12 showed statistically significant LS mean treatment difference of -44.9%, whereby the Week 12 effect assessed the sole contribution of the 150 mg Q4W dose regimen.

Clinical safety

In the completed studies, or studies with first-step analysis, 391 patients from Phase 1, and 4300 patients from Phase 2 and Phase 3 have been exposed to 1 or more doses of alirocumab. As of 31 December 2014, there are 4818 subjects / patients estimated to be exposed to alirocumab from the blinded phase 3 studies and 1550 patients are exposed to alirocumab in ongoing open label studies.

Phase 2 and Phase 3 safety results:

Safety data was analyzed from pooled phase 2 and phase 3 studies with a Q2W dosing, which included a total of 5234 patients, of which 3340 patients were treated with alirocumab at a dose of 75 or 150 mg Q2W.

In the placebo-controlled and ezetimibe-controlled pooled studies, no dose relationship was noted for any adverse events (AEs) and there was not evidence of a pattern in the type of AEs observed. The percentages of patients who experienced at least 1 TEAE, at least 1 treatment-emergent SAE and any TEAEs leading to permanent treatment discontinuation were similar between the alirocumab and control groups.

There was no safety signal observed with neurologic events and neurocognitive disorders, alanine transaminase (ALT) increase and hepatic disorders, adjudicated CV events, diabetes mellitus, and ophthalmologic disorders.

The most common adverse reactions in patients treated with alirocumab were local injection site reactions (6.2% patients in the alirocumab group versus 4.2% in control groups in the global pool). Injection site reactions, influenza and pruritus were identified as adverse drug reactions (ADRs). Rare and sometimes serious allergic adverse reactions (e.g., hypersensitivity, eczema nummular, urticaria, and hypersensitivity vasculitis) have been reported from clinical studies in patients receiving alirocumab.

There was no safety signal in patients who had at least 2 consecutive values of LDL-C <25 or 15 mg/dL (0.65 or 0.39 mmol/L), particularly in regard to neurological or other adverse effects that could potentially be related to low LDL-C (32). The analysis of the safety data with Q2W dosing did not suggest a safety signal as of 31 December 2014.

Overall, the safety profile of the alirocumab Q4W dosing regimen was similar to alirocumab Q2W regimen, except for the frequency and onset of injection site reactions. The reactions tended to occur sooner after the first drug injection, and last longer, in the alirocumab group.

Further details on alirocumab are provided in the Investigator's Brochure.

Rationale for selection of doses / dose regimens in this study:

This study will explore the alirocumab 150 mg Q4W regimen, which represents a potentially viable alternative to a Q2W regimen for some patients.

Statins increases the activity of nuclear translocation of sterol regulatory element-binding protein 2 (SREBP-2), a transcription factor that activates both the LDL-R and PCSK9 genes. It is proposed that a statin-stimulated increased production of PCSK9 may affect the duration of action of alirocumab in the setting of Q4W dosing, because higher rates of PCSK9 production may result in greater target-mediated clearance of the antibody (33). Compared to statins, fibrates and ezetimibe appear to have less effect on PCSK9 levels (34), and a Q4W dosing regimen is expected to maintain sufficient LDL-C lowering throughout the interdosing interval in patients not receiving a statin but receiving these lipid-lowering therapies as well as for alirocumab monotherapy. The addition of a PCSK9 inhibitor to fibrate therapy may achieve beneficial cholesterol lowering along with the other desirable effects of fibrates (e.g., TG reduction) (35).

For patients receiving alirocumab in monotherapy, phase 1 data consistently suggested that the dose of 150 mg given Q4W should also maintain sufficient LDL-C lowering throughout the interdosing interval; similar profile was observed with a background therapy of ezetimibe or fenofibrate, without statin from PKD12910 study.



[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Rationale for protocol design:

The objective of the present study is to assess the efficacy and safety of alirocumab 150 mg Q4W as a potential starting and treatment dose in patients treated with non-statin LMTs or the lowest strength of statin. This population that is not at LDL-C goal on LMT (non-statin LMTs including diet therapy alone or the lowest strength of statin) with the documented reasons why statin is not appropriate or why statin dose cannot be increased for the patients, represents a group with an identified unmet medical need that can be addressed by adding alirocumab to their LDL-C lowering therapies. This will complement the current program, and help provide well-documented dosing recommendations.

To confirm dose appropriateness of 150 mg Q4W as a starting dose, 150 mg Q2W is also evaluated with the comparison of placebo and compared the dose response with 150 mg Q4W. Showing higher efficacy in 150 mg Q2W than 150 mg Q4W would lead to justify the dose up titration for patients who do not reach LDL-C treatment goal.

This study will be conducted in 2 patient populations concurrently: patients who are on concomitant atorvastatin 5 mg and patients who are on non-statin LMTs including diet therapy alone. The stratification will be done at randomization according to background statin treatment: (Yes/No). “No statin background” will be also stratified according to background fibrate/ezetimibe therapy: (Yes/No).

To demonstrate superiority of 150 mg Q4W or 150 mg Q2W over placebo with a 90% statistical power under an alpha level of 2.5% for each comparison (to obtain an overall study alpha level of 5%), 38 patients (19 in each arm) will be required assuming a difference of 30% in mean percent change in LDL-C between 150 mg Q4W and placebo, between 150 mg Q2W and placebo, and a common standard deviation of 25%, by using Bonferroni adjustment for two paired comparisons

between alirocumab groups (150 mg Q4W, 150 mg Q2W) and placebo. However, requirements for the long-term safety evaluation should also be considered in this study (36). In order to obtain >100 patients with 52 weeks exposure of alirocumab, 159 patients will be needed.

In this study of patients maintaining their background therapy of non-statin LMTs including diet therapy alone or the lowest strength of statin, who do not/cannot receive a standard dose of statin, the choice of placebo as control over the double-blind treatment period appears appropriate for the objectives of this study, since it will provide the most robust assessment of efficacy and safety of 150 mg Q4W and 150 mg Q2W.

The primary efficacy parameter will be assessed at week 12 that is considered sufficient to provide efficacy and safety information of 150 mg Q4W and 150 mg Q2W on LDL-C levels in this study. This treatment duration should also provide a sufficient duration of “exposure” to appreciate tolerability and safety profiles of alirocumab in the context of a therapeutic exploratory study. The effect of alirocumab on other lipid parameters (e.g., Apo-B, non-HDL-C, TC levels) will also be assessed at Week 12 in this study. To obtain additional safety data with this Q4W dosing, patients may participate in an open-label treatment period from Week 12 to Week 64.

5 STUDY OBJECTIVES

5.1 PRIMARY

To demonstrate the reduction of low density lipoprotein cholesterol (LDL-C) by alirocumab 150 mg every 4 weeks (Q4W) or 150 mg every 2 weeks (Q2W) regimen as add-on therapy to non-statin lipid modifying therapy (LMT) including diet therapy alone or the lowest strength of statin in comparison with placebo after 12 weeks of treatment in patients with hypercholesterolemia.

5.2 SECONDARY

The secondary objectives are:

- To evaluate the effect of two treatment regimens of alirocumab on other lipid parameters: apolipoprotein B (Apo-B), non-high-density lipoprotein cholesterol (non HDL-C), total cholesterol (TC), lipoprotein (a) [Lp(a)], high density lipoprotein cholesterol (HDL-C), triglyceride (TG), apolipoprotein A-1 (Apo A-1).
- To evaluate the safety and tolerability of alirocumab 150 mg Q4W and 150 mg Q2W.
- To evaluate the development of anti-alirocumab antibodies
- To evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) profiles of alirocumab 150 mg Q4W and 150 mg Q2W.
- To evaluate the long-term safety in patients receiving open-label alirocumab 150 mg Q4W and 150 mg Q2W.

6 STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, parallel-group, balanced (1:1:1, alirocumab 150 mg Q4W: alirocumab 150 mg Q2W: placebo, subcutaneous injection), multi-center phase 3 study. Randomization will be stratified according to background statin therapy (Yes/No). “No statin background” will be also stratified according to background fibrates/ezetimibe therapy (Yes/No), where ‘Yes’ represents fibrates or ezetimibe, and ‘No’ represents diet therapy alone.

Approximately 159 subjects (53 subjects per treatment arm) will be recruited and randomized

6.1 DESCRIPTION OF THE PROTOCOL

The study consists of 4 periods: run-in, screening, double-blind treatment, and open-label treatment

- **A run-in period of 4 weeks.** Patients will be treated with stable non-statin LMTs, stable daily atorvastatin 5mg, or stable diet therapy. Patients who will have already been treated with stable non-statin LMTs, stable diet therapy alone, or stable daily atorvastatin 5mg for at least 4 weeks will be able skip this period.
- **A screening period of up to 3 weeks.** The patients and designated person (such as spouse, relative, etc.) will be trained for self-injection / injection with a placebo for alirocumab when it is necessary.
- **A double-blind treatment period (DBTP) of 12 weeks.** Patients will receive double-blind treatment as follows,
 - Alirocumab 150 mg every 4 weeks (Q4W) alternating with placebo Q4WOR
 - Alirocumab 150 mg every 2 weeks (Q2W)OR
 - Placebo for alirocumab Q2W

The laboratory measurement of lipid parameters will be performed by a Central Laboratory (Central Lab) during the study. Local laboratory testing for lipid parameters is generally prohibited after randomization of the patient, except for the safety of the patient as per Investigator’s judgment. Lipid values obtained during the DBTP will not be communicated to investigator and sponsor to maintain the blind.

During the double-blind treatment period, patients should continue taking their therapies (daily 5mg atorvastatin, non-statin LMTs with ezetimibe, feno- or beza-fibrate, and/or diet therapy). Other LMTs red yeast rice, fibrate (other than feno- or beza-fibrate), ethyl icosapentate (EPA), and niacin and bile acid sequestrants are not allowed.

Permitted atorvastatin at a dose of 5mg daily, non-statin LMTs, or diet therapy should remain stable (including dose) from screening through the end of double-blind treatment visit (Week 12) barring exceptional circumstances:

- Exceptional circumstances per the investigator's judgement.
- If patient meets the pre-specified TG alert ($TG \geq 500$ mg/dL [5.65mmol/L]), lab alert will be sent and repeat testing should be done as soon as possible. Then diet will have to be reinforced. If necessary LMTs (newly added or dose modifications) might be considered based on the best clinical judgement of the investigators.
- If patient meets the pre-specified low LDL alert (2 consecutive calculated LDL-C < 25 mg/dL (0.65 mmol/L), the sites may receive the alert (See [Section 10.6.4](#)).

It is noted that the reasons of any adjustment should be documented and recorded in the electric case report form (e-CRF).

The lipid results will be masked from specimens obtained after randomization to Week 12 in order to keep the double-blind manner of DBTP. No attempts should be made by the investigator or patient to routinely have the patient's lipid values independently evaluated after randomization.

- **An open-label treatment period (OLTP) of 52 weeks.** All patients will receive alirocumab 150mg Q4W from the start of OLTP. Lipid values until Week 20 will not be opened and the values will be communicated to the investigator from Week 24.

At Week 24, the up-titration to alirocumab 150mg Q2W will be automatically conducted through Interactive Web Response System (IWRS) under the following circumstances:

- In patients with heFH or in patients with non-FH with documented coronary heart disease (CHD), LDL-C is ≥ 100 mg/dL (2.59mmol/L) at Week 20.
- In patients with non-FH classified as primary prevention category III, LDL-C is ≥ 120 mg/dL (3.10 mmol/L) at Week 20.

During the OLTP, permitted atorvastatin at a dose of 5mg daily, non-statin LMTs, or diet therapy also should remain stable (including dose) similar to the DBTP barring exceptional circumstances:.

- Exceptional circumstances per the investigator's judgement.
- If patient meets the pre-specified TG alert ($TG \geq 500$ mg/dL [5.65mmol/L]), lab alert will be sent and repeat testing should be done as soon as possible. Then diet will have to be reinforced. If necessary, LMTs (newly added or dose modifications) might be considered based on the best clinical judgement of the investigators.

All investigational medicinal product (IMP) injections will be conducted by site staff, patients, or another designated person (such as spouse, relative, etc.) if patients cannot conduct the injection.

- Injection training is planned at Week -1 with a placebo for alirocumab in case that the injections will be conducted by patients or another designated person from Week 0.
- From Week 0 to Week 10, all IMP injections will be conducted at the study site by site staff or patients/designated person under direct supervision of the site staff.

From Week 12, all IMP injections could be conducted by patients or the designated persons at home if patients agree. Otherwise, the IMP injections will be conducted by the site staff at “IMP injection site visits” (See [Section 10.1.4.2](#) for detailed procedures).

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

The study duration includes a run-in period of 4 weeks, a screening period of up to 3 weeks, a 12-week DBTP for efficacy, and 52-week OLTP for efficacy and safety assessment.

Thus, the study duration per patient is approximately 71 weeks (i.e., 18 months maximum) (up to 4 weeks of run-in period + up to 3 weeks screening + 12 weeks double-blind treatment + 52 weeks open-label treatment).

Patients, who experience ongoing SAEs or adverse events of special interest (AESI), at the prespecified study end date, should be followed until resolution, stabilization, or death and related data will be collected.

6.2.2 Determination of end of clinical trial (all patients)

The end of the study per patient is the last protocol planned visit or the resolution/stabilization of all SAEs, and AESI, whichever comes last.

6.3 TWO-STEP ANALYSIS

The analyses will be conducted in two steps. The first analysis will be conducted as soon as all patients have been randomized and have at least all their data up to Week 24 (including 12 weeks DBTP and 12 weeks OLTP) collected and validated, and will consist in the final analysis of the primary efficacy endpoint and the secondary efficacy endpoints up to Week 12. The safety analysis will be performed on all safety data up to Week 24 collected and validated. The second analysis will be conducted at the end of the study with all data including the data of the OLTP, and will consist in the final analysis of the safety endpoints and exploratory efficacy assessment during the OLTP.

For further detail, see [Section 11.5](#), “Timing of analyses”.

6.4 STUDY COMMITTEES

Data Monitoring Committee (DMC):

An independent DMC, composed of members independent of the Sponsor and the study Investigators, is implemented in order to monitor patient safety by conducting formal reviews of accumulated safety data that will be blinded by treatment group; if requested, the DMC may have access to the treatment allocation code or any other requested data for the purposes of a risk benefit assessment (e.g., lipid efficacy data). The DMC will provide the Sponsor with appropriate recommendations on the conduct of the clinical trial to ensure the protection and safety of the patients enrolled in the study. In addition, the DMC will also institute any measures that may be required for ensuring the integrity of the study results during the study execution. All activities and responsibilities of the DMC are described in the DMC charter.

Additionally, the DMC will be charged with reviewing the safety of patients with 2 consecutive LDL-C <25 mg/dL (0.65 mmol/L) and more particularly, will review adverse events (AEs) potentially associated with LDL-C <25 mg/dL (0.65 mmol/L) in conjunction with the Independent Physician (see [Section 10.6.4](#) and Appendix I).

Clinical Events Committee (CEC):

The clinical events committee (CEC) is composed of experts in the field of CVDs, independent from the Sponsor and the Investigators. This committee will be responsible for defining, validating and classifying, in a blinded fashion, pre-specified CV events and all deaths. Classification of events will be as follows: CHD death, non-fatal myocardial infarction (MI), fatal and non-fatal ischemic stroke, unstable angina requiring hospitalization, congestive heart failure requiring hospitalization and ischemia-driven coronary revascularization procedure (percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG]). In addition, the classification of the cause of all deaths will occur.

A charter and an adjudication operational manual will specify the procedures, criteria, and classification used for adjudication of these events.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

Patients meeting all of the following criteria will be considered for enrollment into the study:

- I 01. Patients with hypercholesterolemia[§] (heFH* or non-FH) receiving non-statin LMTs**, or the lowest strength of statin***.

* Diagnosis of heFH must be made either by genotyping or by clinical criteria before randomization. For those patients not genotyped, the clinical diagnosis may be based on JAS Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2012. If the clinical criteria are not met but heFH is strongly suspected by Investigator, genotyping will be conducted during the screening period after signed written informed consent for obtaining genotype information.

** Fibrate or ezetimibe, or diet therapy alone.

*** Defined as atorvastatin 5 mg.

§Patients receiving monotherapy with 5mg daily atorvastatin, fibrate, or ezetimibe are allowed to enter the study. It is noted that patients with any combined drug therapy, such as atorvastatin + fibrate, atorvastatin + ezetimibe, or fibrate + ezetimibe, are not allowed. Patients with diet therapy alone or diet therapy with drug monotherapy (atorvastatin, fibrate, or ezetimibe) are allowed to enter the study.

- In patients with heFH, patients with or without a history of documented CHD.
- In patients with non-FH, patients must have a history of documented CHD; otherwise patients have a history of documented diseases or other risk factors classified as primary prevention category III

A) Definitions for CHD (includes one or more of the following):

- Myocardial infarction
- Unstable angina
- Coronary revascularization procedure (e.g., percutaneous coronary intervention [PCI] or coronary artery bypass graft surgery [CABG])
- Clinically significant CHD diagnosed by invasive or non-invasive testing (such as coronary angiography, stress test using treadmill, stress echocardiography or nuclear imaging)

B) Definitions for documented diseases or other risk factors classified as primary prevention category III:

1. Ischemic stroke (excluding cardiogenic cerebro-embolism and/or transient ischemic attack [TIA]):
 - Documented previous ischemic stroke with a focal ischemic neurological deficit that persisted more than 24 hours, considered as being of atherothrombotic origin.
 - Computed tomography (CT) or magnetic resonance imaging (MRI) must have been performed to rule out hemorrhage and non-ischemic neurological disease.
2. Peripheral arterial disease (PAD) (one of the following criteria [a, b, or c] must be satisfied):
 - a) Current intermittent claudication (muscle discomfort in the lower limb produced by exercise that is both reproducible and relieved by rest within 10 minutes) of presumed atherosclerotic origin TOGETHER WITH ankle-brachial index equal to or less than 0.90 in either leg at rest OR
 - b) History of intermittent claudication (muscle discomfort in the lower limb produced by exercise that is both reproducible and relieved by rest within 10 minutes) TOGETHER WITH endovascular procedure or surgical intervention in one or both legs because of atherosclerotic disease OR
 - c) History of critical limb ischemia TOGETHER WITH thrombolysis, endovascular procedure or surgical intervention in one or both legs because of atherosclerotic disease
3. Diabetes:
 - Type 1 or type 2 diabetes mellitus with or without target organ damage (i.e., retinopathy, nephropathy, and/or micro-albuminuria).
4. Chronic kidney disease (CKD):
 - Documented moderate CKD as defined by $30 \leq$ estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² for 3 months or more, including the screening visit.
5. Other risk factors
 - 10-year fatal CHD risk SCORE $\geq 2\%$ (JAS Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2012).
 - 10-year fatal CHD risk SCORE $\geq 0.5\%$ and $< 2\%$, and have one or more of the following criteria (JAS Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2012).
 - a) Hypo HDL-C (< 40 mg/dL).
 - b) Family history of premature coronary artery disease (first-degree relative and male: < 55 year-old, female: < 65 year-old).
 - c) Impaired glucose tolerance (defined as a fasting blood glucose [FBG] < 126 mg/dL [< 7.0 mmol/L], and a two- hour post glucose challenge value: 140-199 mg/dL [7.8-11.1 mmol/L] [Oral glucose tolerance test, OGTT]).

- I 02. Hypercholesterolemia patients (heFH or non-FH) with one or more following factors for a history or risk of statin tolerability why statin is not appropriate or why statin dose cannot be increased from the lowest strength for the patients.
- History of side effects caused by statin (Hypersensitivity, elevated serum ALT, aspartate aminotransferase [AST], γ -glutamyl transferase [γ GT], alkaline phosphatase [ALP] and/or lactate dehydrogenase [LDH] levels, statin-induced liver dysfunction, abnormal values in creatine phosphokinase [CPK], Skeletal muscle-related symptoms, etc.).
 - CYP3A4 inhibitor (fibrate, immunosuppressant,azole antifungal agents or erythromycin).
 - Hepatic dysfunction or abnormal liver function (except fatty liver and confirmed other types of liver disease, history of hepatic dysfunction related to other causes).
 - Renal impairment or abnormal renal function (except history of renal impairment with defined cause).
 - Hypothyroidism.
 - Impaired glucose tolerance as defined previously or impaired fasting glycaemia (FBG 110 - 125 mg/dL [6.1 - 6.9 mmol/L]).
 - Diabetic nephropathy
 - Elderly with body mass index (BMI) $<18.5 \text{ kg/m}^2$
 - Other documented factors medically judged by investigators why statin is not appropriate or why statin dose cannot be increased from the lowest strength for the patients than the factors described above.
- I 03. Signed written informed consent

7.2 EXCLUSION CRITERIA

Patients who have met all the above inclusion criteria listed in [Section 7.1](#) will be screened for the following exclusion criteria which are sorted and numbered in the following 4 subsections:

7.2.1 Exclusion criteria related to study methodology

- E 01. LDL-C $<100 \text{ mg/dL}$ ($<2.59 \text{ mmol/L}$) at the screening visit (Week -3) in patients with heFH or in patients with non-FH who have a history of documented CHD as described in [Section 7.1](#)
- E 02. LDL-C $<120 \text{ mg/dL}$ ($<3.10 \text{ mmol/L}$) at the screening visit (Week -3) in patients with non-FH patients who have a history of documented diseases or other risk factors as categorized in primary prevention category III as described in [Section 7.1](#)
- E 03. Not on a stable dose of LMTs (including diet therapy alone) in the run-in period or the screening period.

- E 04. Use of statins other than atorvastatin 5 mg daily in the run-in period or the screening period.
- E 05. Use of fibrates, other than fenofibrate or bezafibrate in the run-in period or the screening period.
- E 06. Use of nicotinic acid or bile acid-binding sequestrants or probucol or EPA or red yeast rice products in the run-in period or the screening period.
- E 07. Use of nutraceutical products or over-the-counter therapies that may affect lipids which have not been at a stable dose / amount in the run-in period or the screening period.
- E 08. Patient who has received plasmapheresis treatment within 4 weeks prior to the screening visit (Week -3), or has plans to receive during the study.
- E 09. History of a MI, unstable angina leading to hospitalization, CABG, PCI, uncontrolled cardiac arrhythmia, stroke, transient ischemic attack, carotid revascularization, endovascular procedure or surgical intervention for peripheral vascular disease within 3 months prior to the run-in visit (Week -7) or the screening visit (Week -3).
- E 10. Planned to undergo scheduled PCI, CABG, carotid or peripheral revascularization during the study.
- E 11. Systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg at the run-in visit (Week -7), the screening visit (Week -3), or randomization visit (Week 0).
- E 12. History of New York Heart Association (NYHA) Class III or IV heart failure within the 12 months prior to the run-in visit (Week -7) or the screening visit (Week -3).
- E 13. Known history of hemorrhagic stroke.
- E 14. Age <20 years at the run-in visit (Week -7) or the screening visit (Week -3).
- E 15. Patients not previously instructed on a cholesterol-lowering diet prior to the screening visit (Week -3).
- E 16. Poorly controlled diabetes (hemoglobin A_{1c} [HbA_{1c}] >9%) at the screening visit (Week -3).
- E 17. Presence of any clinically significant uncontrolled endocrine disease known to influence serum lipids or lipoproteins.

Note: Patients on thyroid replacement therapy can be included if the dosage has been stable for at least 12 weeks prior to screening and between the screening and randomization visits, and TSH level is within $\pm 10\%$ of normal range of the Central Laboratory at the run-in visit (Week -7) or the screening visit (Week -3).

- E 18. History of bariatric surgery within 12 months prior to run-in visit (Week -7) or the screening visit (Week -3).

- E 19. Unstable weight defined by a variation >5 kg within 2 months prior to run-in visit (Week -7) or the screening visit (Week -3).
- E 20. Known history of homozygous familial hypercholesterolemia.
- E 21. Known history of loss of function of PCSK9 (i.e., genetic mutation or sequence variation).
- E 22. Use of systemic corticosteroids, unless used as replacement therapy for pituitary/adrenal disease with a stable regimen for at least 6 weeks prior to the randomization visit (Week 0).

Note: Topical, intra-articular, nasal, inhaled and ophthalmic steroid therapies are not considered as 'systemic' and are allowed.

- E 23. Use of continuous estrogen or testosterone hormone replacement therapy unless the regimen has been stable in the past 6 weeks prior to the run-in (Week -7) or the screening visit (Week -3) and no plans to change the regimen during the study.
- E 24. History of cancer within the past 5 years prior to the run-in visit (Week -7) or the screening visit (Week -3), except for adequately treated basal cell skin carcinoma, squamous cell skin carcinoma or in situ cervical cancer.
- E 25. Known history of a positive human immunodeficiency virus (HIV) test
- E 26. Patient who has taken any investigational drugs other than the alirocumab training placebo kits within 1 month or 5 half-lives, whichever is longer.
- E 27. Patient who has been previously treated with at least one dose of alirocumab or any other anti-PCSK9 monoclonal antibody in other clinical trials.
- E 28. Conditions/situations such as:
 - Any clinically significant abnormality identified at the time of run-in (Week -7) or screening (Week -3) that in the judgment of the Investigator or any sub-Investigator would preclude safe completion of the study or constrain endpoints assessment such as major systemic diseases, patients with short life expectancy.
 - Considered by the Investigator or any sub-Investigator as inappropriate for this study for any reason, e.g.:
 - Deemed unable to meet specific protocol requirements, such as scheduled visits.
 - Deemed unable to administer or tolerate long-term injections as per the patient or the investigator.
 - Investigator or any sub-investigator, pharmacist, study coordinator, other study staff or relative thereof directly involved in the conduct of the protocol, etc.
 - Presence of any other conditions (e.g., geographic, social) actual or anticipated, that the investigator feels would restrict or limit the patient's participation for the duration of the study.

E 29. Laboratory findings during the screening period (not including randomization Week 0 labs):

- Positive test for Hepatitis B surface antigen
- Positive test for Hepatitis C antibody (if positive, then confirmed by Hepatitis C Virus [HCV] polymerase chain reaction [PCR]).
- Positive serum beta-human chorionic gonadotropin (hCG) or urine pregnancy test (including Week 0) in women of childbearing potential
- Fasting TG >400 mg/dL (>4.52 mmol/L) (1 repeat lab is allowed)
- Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m² according to 4-variable Modification of diet in renal disease (MDRD) Study equation (Calculated by central lab)
- ALT or AST >3 x upper limit of normal range (ULN) (1 repeat lab is allowed)
- CPK >3 x ULN (1 repeat lab is allowed)
- Thyroid stimulating hormone (TSH) <lower limit of normal range (LLN) or >ULN (1 repeat lab is allowed. For patients with thyroid replacement therapy, refer to E 17.).

7.2.2 Exclusion criteria related to the active comparator and/or mandatory background therapies

E 30. All contraindications to the background therapies or warning/precaution of use (when appropriate) as displayed in the respective the Japanese Product labeling.

7.2.3 Exclusion criteria related to the current knowledge of Sanofi compound

E 31. Known hypersensitivity to monoclonal antibody or any component of the drug product.

E 32. Pregnant or breastfeeding woman.

E 33. Women of childbearing potential not protected by highly-effective method(s) of birth control and/or who are unwilling or unable to be tested for pregnancy.

Note: Women of childbearing potential must have a confirmed negative pregnancy test at screening and randomization visits. They must use an effective contraceptive method throughout the entire duration of the study treatment, and for 10 weeks after the last intake of IMP, and agree to repeat urine pregnancy test at designated visits. The applied methods of contraception have to meet the criteria for a highly effective method of birth control according to the "Note for guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. M3 (R2): Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals. International Conference on Harmonisation (ICH). 2009 June: 1-25). Postmenopausal women must be amenorrheic for at least 12 months.

7.2.4 Additional exclusion criteria during or at the end of screening or run-in phase before randomization

- E 34. Patient who has withdrawn consent before enrollment/randomization (starting from signed informed consent form).
- E 35. Despite screening of the patient, enrolment/randomization is stopped at the study level.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

Sterile alirocumab drug product will be supplied at a concentration of 150 mg/mL in histidine, pH 6.0, polysorbate 20 and sucrose with 1 mL volume in an autoinjector.

Sterile placebo for alirocumab will be prepared in the same formulation as alirocumab without the addition of protein as 1 mL volume in an autoinjector.

Alirocumab 150 mg and placebo for alirocumab will be indistinguishable from each other.

8.1.1 Route and method of administration

The investigational medicinal product (IMP) will be administered subcutaneously in the abdomen, thigh or outer area of upper arm by site staff, the patient or by another designated person (such as a spouse, relative, etc.). The injection site will be rotated among the abdomen, thigh, and outer area of upper arm to minimize local site reaction by the IMP injection.

A manual for IMP administration (injection instruction manual) will be provided to the study sites containing detailed instructions on use. It is recommended that the IMP injections should be rotated within anatomical areas (e.g., right thigh then left thigh or right abdomen then left abdomen). Patients also have the option to inject the IMP in different anatomical area (e.g., thigh, abdomen, and then outer area of upper arm). It is noted that the injection in the upper arms could be done only by a trained person (spouse, relative, etc.) or health care professional but not the patient themselves. If another concomitant drug is being injected at the same site planned for the IMP injection, then the IMP injection should be conducted in an alternate location. The used autoinjector will be discarded in a sharps container which will be provided to patients.

Investigators or Pharmacists (and patients who plan self-administration of the IMP) will be asked to store the IMP in a refrigerator. Prior to administration, the IMP should be set outside in a safe location at room temperature for approximately 30 to 40 minutes. The IMP must be administered within 4 hours of removal from the refrigerator.

Instructions for IMP administration as outlined above should be provided to the patient and/or other designated person (such as a spouse, relative, etc.) who will administer the IMP at training and as needed during the course of the study. Close supervision and feedback should be given at the injection training visit, the randomization visit and the other visits as needed. Anyone that plans to administer the IMP must be trained by the site staff.

8.1.2 Timing of administration

Screening period (from Week -3 to Week 0): Training Injection

During the screening period, a training injection is planned on Week -1 with a placebo for alirocumab. If needed, a second training injection is authorized before the randomization visit. It is noted that further training with the scheduled double-blind / open-label IMP can be done at any time during the study as necessary.

Double-blind treatment period (from Week 0 to Week 12):

During the double-blind treatment period, patients will be randomized to receive:

- Alirocumab 150mg Q4W alternating with placebo for alirocumab Q4W
OR
- Alirocumab 150 mg Q2W
OR
- Placebo for alirocumab Q2W.

Alirocumab will be administered at Week 0, Week 2, Week 4, Week 6, Week 8, and Week 10 (Q2W), or at Week 0, Week 4, and Week 8 with alternating placebo for alirocumab administration at Week 2, Week 6, and Week 10 (Q4W). The first IMP administration at Week 0 will start as soon as possible after the call for randomization using the treatment kit number provided by the IWRS. Patients will be monitored at the study site for at least 30 minutes after the first IMP administration.

All IMP injections will be conducted at the study site under direct site staff supervision after all study assessments have been performed and all laboratory samples have been collected.

Open-label treatment period (from Week 12 to Week 64):

All patients will receive alirocumab 150 mg Q4W from the beginning of the OLTP (Week 12). At the beginning of the OLTP, all patients will be monitored at the study site for at least 30 minutes after the first IMP administration.

At Week 24, the up-titration to alirocumab 150 mg Q2W will be conducted through interactive Web Response System (IWRS) under the following circumstances:

- In patients with heFH or in patients with non-FH with documented CHD, LDL-C is ≥ 100 mg/dL (2.59 mmol/L) at Week 20.
- In patients with non-FH classified as primary prevention category III, LDL-C is ≥ 120 mg/dL (3.10 mmol/L) at Week 20.

In patients with alirocumab 150 mg Q4W, the last injection will be conducted at Week 60. In patients with up-titrated alirocumab 150 mg Q2W, the last injection will be conducted at Week 62.

All IMP injections can be conducted home if patients are able to perform (See [Section 10.1.4](#) and [Section 10.1.4.4](#)).

Throughout the entire study duration:

When IMP injection is delayed more than 7 days from the scheduled injection time, or is completely missed, the patient should return to the original schedule of the IMP administration without administering the delayed injection. If the delay is less than or equal to 7 days from the missed date, the patient should administer the delayed injection and then resume the original dosing schedule of the IMP administration. At least 7 days must be needed between the IMP injections.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCT(S)

The following classes of drugs are identified as non-investigational medicinal products (NIMPs) because the medication is either background therapy or a potential medication:

- Statin (atorvastatin, 5mg daily)
- Cholesterol absorption inhibitor (ezetimibe)
- Fibrate (fenofibrate, bezafibrate, but not other fibrates)

For NIMP not provided by the Sponsor, tracking and reconciliation has to be achieved by the Investigator according to the system proposed by the Sponsor.

Please see [Section 8.8](#) for further information.

8.3 BLINDING PROCEDURES

8.3.1 Methods of blinding

Alirocumab and placebo for alirocumab will be provided in identically matched autoinjector and packaged identically which includes labeling to protect the blind.

Each double-blind treatment kit will be labeled with a number, which will be generated by a computer program from Sanofi. The treatment kit numbers will be obtained by the Investigator at the time of patient randomization and subsequent patient visits scheduled via a centralized treatment allocation system that will be available 24 hours a day, 7 days a week.

In accordance with the double-blind design, patients, Investigators, and study site personnel will remain blinded to the study treatment and will not have access to the randomization (treatment codes) except under circumstances described in [Section 8.3.2](#) (suspected unexpected adverse drug reaction unblinded by the Sponsor).

During the double-blind study period, neither the Investigator nor the Sponsor will have access to the individual data for the primary efficacy parameter obtained after the baseline visit in each

patient. However, the study team may review the data for the primary efficacy parameter in descriptive statistics with the name of the IMP treatment masked during data review meeting. The descriptive statistics for use in any data review meeting will be generated by an independent statistician/programmer, who will not be involved in the study operation and execution.

8.3.1.1 Lipid parameters

Lipid parameter values from blood samples obtained after the randomization visit (from Week 0 to Week 20), run by the Central Lab, will not be communicated to the sites so that they cannot deduce the treatment group of their patients based on LDL-C level attained. The sponsor's operational team will not have access to lipid parameters after the randomization visit (from Week 0 to Week 20) and will not be able to deduce the treatment group of patients based on LDL-C level attained during the double-blind treatment period.

Lipid parameter values from blood samples obtained from Week 24 to Week 64 will be communicated to the sites and the Sponsor's operational team from Week 24.

During the DBTP, patients who achieve 2 consecutive calculated LDL-C <25 mg/dL (0.65 mmol/L) will be monitored according to process outlined in [Section 10.6.4](#) and Appendix I. In order to maintain the integrity of the blind as much as possible with this monitoring process, following process will be undertaken:

- Specific steps will be in place to ensure the Central Lab work and communication with the independent external physician(s) (also known as independent physician), who is responsible for closely monitoring patients with 2 consecutive calculated LDL-C <25 mg/dL (0.65 mmol/L), will be in strict confidence.
- The independent physician(s) and DMC member (who is also responsible for this specific monitoring) will work independently from the clinical team and the sites. Communication with such groups will take place via specific process and only when needed.
- The actual LDL-C levels will not be reported to the sites receiving alerts related to 2 consecutive calculated LDL-C <25 mg/dL (0.65 mmol/L).
- In order to maintain the integrity of the blind, study sites may receive true alerts or sham alerts. A sham alert is the alert that patient does not meet criteria of the low LDL-C alert, which is 2 consecutive calculated LDL-C <25 mg/dL (0.65 mmol/L). Sham alerts for 2 consecutive calculated LDL-C <25 mg/dL (0.65 mmol/L) will be applied to randomly selected placebo patients in any site, who do not meet the criterial for an alert related to 2 consecutive calculated LDL-C <25 mg/dL (0.65 mmol/L). Study staff and the monitoring team will know the alert has occurred, but will not know if it is sham or a true alert.

8.3.1.2 Anti-alirocumab antibodies

Patients' anti-alirocumab antibody results will not be communicated to the sites.

The sponsor's operational team will not have access to anti-alirocumab antibodies associated with patient identification until the database lock will be completed.

The lab technicians involved in the determination of patients' anti-alirocumab antibodies are excluded from the operational team and a process will be set up to prevent any potential unblinding.



8.3.1.3 Pharmacokinetics measurements, total and free PCSK9 concentrations

At the assay institutions charged for PK measurements, total and free PCSK9 concentrations, samples will be analyzed prior to the database lock leading to unblinding of responsible bioanalysts. Bioanalysts are excluded from the operation's team and a process will be set up to prevent any potential unblinding.

8.3.1.4 Committee

The DMC will receive confidential reports blinded by treatment group or unblinded (if necessary) from an independent statistician for review ([Section 6.4](#)).

The CEC will review and adjudicate their respective events in a blinded manner ([Section 6.4](#)).

A charter and an adjudication operational manual will specify the procedures, criteria, and classification used for adjudication of these events.

8.3.2 Randomization code breaking during the study

In case of an adverse event (AE), the code should only be broken in circumstances when knowledge of the IMP is required for treating the patient. If possible, a contact should be initiated with the Monitoring Team/Medical Monitor before breaking the code.

Code breaking can be performed at any time by using the proper module of the interactive voice response system (IVRS) / interactive web response system (IWRS) and/or by calling any other phone number provided by the Sponsor for that purpose. If the blind is broken, the Investigator should document the date, time of day, and reason for code breaking, and report this information on the appropriate page of the e-CRF.

Note that when documenting the reason for unblinding, the Investigator must not provide any detail regarding the nature of the IMP. The Investigator should not divulge IMP detail to the Sponsor or to any staff members until database closure. Furthermore, when completing forms (e.g., AE, SAE), the study treatment should not be disclosed on the forms.

The code breaking can also be performed by contacting the "24-hour alert system", but this system should only be used in very exceptional cases (i.e., unavailability of a centralized treatment allocation system or inability to contact investigator and/or site staff). The Investigators will be informed by the clinical monitoring team about the availability of the local code breaking details (through an emergency centralized 24-hour telephone system). A patient card, including

the relevant “24-hour alert system” telephone number will be provided to every patient who will participate in the study.

If the code is broken, the patient must be withdrawn from IMP administration but must be followed until the end of the study.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

The randomized list of treatment kit numbers will be generated centrally by Sanofi. The IMP (alirocumab 150 mg kit or placebo kit) will be packaged in accordance with this list.

The Trial Supply Operations Manager will provide the randomized list of treatment kit numbers and the Study Biostatistician will provide the randomization scheme to the IWRS. Then, the IWRS will generate the patient randomization list according to which treatment kits will be allocated to the patients.

Before randomizing a patient, the Investigator or designee will have to contact the IWRS.

A randomized patient is defined as a patient who is registered and assigned with a treatment kit number from the centralized treatment allocation system, as documented from its log file. A patient cannot be randomized more than once in the study. If a treatment is used without contacting the centralized treatment allocation system, patient will be considered as not randomized and withdrawn from the study.

During the DBTP, patients will be randomized to receive alirocumab 150mg Q4W, alirocumab 150 mg Q2W, or placebo at a ratio of 1:1:1 with permuted-block randomization. Randomization will be stratified according to the statin therapy (Yes/No). “No statin background” will be also stratified according to background fibrate/ezetimibe therapy (Yes/No), where ‘Yes’ represents fibrate or ezetimibe, and ‘No’ represents diet therapy alone.

During the OLTP, all patients will receive alirocumab 150 mg Q4W from the beginning of the OLTP (Week 12).

At Week 24, the up-titration to alirocumab 150 mg Q2W will be conducted based on LDL-C level at Week 20 following the up-titration rules (see [Section 6.1](#)).

The treatment kit numbers will be allocated using the IWRS on randomization visit (Day 1, Week 0), and then at Week 2, Week 4, Week 6, Week 8, Week 10, Week 12, Week 24, Week 36, and Week 48 as re-supply visits, and at unscheduled visits if necessary.

8.5 PACKAGING AND LABELING

Packaging is in accordance with the administration schedule. The content of the labeling is in accordance with the local regulatory specifications and requirements.

For the DBTP, each double-blind treatment kit containing a single autoinjector, either alirocumab or placebo, will be prepared.

In order to protect the blind, all double-blind treatment kit boxes will have the same look and feel, and therefore will be labeled with a double-blind label.

For the OLTP, each open-label treatment kit containing 4 autoinjectors of alirocumab/kit (wallet) labeled with an open-label way will be prepared.

In addition to the double-blind and open-label treatment kits, training kits containing 1 placebo autoinjector per kit will be prepared for the purpose of instructing patients on injection administration which is to be performed prior to randomization at the injection training visit Week-1 (V2). If needed a second training injection is authorized at least one day before the randomization visit.

Written details of packaging and labeling of the IMP will be provided as a pharmacy manual.

8.6 STORAGE CONDITIONS AND SHELF LIFE

Investigators or other authorized persons (e.g., pharmacists) are responsible for storing the IMP in a secure and safe place in accordance with local regulations, labeling specifications, policies, and procedures.

Control of IMP storage conditions, especially control of temperature (e.g., refrigerated storage) and information on in-use stability and instructions for handling the Sanofi compound should be managed according to the rules provided by the Sponsor.

The IMP (alirocumab or placebo) has to be stored in a refrigerator between +2°C and +8°C (36°-46°F) by the site. The temperature of the site refrigerator should be checked once a day during business days and recorded on a log sheet. Investigators or other authorized persons (e.g., pharmacists) must maintain the records documenting that all received IMPs are stored under adequately controlled conditions.

8.7 RESPONSIBILITIES

The Investigators, the pharmacists, or other persons, who are allowed to store and dispense the IMP, will be responsible for ensuring that the IMP used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.

All IMPs will be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of IMP issued and returned is maintained.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc.) should be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure.

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall IMP and eliminate potential hazards.

Under no circumstances the Investigator will supply IMP to a third party, allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

8.7.1 Treatment accountability and compliance

Measures taken to ensure and document IMP compliance and accountability are described below:

- The Investigator or designee will obtain the treatment kit number(s) via IVRS / IWRS and he/she will dispense the treatment kit(s) to the patient.
- The Investigator, the pharmacist or designee will complete the corresponding treatment log form.
- The Investigator / study coordinator will enter data in the appropriate electronic case report form (e-CRF) pages, according to data recorded in the treatment log form.
- The monitor will check the data consistency between e-CRF pages, treatment log forms, and returned unused autoinjectors of corresponding kits.

8.7.2 Return and/or destruction of treatments

Unused treatments kits will be retrieved by the Sponsor. A detailed treatment log of the retrieved IMP will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the monitoring team. The Investigator will not destroy the unused IMP unless the Sponsor provides written authorization.

“Partially-used and/or used IMP will be destroyed on site according to the standard practices of the site.”

8.8 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient concomitantly to the study (until Week 64 [Visit 23]).

Concomitant medications should be kept to a minimum during the study. However, if these are considered necessary for the patient’s welfare and are unlikely to interfere with the IMP, they may be given at the discretion of the Investigator, with a stable dose (when possible). Besides the specific information related to concomitant medications provided in this section, any other concomitant medication(s) will be allowed and will have to be recorded in the e-CRF and source data.

For background LMT, including statin, study sites must follow the national product label of the safety monitoring and management of patients.

Nutraceutical products or over-the-counter therapies that may affect lipids are allowed only if they have been used at a stable dose at run-in visit, and maintained during the first 12 weeks of the DBTP. After the Week 12 visit, modification to these nutraceutical products or over-the-counter therapies may be allowed but in general should be avoided unless these products are required for medical reasons. Examples of such nutraceutical products or over-the-counter therapies include omega-3 fatty acids at doses <1000 mg, plant stanols such as found in Benecol, flax seed oil, or psyllium.

8.8.1 Management of background lipid modifying therapy

Patients must have been on stable 5mg of daily dose of atorvastatin, other LMTs, or diet therapy for at least 4 weeks before the screening visit (Week -3).

During the DBTP, the patients must stay on these stable daily doses of statin, non-statin LMTs, or diet therapy. Lipid profile values from samples obtained after randomization will be blinded until Week 24. During the OLTP after Week 24, the background LMT might be modified under the situations which overriding concerns warrant such changes, as per the Investigator's judgment.

8.8.2 Contraception

Women of childbearing potential, who are the study participants or the partner of the male participant, must take an effective contraceptive method throughout the study treatment, and for 10 weeks after the last IMP injection.

8.8.3 Prohibited concomitant medications

Forbidden concomitant medications from the run-in visit or initial screening visit until Week 64 (Visit 23) include the following:

- Statin except atorvastatin 5mg.
- Bile acid-binding sequestrants (colestimide, cholestyramine).
- Nicotinic acid (niceritrol, nicomol, tocopherol nicotinate).
- Fibrates, other than fenofibrate or bezafibrate.
- Probucol.
- EPA (ethyl icosapentate)
- Red yeast rice products

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 EFFICACY ENDPOINT

9.1.1 Primary efficacy endpoint

The primary efficacy endpoint is the percentage change in calculated LDL-C from baseline to Week 12 in the intent-to-treat (ITT) population, using all LDL-C values regardless of adherence to treatment (ITT estimand). It is defined as: $100 \times (\text{calculated LDL-C value at Week 12} - \text{calculated LDL-C value at baseline}) / \text{calculated LDL-C value at baseline}$.

The baseline calculated LDL-C value will be the last LDL-C level obtained before the first double-blind IMP injection. For patients randomized and not treated, the baseline value is defined as the last available value obtained up to randomization.

The calculated LDL-C at Week 12 will be the LDL-C level obtained within the Week 12 analysis window.

All calculated LDL-C values (scheduled or unscheduled, fasting or not fasting) may be used in the analysis if appropriate according to above definition and analysis window used to allocate a time point to a measurement. The analysis window will be defined in the statistical analysis plan (SAP).

9.1.2 Secondary endpoints

9.1.2.1 Key secondary efficacy endpoints

The key secondary efficacy will be considered in the following order:

1. The percentage changes in calculated LDL-C from baseline to Week 12 in the modified ITT (mITT) population, using all LDL-C values during the efficacy double-blind treatment period (as are defined in [Section 11.3.1.2](#)) (on-treatment estimand).
2. The percentage change in calculated LDL-C from baseline to average Week 10-12 (ITT estimand).
3. The percentage change in calculated LDL-C from baseline to average Week 10-12 (on-treatment estimand).
4. The percentage change in Apo-B from baseline to Week 12 (ITT estimand).
5. The percentage change in Apo-B from baseline to Week 12 (on-treatment estimand).
6. The percentage change in non-HDL-C from baseline to Week 12 (ITT estimand).
7. The percentage change in non-HDL-C from baseline to Week 12 (on-treatment estimand).
8. The percentage change in TC from baseline to Week 12 (ITT estimand).

9. The proportion of patients reaching LDL-C goal at Week 12, i.e., calculated LDL-C <100 mg/dL (2.59 mmol/L) for heFH or non-FH patients who have a history of documented CHD patients, or LDL-C <120 mg/dL (3.10 mmol/L) for non-FH patients who have a history of documented diseases or other risk factors classified as primary prevention category III (ITT estimand).
10. The proportion of patients reaching LDL-C goal at Week 12, i.e., calculated LDL-C <100 mg/dL (2.59 mmol/L) for heFH or non-FH patients who have a history of documented CHD patients, or LDL-C <120 mg/dL (3.10 mmol/L) for non-FH patients who have a history of documented diseases or other risk factors classified as primary prevention category III (on-treatment estimand).
11. The percentage change in Lp(a) from baseline to Week 12 (ITT estimand).
12. The percentage change in HDL-C from baseline to Week 12 (ITT estimand).
13. The percentage change in fasting TG from baseline to Week 12 (ITT estimand).
14. The percentage change in Apo A-1 from baseline to Week 12 (ITT estimand).

9.1.2.2 Other Secondary Efficacy Endpoints

- The proportion of patients with calculated LDL-C <100 mg/dL (2.59 mmol/L) at Week 12 (ITT estimand).
- The proportion of patients with calculated LDL-C <120 mg/dL (3.10 mmol/L) at Week 12 (ITT estimand).
- The proportion of patients with calculated LDL-C <70 mg/dL (1.81 mmol/L) at Week 12 (ITT estimand).
- The absolute change in LDL-C from baseline to Week 12 (ITT estimand).
- The change in Apo-B/Apo A-1 ratio from baseline to Week 12 (ITT estimand).
- The proportion of patients with Apo-B <80 mg/dL (0.8 g/L) at Week 12 (ITT estimand).
- The proportion of patients with non HDL-C <130 mg/dL (3.37 mmol/L) at Week 12 (ITT estimand).
- The proportion of patients achieving at least 50% reduction in LDL-C at Week 12 (ITT estimand).
- The percentage change in TC, Lp(a) from baseline to Week 12 (on treatment estimand)

9.1.3 Efficacy assessment method

9.1.3.1 Lipid parameters

The TC, HDL-C, TG, Apo-B, Apo A-1, and Lp(a) will be directly measured by the Central Laboratory as per the schedule in [Section 1.2](#). The LDL-C will be calculated using the Friedwald formula (37). If TG values exceed 400 mg/dL (4.52 mmol/L), then the Central Laboratory will reflexively measure (via the beta quantification method) the LDL-C rather than calculating the

LDL-C levels. Non-HDL-C will be calculated by subtracting HDL-C from the TC. Ratio Apo-B/Apo A-1 will be calculated. Detailed procedures of sample preparation, storage, and shipment will be described in the specific laboratory manual which will be provided to study sites.

Efficacy endpoints will not be considered as AEs, such as those involving abnormalities in lipid levels, unless meeting the criteria in [Section 10.4.1](#).

9.2 SAFETY ENDPOINTS

- Safety parameters (adverse events [including adjudicated cardiovascular events], laboratory data, and vital signs) assessed throughout the study.

Observation period

The observation of safety data will be as follows:

- **PRE-TREATMENT period**: The pre-treatment observation period is defined from the signed informed consent up to the first dose of double-blind IMP injection.
- **DOUBLE-BLIND TEAE period**: The double-blind TEAE observation period is defined as the time from the first dose of double-blind IMP to the last dose of double-blind IMP administration + 70 days (10 weeks) or the first administration in the OLTP, whichever comes first.
- **OPEN-LABEL TEAE period**: The open-label TEAE observation period is defined as the time from the first dose of open-label IMP injection to the last dose of open-label IMP injection + 70 days (10 weeks).
- **POST-TREATMENT period**: The Post-treatment observation period is defined as the time starting the day after the end of the TEAE period up to the end of the study (see definition in [Section 6.2](#)).

Note: Double-blind and open-label TEAE periods will be defined for the long-term safety at the time of the first analysis.

- **TEAE observation period for long-term safety of alirocumab (DBTP and OLTP):**
 - For 150 mg Q4W group and 150 mg Q2W group: The time from the first dose of double-blind IMP injection to the last dose of IMP injection (double-blind or open-label) + 70 days (10 weeks).
 - For placebo group: The time from the first dose of open-label IMP injection to the last dose of open-label IMP injection + 70 days (10 weeks).

9.2.1 Adverse events

- All AEs diagnosed by the Investigator, irrespective of the result of the adjudication for CV events, will be reported and described.
- All AEs will be coded to a "Lowest Level Term (LLT)", "Preferred Term (PT)", "High Level Term (HLT)", "High Level Group Term (HLGT)" and associated primary "System

Organ Class (SOC)" using the version of MedDRA (Medical Dictionary for Regulatory Activities) currently in effect at Sanofi at the time of the considered database lock.

- AEs of special interest (AESI) include events such as the following:
 - General allergic events (please refer to [Section 10.4.4.1](#) and [Section 10.6.2](#))
 - Local injection site reactions (using special e-CRF pages) (please refer to [Section 10.4.4.2](#) and [Section 10.6](#)).
 - Hemolytic anemia (using special e-CRF pages, see [Section 10.4.4.1](#), Appendix D).
 - Neurologic (including neurocognitive) adverse events (please refer to [Section 10.4.4.1](#) and Appendix D).
 - Ophthalmologic adverse events (using special e-CRF pages, see [Section 10.4.4.1](#) and Appendix D).
 - Skeletal muscle-related adverse events (using special e-CRF pages, see [Section 10.4.4.2](#)).
 - Asymptomatic or symptomatic overdose with IMP (see [Section 10.4.4.1](#), [Section 10.4.4.2](#), and Appendix D).
 - Pregnancy of female patient (including male patient's partner) (see [Section 10.4.4.1](#) and Appendix D).
 - ALT increase (see [Section 10.4.4](#) and [Section 10.4.5](#)).

Refer to [Section 10.4](#) and [Section 10.6](#) for details.

Adjudicated CV events include all CV AEs and CV procedures positively adjudicated (see [Section 10.6.3](#)) occurring from randomization until end of the study. The adjudication categories are the following:

- CHD death.
- Non-fatal MI.
- Fatal and non-fatal ischemic and/or hemorrhagic stroke.
- Unstable angina requiring hospitalization.
- Congestive heart failure requiring hospitalization.
- Ischemia-driven coronary revascularization procedure.

In addition, the classification of all deaths will occur.

Adverse event observation period:

- The AE observations are per the observation periods defined above.

Death observations period:

- The death observations are per the observation period defined above. In addition, “post-study” death includes all deaths reported after the end of the study (see definition of end of study period per patient in [Section 6.2.2](#)).

9.2.2 Laboratory safety variables,

The clinical laboratory data consist of urinalysis, hematology (red blood cell count, hemoglobin, red blood cell distribution width [RDW], reticulocyte count, hematocrit, platelets, white blood cell count with differential blood count), standard chemistry (glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, eGFR, uric acid, total protein, albumin, and γ -GT, haptoglobin, LDH), Hepatitis C antibody, liver panel (ALT, AST, ALP, and total bilirubin), and CPK.

Some additional safety laboratory parameters may be reflexively measured based on actual data (please refer to [Section 10.4.5](#)).

Clinical laboratory values will be analyzed after conversion into standard international units. International units will be used in all listings and tables.

9.2.3 Vital signs

- Vital signs include heart rate (HR), and systolic / diastolic blood pressure (BP) in sitting position.

9.2.4 Electrocardiogram variables

- Electrocardiogram (ECG) data will be assessed by the Investigator based on the automatic device reading.

9.3 OTHER ENDPOINTS

9.3.1 Anti-alirocumab antibodies assessments

Anti-alirocumab antibodies include the antibody status (positive / negative) and antibody titers. In patients with antibody positive status, neutralizing antibody status will be also included. The anti-alirocumab antibodies will be assessed throughout the study.

9.3.1.1 Sampling time

Serum samples for anti-alirocumab antibodies determination will be drawn periodically throughout the study as per schedule noted in the study flowchart of [Section 1](#). All scheduled samples will be obtained before IMP injection (pre-dose).



[REDACTED]

9.3.1.2 Sample procedure

Detailed procedure of sample preparation, storage, and shipment will be described in the specific laboratory manual which will be provided to study sites. Five (5) mL blood volume is to be collected for each anti-alirocumab antibodies samples.

9.3.1.3 Bioanalytical method

[REDACTED]

[REDACTED]

9.3.2 Hemoglobin A_{1c} (HbA_{1c})

The absolute change in HbA_{1c} (%) will be assessed from baseline (Week -3) to Week 12, Week 24 (Visit 13), Week 36, Week 48, and Week 64 (Visit 23, end of OLTP).

9.3.3 Pharmacokinetics

Pharmacokinetic variable include total serum alirocumab concentration. Total and free PCSK9 concentration will be measured from the same PK sample.

9.3.3.1 Sampling time

Serum sample for total alirocumab concentration will be collected before IMP (pre-dose) at Week 0 (randomization visit) and then at several visits until the end of the OLTP period, as per the study flow chart (see [Section 1.1](#)).

Exact date and time of last IMP administration and PK sampling are to be recorded.

9.3.3.2 *Pharmacokinetics handling procedure*

Detailed procedure of sample preparation, storage and shipment will be described in the specific laboratory manual which will be provided to sites. Five (5) ml blood volume is to be collected for each PK sample.

9.3.3.3 *Bioanalytical method*

[Redacted]

[Redacted]

9.3.4 Pharmacogenetic assessment

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

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[Redacted]

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[Redacted]

[Redacted]

[Redacted]

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[Redacted]

[REDACTED]

9.3.4.1 Optional stored DNA sample

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

9.3.5 Proportion of patients who are up-titration to alirocumab 150 mg Q2W

Proportion of patients who are up-titrated to alirocumab 150 mg Q2W during the OLTP will be calculated.

9.4 FUTURE USE OF SAMPLES

[REDACTED]

[REDACTED]

[REDACTED]

9.5 APPROPRIATENESS OF MEASUREMENTS

The efficacy and safety assessments used in the study are standard for the evaluation of patients with hypercholesterolemia (please refer to [Section 4](#) for details).

9.6 ASSESSMENT SCHEDULE

The assessment schedule will be as follows:

- **Patient assessments in the run-in period:**
 - On-site visits: Week -7 (run-in visit)
- **Patients assessments in the screening period:**
 - On-site visits: Week -3 (screening visit). Week -1 (Injection training visit)
- **Patient assessments in the DBTP:**
 - On-site visits: Week 0 (randomization visit), Week 2, Week 4, Week 6, Week 8, Week 10, and Week 12 (end of DBTP)
- **Patients assessment during the OLTP:**
 - On-site visits: Week 12 (Start of OLTP), Week 20, Week 24, Week 36, and Week 48.
 - Phone call visits: Week 16, Week 28, Week 32, Week 40, Week 44, Week 52, Week 56, and Week 60.

- On-site visits: Week 64 (end of the OLTP)

Note: Patients who will be up-titrated to alirocumab 150 mg Q2W from Week 24 and/or patients who prefer on-site IMP injection during OLTP will have additional on-site visits during the OLPT (see Section 10.1.4 and Section 10.1.4.4).

10 STUDY PROCEDURES

For all visits after Day 1/Week 0 (randomization visit), a timeframe of a certain number of days will be allowed. The window period for visits at Week 10, Week 12, Week 24, Week 36, and Week 48 are ± 3 days, at Week 64 is ± 5 days, and for all other site visits it is ± 7 days for the study period.

For all visits after Day 1/randomization visit, if one visit date is changed, then the next visit should take place according to the original schedule as outlined [Section 1.2](#).

Blood sampling:

The blood sampling for determination of lipid parameters (i.e., total-C, LDL-C, HDL-C, TG, non-HDL-C, Apo-B, Apo A-1, ratio Apo-B/Apo A-1, Lp[a]) should be performed in the morning, in fasting condition (i.e., overnight, at least 10 to 12 hours fast and refrain from smoking) for all site visits throughout the study. Alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the blood sampling are discouraged.

Note: If a patient is not in fasting conditions, the blood sample will not be collected and a new appointment will be given the day after (or as close as possible to this date) to the patients with instruction to be fasted (see above conditions).

Laboratory tests:

The laboratory data are collected in accordance with the study schedule in [Section 1.2](#) and forwarded to the central laboratory.

- Hematology,
- Chemistry,
- Lipid panel 1: TC, calculated LDL-C, HDL-C, TG, non-HDL-C
- Lipid panel 2: Apo-B, Apo A-1, Apo-B/Apo A-1ratio, and Lp(a)
- Liver panel: in case of total bilirubin values above the normal range, differentiation into conjugated and non-conjugated bilirubin will occur automatically,
- Creatine Phosphokinase (CPK),
- Hepatitis B surface antigen,
- Hepatitis C antibody: positive tests will be confirmed with reflexive testing,
- Serum pregnancy test
- Urine pregnancy test.

Urine samplings:

- Urinalysis – dipstick will be performed at the Central Laboratory and will assess for pH, specific gravity, and for the presence of blood, protein, glucose, ketones, nitrites, leukocyte esterase, urobilinogen, and bilirubin. The standard microscopic assessment will be conducted.

Notes: Any clinically relevant abnormal laboratory value should be immediately rechecked (whenever possible using the central laboratory) for confirmation before making any decision for the concerned patient. It should be documented as an AE/SAE as applicable. Please also refer to [Section 10.4.4.1](#).

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in Appendix E, and Appendix F, and should be followed by Investigators.

Other endpoint assessment methods:

All other blood parameters will also be measured by a Central Laboratory during the study (as per the schedule in [Section 1.2](#), on blood samples taken preferably in the morning in fasting condition (at least 10 to 12 hours fast and refrain from smoking). Alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the blood sampling are discouraged.

Glycemic parameters (HbA_{1c} and serum glucose) will be measured by a Central Laboratory, periodically throughout the study as per the schedule in [Section 1.2](#).

Pharmacokinetic samples (alirocumab concentration):

Serum samples for assessment of alirocumab concentration will be obtained periodically throughout double-blind trial period as per schedule note in study flowchart of [Section 1.2](#).

Blood sample will be collected before IMP injection for Week 0 (Visit 4), Week 4 (Visit 6), Week 8 (Visit 8), Week 10 (Visit 9), and Week 12 (Visit 10).

Note: It has to be made certain of blood sample collection before the IMP injection.

Serum Samples for anti-alirocumab antibody concentration:

Serum samples for assessment of anti-alirocumab antibody concentration will be obtained periodically throughout the study as per schedule note in study flowchart of [Section 1.2](#).

Blood sample will be collected before IMP injection for Week 0 (Visit 4), Week 4 (Visit 6), Week 12 (Visit 10), Week 24 (Visit 13), Week 36 (Visit 16), Week 48 (Visit 19), and Week 64 (Visit 23).

Note: It has to be made certain of blood sample collection before the IMP injection.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Physical examination:

A general physical examination should be performed at the time points indicated in the study schedule flowchart of [Section 1.2](#). If a new clinically significant abnormality or worsening from baseline is detected after randomization, then an AE should be reported and the patient should be considered for further clinical investigations and/or specialist consultation as per the Investigator's medical judgement.

Blood pressure / heart rate:

Blood pressure (BP) should be measured in sitting position under standardized conditions, approximately at the same time of the day, on the same arm, with the same apparatus (after the patient has rested comfortable in sitting position for at least 5 minutes). The BP measurement will be repeated 3 times. The obtained BP values are averaged and recorded in the e-CRF; both systolic and diastolic BP should be recorded. At the first screening visit, BP should be measured in both arms. The arm with the highest diastolic BP will be determined at this visit, and BP should be measured on this arm throughout the study. This highest BP value will be recorded in the e-CRF.

The heart rate (HR) will also be measured at the time of the measurement of BP.

Note: in case of high BP values at run-in or screening the Investigator is responsible for the optimization of the patient's treatment to achieve BP targets as defined by local guidelines (Japanese Society of Hypertension) or the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7).

Electrocardiogram:

The 12-lead electrocardiogram (ECG) should be performed after at least 10 minutes rest and in the supine position.

The electrodes should be positioned at the same place as much as possible, for each ECG recording throughout the study. The ECG will be interpreted locally by the Investigator. Any new and /or clinically significant changes in ECG parameters should be immediately rechecked for confirmation before making any decision for the concerned patient. Any clinically significant abnormality should be documented as an AE/SAE as applicable. Please also refer to [Section 10.4.2](#) (General guidelines for reporting adverse events). Each trace will be analyzed in comparison with the screening recorded trace. All ECG traces will be kept as source data.

Body weight and height:

Body weight should be obtained with the patient wearing undergarments or very light clothing and no shoes, and with an empty bladder. The same scale should be used throughout the study. The use of calibrated balance scales is mandatory. Self-reported weights are not acceptable; patients must not read the scales themselves. Height needs to be measured and self-reported heights are not acceptable.

10.1 VISIT SCHEDULE

10.1.1 Run-in period

Following the screening for inclusion / exclusion criteria as noted in [Section 7](#), patients not at stable doses of atorvastatin or other statins, unstable non-statin LMTs, or unstable diet therapy alone are enrolled (Week -7 / Visit 1). Stabilization of daily 5mg atorvastatin dosing, non-statin LMTs, or diet therapy will be carried out as necessary.

- On site visit
- Complete informed consent – the patients will receive complete information about the study both verbally and in writing. Written informed consent for the study must be obtained prior to any study related investigations.

Note: All AEs and SAEs will be collected from the time of informed consent signature and throughout the study until Week 64 (Visit 23).

- Obtain patient demography – age, gender, and race.
- Assess inclusion / exclusion criteria
- Obtain medical history (including menopausal status), surgical history, alcohol habits, and smoking habits.
- Obtain family medical history (including risk factors relating to premature CHD [before 55 years of age in a male and 65 years in a female first degree relative], allergy and type-2 diabetes).
- Document prior medication history within the previous 8 weeks, especially for lipid modifying therapies (including statin) and nutraceutical products that may affect lipids (e.g., omega-3 fatty acids, plant stanols such as found in Benecol, flax seed oil, psyllium).
- Perform physical examination

- Contact IVRS/IWRS for notification of entering the run-in period. Patient number will be allocated by the IVRS / IWRS. This patient number is composed of a 9-digit number containing the 3-digit country code, the 3-digit center code and the 3-digit patient chronological number (3-digit patient chronological number is 001 for the first patient screened in a center, 002 for the second patient screened in the same center).
- Review patient's diet. Patient should be on a diet following Japan Atherosclerosis Society Guideline or equivalent (see [Section 17](#), Appendix B).
- Record concomitant medication.
- Measure vital signs including HR and BP.
- Collect AEs/SAEs information from this point onward.
- An appointment will be given for the next visit.
- Provide instruction on diet.

10.1.2 Screening period

Only patients with stable 5 mg daily atorvastatin, non-statin LMTs, or diet therapy alone, who meet the inclusion criteria as noted in [Section 7.1](#) should be screened. The screening period will take place up to 3 weeks or 21 days (and as short as possible, upon receipt of laboratory eligibility criteria) prior to randomization / Day 1 visit (Week 0). The first screening visit (Week -3) can take place from 8 to 21 days before the randomization visit. If it is planned to have another designated person administer the injections to the patient during the study, then this person should be present at the injection training visit (Week -1).

Screening Visit (Visit 2 / Week -3 / Day -21 up to Day -8):

- On-site visit.
Complete informed consent if the patients skip the run-in period and directly enter the screening period. The patients will receive complete information about the study both verbally and in writing. Written informed consent for the study must be obtained prior to any study related investigations.
Note: All AEs and SAEs will be collected from the time of informed consent signature and throughout the study until Week 64 (Visit 23).
- Obtain patient demography - age, gender, and race of the patient can skip the run-in period.
- Assess inclusion / exclusion criteria.
- Obtain medical history (including menopausal status), surgical history, alcohol habits, and smoking habits.
- Obtain family medical history (including risk factors relating to premature CHD [before 55 years of age in a male and 65 years in a female first degree relative], allergy and type-2 diabetes).

- Document prior medication history within the previous 12 weeks, especially for lipid modifying therapy (including statin) and nutraceutical products that may affect lipids (e.g., omega-3 fatty acids, plant stanols such as found in Benecol, flax seed oil, psyllium).
- Perform physical examination
- Measurement of body weight and body height.
- Contact IVRS/IWRS for notification of screening. Patient number will be allocated by the IVRS/IWRS. This patient number is composed of a 9-digit number containing the 3-digit country code, the 3-digit center code and the 3-digit patient chronological number (3-digit patient chronological number is 001 for the first patient screened in a center, 002 for the second patient screened in the same center).

Review patient's diet. Patient should be on a diet following Japan Atherosclerosis Society Guideline or equivalent (see [Section 17](#), Appendix B).

- Record concomitant medication.
- Collect AEs/SAEs information.
- Measure vital signs including HR and BP.
- Perform 12-lead ECG recording
- Obtain fasting blood sample for:
 - Lipids: total-C, measured and/or calculated LDL-C, HDL-C, TG, non-HDL-C.
 - Hematology: CBC including hematocrit, RDW, reticulocyte count, hemoglobin, red blood cell count, white blood cell count with differential count and platelets.
 - Chemistry: glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, eGFR, uric acid, LDH, total protein, albumin, haptoglobin and γ -GT.
 - CPK.
 - Liver panel (ALT, AST, ALP, and total bilirubin).
 - Hepatitis B surface antigen and hepatitis C antibody tests.
 - Serum pregnancy test (women of childbearing potential only).
 - HbA_{1c}.
 - TSH.
- Urinalysis (dipstick including pH, specific gravity, the presence of blood, protein, glucose, ketones, nitrites, leukocyte esterase, urobilinogen, and bilirubin, and microscopic examination).

Note: All patients will be qualified for randomization based on the laboratory results LDL-C value obtained at this visit.

- An appointment will be given for the next visit (Week -1).

- Provide instruction on diet.
- If it is planned to have another designated person administer the injections to the patient during the study, then the person also should be present at the next visit (injection training visit at Week -1).

Injection training visit at Screening (Visit 3 / Week -1 / Day -7 ± 6):

Note: Injection training will be carried out if patient prefers self-IMP injection.

- On-site visit
- IVRS/IWRS contact for allocation of a batch number for training kit.
- Record batch number allocated in e-CRF.
- Injection training should be provided as outlined in [Section 8.1](#). The placebo for alirocumab should be administered by the patient or another designated person (such as spouse, relatives, etc.) at the study site under direct supervision of site staff with appropriate feedback.
- Measure vital signs including HR and BP.
- Collect AEs / SAEs information.
- If patient will undergo the second optional injection training with alirocumab placebo, then the following steps are required. However, if patient does not need a second optional training injection with alirocumab placebo then do not perform these steps:
 - Re-contact IVRS / IWRS for allocation of a second new batch number for a second training kit.
 - Record and dispense the second batch number allocated in e-CRF.
 - Dispense the second placebo training injection to the patient for self-administration.

Note: Further training with the scheduled double-blind / open-label IMP can be done at any time during the study as necessary. The required process for the training is described above.

- An appointment will be given for the next visit (Week -1 or 0).
- Remind patient to be in fasting conditions (i.e., overnight, at least 10 to 12 hours fast and refrain from smoking) for next visit. Also alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the next visit are discouraged.

10.1.3 Double-blind treatment period (Study Site Visits)

10.1.3.1 Randomization visit (Visit 4 / Week 0 / Day 1)

Note: Blood sample should be collected before IMP administration.

- On-site visit
- Assess Inclusion / Exclusion Criteria.

- Perform physical examination.
- Measure body weight.
- If the patient is confirmed eligible (and in fasting conditions), the Investigator will start the next study procedures:
 - IVRS/IWRS contact for randomization and allocation of a 7-digit treatment kit number according to the randomization list for the alirocumab injection. Investigator should never allocate a treatment kit number to a patient without contacting IVRS/IWRS.
 - Double-blind IMP kits dispensation as per treatment kit numbers provided by IVRS/IWRS along with schedule reminder. The patient injection instruction manual and treatment administration package should be provided.
 - The first double-blind IMP injection will take place at the study site, but only after the collection of the fasting blood samples and after the assessment of all evaluations planned at that visit.
 - The patients should be observed for at least 30 minutes after the IMP injection.
 - In case of self-IMP injection, close supervision, feedback and further training to be provided for IMP administration when necessary.
- Review patient's diet. Patient should be on a diet recommended by the Japan Atherosclerosis Society Guideline or equivalent.
- Record concomitant medication.
- Measure vital signs including HR and BP.
- Collect AEs / SAEs information.
- Obtain fasting blood sample for:
 - Lipids: total-C, measured and/or calculated LDL-C, HDL-C, TG, non-HDL-C, Apo-B, Apo A-1, Apo-B / Apo A-1 ratio, and Lp(a).
 - Hematology: CBC including hematocrit, RDW, reticulocyte count, hemoglobin, red blood cell count, white blood cell count with differential count and platelets.
 - Chemistry: glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, eGFR, uric acid, LDH, total protein, albumin, haptoglobin and γ -GT.
 - CPK.
 - Liver panel (ALT, AST, ALP, and total bilirubin).
- Urinalysis (dipstick and microscopy).
- Urine pregnancy test (WOCBP).
- Anti-alirocumab antibodies.
- Serum alirocumab concentration (PK).
- [REDACTED]

- [REDACTED]
- [REDACTED]
- Reminders:
 - An appointment will be given for the next study site visit (Week2).

Note: If patients (and/or their designated persons [such as a spouse, relative, etc.]), who prefer self-IMP administration and their self-IMP injection capabilities are accepted by the site Investigators based on the Injection training session(s) during the Screening visit (Week -1), patients will administer the IMP by themselves during the course of study. The self-IMP administration will be carried out during the DBTP under direct supervision of Investigators and the site staff so that both of patient and the site Investigator can confirm the self-IMP administration capability of the patient before the OLTP will start.

10.1.3.2 Visit 5 / Week 2 (Day 15 ± 7)

Note: No blood sampling is scheduled.

- On-site visit
- IVRS/IWRS contact for allocation of a treatment kit according to the randomization list.
- IMP administration and compliance check, and 30 minutes observation after the IMP administration.
- Record concomitant medication.
- Measure vital signs including HR and BP.
- Collect AEs/SAEs information.
- Reminders:
 - An appointment will be given for the next study site visit (Week 4).
 - Remind patient to be in fasting conditions (i.e., overnight, at least 10 to 12 hours fast and refrain from smoking) for next study site visit. Also alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the next study site visit are discouraged.

10.1.3.3 Visit 6 / Week 4 (Day 29 ± 7)

Note: Blood sample should be collected before IMP administration.

- On-site visit
- IVRS/IWRS contact for allocation of a treatment kit according to the randomization list.
- IMP administration and compliance check, and 30 minutes observation after the IMP administration.

- Record concomitant medication.
- Measure vital signs including HR and BP.
- Collect AEs / SAEs information.
- Obtain fasting blood sample for:
 - Lipids: total-C, measured and/or calculated LDL-C, HDL-C, TG, and non-HDL-C.
 - Liver panel (ALT, AST, ALP, and total bilirubin).
- Anti-alirocumab antibodies.
- Serum alirocumab concentration (PK).
- Reminders:
 - An appointment will be given for the next study site visit (Week 6).

10.1.3.4 Visit 7 / Week 6 (Day 43 ± 7)

Note: No blood sampling is scheduled.

- On-site visit
- IVRS/IWRS contact for allocation of a treatment kit according to the randomization list.
- IMP administration and compliance check, and 30 minutes observation after the IMP administration.
- Record concomitant medication.
- Measure vital signs including HR and BP.
- Collect AEs / SAEs information.
- Reminders:
 - An appointment will be given for the next study site visit (Week 8).
 - Remind patient to be fasting conditions (i.e., overnight, at least 10 to 12 hours fast and refrain from smoking) for next study site visit. Also alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the next study site visit are discouraged.

10.1.3.5 Visits 8 / Week 8 (Day 57 ± 7)

Note: Blood sample should be collected before IMP administration.

- On-site visit
- IVRS/IWRS contact for allocation of a treatment kit according to the randomization list.
- IMP administration and compliance check, and 30 minutes observation after the IMP administration.

- Record concomitant medication.
- Measure vital signs including HR and BP.
- Collect AEs / SAEs information.
- Obtain fasting blood sample for:
 - Lipids: total-C, measured and/or calculated LDL-C, HDL-C, TG, non-HDL-C, Apo-B, Apo A-1, Apo-B / Apo A-1ratio, and Lp(a).
 - Liver panel (ALT, AST, ALP, and total bilirubin).
- Serum alirocumab concentration (PK).
- Reminders:
 - An appointment will be given for the next study site visit (Week 10).
 - Remind patient to be fasting conditions (i.e., overnight, at least 10 to 12 hours fast and refrain from smoking) for next study site visit. Also alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the next study site visit are discouraged.

10.1.3.6 Visit 9 / Week 10 (Day 71 ± 3)

Note: Blood sample should be collected before IMP administration.

- On-site visit.
- IVRS/IWRS contact for allocation of a treatment kit according to the randomization list.
- IMP administration and compliance check, and 30 minutes observation after the IMP administration.
- Record concomitant medication.
- Measure vital signs including HR and BP.
- Collect AEs / SAEs information.
- Obtain fasting blood sample for:
 - Lipids: total-C, measured and/or calculated LDL-C, HDL-C, TG, non-HDL-C, Apo-B, Apo A-1, Apo-B / Apo A-1 ratio, and Lp(a).
- Serum alirocumab concentration (PK).
- Reminders:
 - An appointment will be given for the next study site visit.
 - Remind patient to be fasting conditions (i.e., overnight, at least 10 to 12 hours fast and refrain from smoking) for next study site visit. Also alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the next study site visit are discouraged.

10.1.3.7 Visit 10 / Week 12 (Day 85 ± 3): End of DBTP and Start of OLTP

Note: Blood sample should be collected before IMP administration.

- On-site visit.
- Perform physical examination.
- Measure body weight.
- IVRS / IWRS contact for allocation of a treatment kit according to the randomization list.
- Review patient's diet. Patient should be on a diet recommended by the Japan Atherosclerosis Society Guideline or equivalent.
- IMP administration and compliance check, and 30 minutes observation after the IMP administration.
- Record concomitant medication.
- Measure vital signs including HR and BP.
- Collect AEs/SAEs information.
- Record 12-lead ECG.
- Obtain fasting blood sample for:
 - Lipids: total-C, measured and/or calculated LDL-C, HDL-C, TG, non-HDL-C, Apo-B, Apo A-1, Apo-B / Apo A-1 ratio, and Lp(a).
 - Hematology: complete blood cell count (CBC) including hematocrit, red blood cell distribution width (RDW), reticulocyte count, hemoglobin, red blood cell count, white blood cell count with differential count and platelets. (Reticulocyte count and haptoglobin are measured only when hemoglobin is decrease with ≥ 1.5 g/dL from the baseline).
 - Chemistry: glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, eGFR, uric acid, lactate dehydrogenase (LDH), total protein, albumin, haptoglobin and γ -GT.
 - CPK.
 - Liver panel (ALT, AST, ALP, and total bilirubin).
- Urinalysis (dipstick and microscopy).
- Urine pregnancy test (WOCBP).
- HbA_{1c}
- Anti-alirocumab antibodies.
- Serum alirocumab concentration (PK).
- [REDACTED]

10.1.4 Open-label treatment period (Study Site Visits or Phone Call Visits)

10.1.4.1 Visit 10 / Week 12 (Day 85 ± 3): End of DBTP and Start of OLTP

Note: The OLPT starts from this visit and it is also the last visit of the DBTP. Blood sample should be collected before the IMP administration. The patient who performs self-IMP administration during the DBTP will continue the self-IMP administration at his/her home during the OLTP. Site staff has to carefully monitor the IMP administration compliance and AEs and SAEs collection through phone-visit call.

- On-site visit.
- Perform physical examination.
- Measure body weight.
- IVRS / IWRS contact for allocation of a treatment kit and the IMP will be supplied before Week 24 scheduled visit.

Note: All patients will be treated with alirocumab 150 mg Q4W from this time point.

- IMP administration and compliance check, and 30 minutes observation after the IMP administration.
- Review patient's diet. Patient should be on a diet recommended by the Japan Atherosclerosis Society Guideline or equivalent.
- Record concomitant medication.
- Measure vital signs including HR and BP.
- Collect AEs / SAEs information.
- Record 12-lead ECG.
- Obtain fasting blood sample for:
 - Lipids: total-C, measured and/or calculated LDL-C, HDL-C, TG, non-HDL-C, Apo-B, Apo A-1, Apo-B / Apo A-1 ratio, and Lp(a).
 - Hematology: CBC including hematocrit, RDW, reticulocyte count, hemoglobin, red blood cell count, white blood cell count with differential count and platelets. (Reticulocyte count and haptoglobin are measured only when hemoglobin is decrease with $\geq 1.5\text{g/dL}$ from the baseline).
 - Chemistry: glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, eGFR, uric acid, LDH, total protein, albumin, haptoglobin and γ -GT.
 - CPK.
 - Liver panel (ALT, AST, ALP, and total bilirubin).
- Urinalysis (dipstick and microscopy).
- Urine pregnancy test (WOCBP).

- HbA_{1c}
- Anti-alirocumab antibodies.
- Reminders:
 - An appointment will be given for the next study site visit (Week 16).

10.1.4.2 Visit 11 / Week 16 (Day 113 ± 7)

- Phone call visit (or IMP injection site visit).

Note: If the patient decides not to have self-IMP administration at his/her home, the patient can visit the site as the “IMP injection site visit” for IMP administration, and the site staff or the patient under direct site staff supervision can administer the IMP.

- IMP administration and compliance check, and 30 minutes observation after the IMP administration.
- Record concomitant medication.
- Collect AEs / SAEs information.
- Reminders:
 - An appointment will be given for the next study site visit (Week 20).
 - Remind patient to be fasting conditions (i.e., overnight, at least 10 to 12 hours fast and refrain from smoking) for the Week 20 scheduled study site visit. Also alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the next study site visit are discouraged.

10.1.4.3 Visit 12 / Week 20 (Day 141 ± 7)

Note: Blood sample should be collected before IMP administration.

- On-site visit.
- IMP administration and compliance check, and 30 minutes observation after the IMP administration.
- Record concomitant medication.
- Measure vital signs including HR and BP.
- Collect AEs/SAEs collection.
- Obtain fasting blood sample for:
 - Lipids: total-C, measured and/or calculated LDL-C, HDL-C, TG, and non-HDL-C.
- Reminders:
 - An appointment will be given for the next study site visit (Week 24).
 - Remind patient to be fasting conditions (i.e., overnight, at least 10 to 12 hours fast and refrain from smoking) for the Week 24 scheduled study site visit. Also alcohol

consumption within 48 hours and intense physical exercise within 24 hours preceding the next study site visit are discouraged.

10.1.4.4 Visit 13 / Week 24 (Day 169 ± 3)

Note: Blood sample should be collected before IMP administration.

- On-site visit.
- Perform physical examination.
- Measure body weight.
- IVRS/IWRS contact for allocation of a treatment kit and the IMP will be supplied before Week 36 scheduled study visit.

Note: Up-titration to the Q2W 150 mg alirocumab treatment will be automatically conducted based on the result of serum LDL-C level of Week 20 (see [Section 6.1](#) for details).

- IMP administration and compliance check, and 30 minutes observation after the IMP administration.
- Review patient's diet. Patient should be on a diet recommended by the Japan Atherosclerosis Society Guideline or equivalent.
- Record concomitant medication.
- Measure vital signs including HR and BP.
- Collect AEs / SAEs information.
- Record 12-lead ECG.
- Obtain fasting blood sample for:
 - Lipids: total-C, measured and / or calculated LDL-C, HDL-C, TG, non-HDL-C, Apo-B, Apo A-1, Apo-B / Apo A-1 ratio, and Lp(a).
 - Hematology: CBC including hematocrit, RDW, reticulocyte count, hemoglobin, red blood cell count, white blood cell count with differential count and platelets. (Reticulocyte count and haptoglobin are measured only when hemoglobin is decrease with ≥ 1.5 g/dL from the baseline).
 - Chemistry: glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, eGFR, uric acid, LDH, total protein, albumin, haptoglobin and γ -GT.
 - CPK.
 - Liver panel (ALT, AST, ALP, and total bilirubin).
- Urinalysis (dipstick and microscopy).
- Urine pregnancy test (WOCBP).
- HbA_{1c}

- Anti-alirocumab antibodies.
- Reminders:
 - An appointment will be given for the next scheduled study site visit (and/or IMP administration site visits).

Instruction of IMP administration in patients receiving Alirocumab 150 mg Q2W up-titration.

Patients, who receive up-titrated alirocumab 150 mg Q2W, can select self-IMP injection at their home / self-IMP injection at study site on scheduled site visits, site staff IMP injection at study site on scheduled site visits and IMP-injection site visits, or mixture of both if necessary. The alirocumab 150 mg Q2W administration will be performed on following timing after Week 24:

- Week 26 (Q2W only)
- Week 28 (Q2W and Q4W, Phone call / IMP injection site visit)
- Week 30 (Q2W only)
- Week 32 (Q2W and Q4W, Phone call / IMP injection site visit)
- Week 34 (Q2W only)
- Week 36 (Q2W and Q4W, Scheduled site visit)
- Week 38 (Q2W only)
- Week 40 (Q2W and Q4W, Phone call / IMP injection site visit)
- Week 42 (Q2W only)
- Week 44 (Q2W and Q4W, Phone call / IMP injection site visit)
- Week 46 (Q2W only)
- Week 48 (Q2W and Q4W, Scheduled site visit)
- Week 50 (Q2W only)
- Week 52 (Q2W and Q4W, Phone call / IMP injection site visit)
- Week 54 (Q2W only)
- Week 56 (Q2W and Q4W, Phone call / IMP injection site visit)
- Week 58 (Q2W only)
- Week 60 (Q2W and Q4W, Phone call / IMP injection site visit)
- and
- Week 62 (Q2W only)

Note: When the patients prefer self-IMP administration at their home, site staff has to make phone call visits on each IMP administration day to carry out IMP administration compliance check, 30 minutes post-IMP administration observation, and collection of AEs/SAEs information. If patients prefer IMP-administration at study sites, the site staff has to carry out IMP compliance check, 30 minutes post-IMP administration observation, and AEs/SAEs information collection after the IMP administration.

10.1.4.5 Visits 14 and 15 / Weeks 28 (Day 197 ± 7) and 32 (Day 225 ± 7)

- Phone call visit (or IMP injection site visits)
- IMP administration and compliance check, and 30 minutes observation after the IMP administration.
- Record concomitant medication.
- Collect AEs/SAEs collection.
- Reminders:
 - An appointment will be given for the next scheduled study site visit (and/or IMP administration site visits).
 - Remind patients to be fasting conditions (i.e., overnight, at least 10 to 12 hours fast and refrain from smoking) for the Week 36 study site visit. Also alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the next study site visit are discouraged.

10.1.4.6 Visit 16 / Week 36 (Day 253 ± 3)

Note: Blood sample should be collected before IMP administration.

- On-site visit.
- Perform physical examination.
- Measure body weight.
- IVRS / IWRS contact for allocation of a treatment kit and the IMP will be supplied before next scheduled visit (Week 48).
- IMP administration and compliance check, and 30 minutes observation after the IMP administration.
- Review patient's diet. Patient should be on a diet recommended by the Japan Atherosclerosis Society Guideline or equivalent.
- Record concomitant medication.
- Measure vital signs including HR and BP.
- Collect AEs / SAEs information.

- Obtain fasting blood sample for:
 - Lipids: total-C, measured and/or calculated LDL-C, HDL-C, TG, non-HDL-C, Apo-B, Apo A-1, Apo-B / Apo A-1 ratio, and Lp(a).
 - Hematology: CBC including hematocrit, RDW, reticulocyte count, hemoglobin, red blood cell count, white blood cell count with differential count and platelets. (Reticulocyte count and haptoglobin are measured only when hemoglobin is decrease with $\geq 1.5\text{g/dL}$ from the baseline).
 - Chemistry: glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, eGFR, uric acid, LDH, total protein, albumin, haptoglobin and γ -GT.
 - CPK.
 - Liver panel (ALT, AST, ALP, and total bilirubin).
- Urine pregnancy test (WOCBP).
- HbA_{1c}
- Anti-alirocumab antibodies.
- Reminders:
 - An appointment will be given for the next study site visit (scheduled visit and/or IMP administration site visits).

10.1.4.7 Visits 17 and 18 / Weeks 40 (Day 281 \pm 7) and Week 44 (Day 309 \pm 7)

- Phone call visit (or IMP injection site visits).
- IMP administration and compliance check, and 30 minutes observation after the IMP administration.
- Record concomitant medication.
- Collect AEs / SAEs information.
- Reminders:
 - An appointment will be given for the next scheduled study site visit (and/or un-scheduled site visits only for the IMP injection).
 - Remind patients to be fasting conditions (i.e., overnight, at least 10 to 12 hours fast and refrain from smoking) for the Week 48 study site visit. Also alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the next study site visit are discouraged.

10.1.4.8 Visit 19 / Week 48 (Day 337 \pm 3)

Note: Blood sample should be collected before IMP administration.

- On-site visit.

- Perform physical examination.
- IVRS / IWRS contact for allocation of a treatment kit and the IMP will be supplied until the final administration (until Week 60 for Q4W, or until Week 62 for up-titrated Q2W).
- IMP administration and compliance check, and 30 minutes observation after the IMP administration.
- Review patient's diet. Patient should be on a diet recommended by the Japan Atherosclerosis Society Guideline or equivalent.
- Record concomitant medication.
- Measure vital signs including HR and BP.
- Collect AEs / SAEs information.
- Obtain fasting blood sample for:
 - Lipids: total-C, measured and/or calculated LDL-C, HDL-C, TG, and non-HDL-C.
 - Hematology: CBC including hematocrit, RDW, reticulocyte count, hemoglobin, red blood cell count, white blood cell count with differential count and platelets.
 - Chemistry: glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, eGFR, uric acid, LDH, total protein, albumin, haptoglobin and γ -GT. (Reticulocyte count and haptoglobin are measured only when hemoglobin is decrease with ≥ 1.5 g/dL from the baseline).
 - CPK.
 - Liver panel (ALT, AST, ALP, and total bilirubin).
- Urine pregnancy test (WOCBP).
- HbA_{1c}
- Anti-alirocumab antibodies.
- Reminders:
 - An appointment will be given for the next study site visit (scheduled visit and/or un-scheduled site visits only for IMP administration).

10.1.4.9 Visits 20, 21, and 22 / Weeks 52 (Day 365 \pm 7), Week 56 (Day 393 \pm 7), and Week 60 (Day 421 \pm 7)

- Phone call visit (or IMP injection site visit).
- IMP administration and compliance check, and 30 minutes observation after the IMP administration.

Note: The last IMP administration of patients with Q4W will be on Week 60, and the last IMP administration of patients with up-titrated Q2W will be on Week 62.

- Record concomitant medication.

- Collect AEs / SAEs information.
- Reminders:
 - An appointment will be given for the next scheduled study site visit (and/or IMP injection site visits).
 - Remind patients to be fasting conditions (i.e., overnight, at least 10 to 12 hours fast and refrain from smoking) for the Week 64 study site visit. Also alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the next study site visit are discouraged.

10.1.4.10 Visit 23 / Week 64 (Day 449 ± 5) / End of OLTP

Note: Blood sample should be collected before IMP administration.

- On-site visit
- Perform physical examination.
- Measure body weight.
- IVRS / IWRS contact to document the end of the treatment for all patients.
- Review patient's diet. Patient should be on a diet recommended by the Japan Atherosclerosis Society Guideline or equivalent.
- Record concomitant medication.
- Measure vital signs including HR and BP.
- Collect AEs / SAEs information.
- Record 12-lead ECG.
- Obtain fasting blood sample for:
 - Lipids: total-C, measured and/or calculated LDL-C, HDL-C, TG, non-HDL-C, Apo-B, Apo A-1, Apo-B / Apo A-1 ratio, and Lp(a).
 - Hematology: CBC including hematocrit, RDW, reticulocyte count, hemoglobin, red blood cell count, white blood cell count with differential count and platelets. (Reticulocyte count and haptoglobin are measured only when hemoglobin is decrease with ≥ 1.5 g/dL from the baseline).
 - Chemistry: glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, eGFR, uric acid, LDH, total protein, albumin, haptoglobin and γ -GT.
 - CPK.
 - Liver panel (ALT, AST, ALP, and total bilirubin).
 - Hepatitis C antibody tests.
- Urinalysis (dipstick and microscopy).

- Urine pregnancy test (WOCBP).
- HbA_{1c}
- Anti-alirocumab antibodies.

10.2 DEFINITION OF SOURCE DATA

Evaluations that are reported in the e-CRF must be supported by appropriately signed identified source documentation related but not limited to the following:

- Agreement, date, and signature of informed consent mentioning the study identification.
- Patient identification, last participation in a clinical trial, medical history, associated disease, and data related to the studied pathology.
- Contraception methods for women of childbearing potential.
- Previous and concomitant medication (including the LMT).
- Study identification.
- Treatment number, dates of administration.
- Dates of visit and assessments including the examination report.
- Vital signs, height, body weight.
- Faxed Central Laboratory reports (dated and signed by the Principal Investigator or sub-Investigator).
- IWRS confirmation report (screening, screen failure, randomization, treatment reallocation, discontinuation, end of DBTP, end of study, unblinding if applicable).
- ECG records signed and dated.
- AEs and follow-up:
 - In case of SAE, the site should file in the source document at least copies of the hospitalization reports and any relevant examination reports documenting the follow-up of the SAE.
- Date of premature study discontinuation (if any) and reasons.

Source documentation may be found in the followings:

- Patient's identity
- Medical history
- Hospital records
- Nursing notes
- Physician's notes

- Laboratory reports

10.3 HANDLING OF PATIENT TEMPORARY OR PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

The IMP administration should be continued whenever possible. In case the IMP administration is interrupted, it should be determined whether the interruption is temporarily; permanent IMP discontinuation should be the last resort. Any IMP discontinuation should be fully documented in the CRF. In any case, the patient should remain in the study as long as possible.

10.3.1 Temporary treatment discontinuation with investigational medicinal product(s)

Temporary treatment discontinuation may be considered by the Investigator because of suspected AEs. Reinitiation of treatment with the IMP will be done under close and appropriate clinical/and or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the IMP(s) in the occurrence of the concerned event was unlikely and if the selection criteria for the study are still met (refer to [Section 7.1](#) and [7.2](#)).

All treatment interruption duration should be recorded by the Investigator in the appropriate e-CRF screens when considered as confirmed.

Treatment interruption is defined as one or more scheduled injections that are not administered to the patient as described by the Investigator.

10.3.2 Permanent treatment discontinuation with investigational medicinal product(s)

Permanent treatment discontinuation (also referred to as treatment discontinuation) is any treatment discontinuation associated with the definitive decision from the Investigator or the patient not to re-expose the IMP at any time.

10.3.3 List of criteria for permanent treatment discontinuation

The patients may withdraw from treatment with the IMP if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision. Patient withdrawal from the study treatment or study should be avoided as much as possible. All efforts should be made to document the reasons for treatment discontinuation and this should be documented in the e-CRF.

Patients should discontinue the IMP administration for the following reasons:

- Pregnancy, intention for pregnancy, or no longer with effective contraceptive method of birth control (in treated female patients).
- Acute injection reaction of clinical concern.
- SAE (or non-serious but severe in intensity) of hypersensitivity reaction considered related to IMP.
- At patient's request.

- If, in the Investigator's opinion, continuation with the administration of the IMP would be detrimental to the patient's well-being.
- Intercurrent condition that requires discontinuation of the IMP (e.g., laboratory abnormalities, please refer to decision tree Appendix F).
- At the specific request of the Sponsor.
- Any code breaking requested by the Investigator.
- Patient receives double-blind treatment prior to randomization.

10.3.4 Handling of patients after permanent treatment discontinuation

- *During DBTP:* Patients who prematurely discontinue study treatment (regardless of reason) will have an unscheduled visit with assessments originally planned at the end of study visit (Week 64, it should take place within 5 days of treatment discontinuation, if possible). The patients will also continue the study and assessments originally planned until the end of DBTP visit (Week 12, V10), and will be followed up until recovery or stabilization of any AE to be followed up as specified in this protocol. If patients prematurely discontinue the study treatment and deny the study continuation, the patients will have an unscheduled visit with assessments originally planned at the end of study visit (Week 64, it should take place within 5 days of treatment discontinuation, if possible) and also the patients will be followed up until recovery or stabilization of any AE to be followed up as specified in this protocol.
- *During OLTP:* Patients, who prematurely discontinue study treatment (regardless of the reasons) during OLTP, will have an unscheduled visit with assessments originally planned at the end of study visit (Week 64, it should take place within 5 days of treatment discontinuation, if possible). The patient, at a minimum, will be followed up until recovery or stabilization of any AE to be followed up as specified in this protocol.

All definitive discontinuation of study treatment should be recorded by the Investigator in the appropriate screens of the e-CRF and in the patient's medical records when considered as confirmed. IWRS should be notified when a patient prematurely discontinues the study treatment.

For patients randomized and not treated, all efforts should be done to perform Week 12 visits in order to collect the lipid data.

10.3.5 Procedure and consequence for patient withdrawal from study

The patients may withdraw from the study, before study completion if they decide to do so, at any time and irrespective of the reason. If possible, the patients should be assessed using the procedure defined above.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the e-CRF and in the patient's medical records (with, in this medical records, at least date of withdrawal and reasons for) when considered as confirmed.

For patients who fail to return to the site, the Investigator should make the best effort to re-contact the patient (e.g., contacting patient's family or private physician, review available registries or health care database), and to determine his/her health status, including at least his/her vital status. Attempts to contact such patients must be documented in the patient's records (e.g., number of times and dates of attempted telephone contact, receipt for sending a registered letter).

The statistical analysis plan (SAP) will specify how these patients lost to follow-up for their primary endpoints will be considered.

Patients who have withdrawn from the study cannot be re-randomized (treated) in the study. Their inclusion and treatment number must not be reused.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

An **adverse event (AE)** is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

10.4.1.2 Serious adverse event

A **serious adverse event (SAE)** is any untoward medical occurrence that at any dose:

- Results in death, or
- Is life-threatening, or

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- Is a medically important event.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention (i.e., specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:

- Intensive treatment in an emergency room or at home for:
 - Allergic bronchospasm
 - Blood dyscrasias (i.e., agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc.),
 - Convulsions (seizures, epilepsy, epileptic fit, absence, etc.).
- Development of drug dependence or drug abuse.
- ALT >3 x ULN + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN.
- Suicide attempt or any event suggestive of suicidality.
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling).
- Bullous cutaneous eruptions.
- Cancers diagnosed during the study or aggravated during the study.
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study.

10.4.1.3 Adverse event of special interest (AESI)

An adverse event of special interest (AESI) is an AE (serious or non-serious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. The AESIs may be added or removed during the study by protocol amendment.

10.4.2 General guidelines for reporting adverse events

All AEs, regardless of seriousness or relationship to IMP / NIMP, spanning from the signature of the informed consent form until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding page(s) or screen(s) of the CRF.

Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP or by the study procedure(s).

The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, in order to ensure the safety of the patients or until death. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be

requested by the monitoring team up to as noticed by the Sponsor. When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.

Laboratory, vital signs, or ECG abnormalities are to be recorded as AEs only if:

- Symptomatic and/or,
- Requiring either corrective treatment or consultation, and/or.
- Leading to IMP discontinuation or modification of dosing, and/or,
- Fulfilling a seriousness criterion, and/or
- Defined as an AESI with immediate notification.

See [Section 17](#), Appendix D for summary of AE reporting guidelines.

10.4.3 Instructions for reporting serious adverse events

In the case of occurrence of an SAE, the Investigator must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send a notification to the Sponsor after approval of the Investigator within the e-CRF or after standard delay.
- SEND (within 24 hours, preferably by fax or e-mail) the signed and dated corresponding page(s) from the CRF to the Sponsor's name, fax number and e-mail address appear in the clinical trial protocol. Care must be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the Sponsor. For laboratory result, include the laboratory normal range.
- All further data updates should be recorded in the e-CRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status, etc.) should be sent (by fax or e-mail) to the monitoring team within 24 hours of acknowledge. In addition, every effort must be made to further document any SAE that is fatal or life threatening within a week (7 days) following the initial notification.
- A back-up plan will be used (using paper flow) when the e-CRF system does not work.

Any SAE brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the IMP with a reasonable possibility, should be reported to the Sponsor.

10.4.4 Guideline for reporting adverse events of special interest

10.4.4.1 Reporting of adverse events of special interest (AESI) with immediate notification

For AESI, the Sponsor must be informed immediately (i.e., within 24 hours), as per SAEs notification described in [Section 10.4.3](#), even if not fulfilling a seriousness criterion, using the corresponding screens in the e-CRF.

- Allergic events:
 - General allergic drug reactions and/or local injection site reactions deemed to be allergic (or have an allergic component) that require consultation with other physician(s) for further evaluation of hypersensitivity/allergy, as per the Investigator's medical judgement or as per [Section 10.6.2](#), should be reported as an AESI with immediate notification.
 - All general allergic events, and all injection site reactions having an allergic component or deemed to be allergic, require completion of the specific e-CRF screen (see [Section 10.6.2](#)), regardless of requirements for immediate reporting.
- Hemolytic anemia (See Appendix F)
 - If there is a decrease in hemoglobin and reflexive testing as per [Section 17](#), Appendix F suggesting hemolysis, then report this as AESI with immediate notification. Special e-CRF screen will need to be completed.
- Pregnancy
 - Pregnancy occurring in a female patient or the partner of a male patient included in the clinical trial. Pregnancy will be recorded as an AESI with immediate notification in all cases. It will be qualified as an SAE only if it fulfills the SAE criteria.
 - In the event of pregnancy of a female patient included in the clinical trial, IMP should be discontinued.
 - The follow-up of the pregnancy will be mandatory until the outcome has been determined.
- Symptomatic Overdose with IMP/NIMP
 - An overdose (accidental or intentional) with the IMP/NIMP is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic injection counts).
 - An overdose with the IMP/NIMP is defined as at least twice of the intended dose within the intended therapeutic interval (e.g., 2 or more injections from the double-blind treatment kit are administered in <7 calendar days).
 - The symptomatic overdose events should be reported using the corresponding screens in the e-CRF using the Term "symptomatic overdose (accidental or intentional)". The circumstances of the overdose should be clearly specified in the verbatim and symptoms, if any, entered on separate AE forms.
 - The patient should be monitored and appropriate symptomatic treatment instituted.

- Neurological (and Neurocognitive) Events:
 - Neurologic (and Neurocognitive) Events that require additional examinations / procedures and/or referral to a specialist should be reported as an AESI with immediate notification (see [Section 17](#), Appendix D).
- Ophthalmologic Events:
 - Ophthalmologic Events that require additional examinations/procedures and/or referral to a specialist should be reported as an AESI with immediate notification.

10.4.4.2 Reporting of adverse events of special interest without immediate notification

For these AEs, the Sponsor does not have to be informed immediately, unless meeting seriousness criterion.

- ALT ≥ 3 ULN (if baseline ALT <ULN) or ALT ≥ 2 times the baseline value (if baseline ALT \geq ULN) (Please refer [Section 17](#), Appendix E, Increase in ALT).
- Asymptomatic overdose with IMP/NIMP.
 - An overdose (accidental or intentional) with the IMP/NIMP is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic injection counts).
 - An overdose with the IMP/NIMP is defined as at least twice of the intended dose within the intended therapeutic interval (e.g., 2 or more injections from the double-blind treatment kit are administered in <7 calendar days).
 - Asymptomatic overdose events should be reported using the corresponding screens in the e-CRF using the Term “asymptomatic overdose (accidental or intentional)”. The circumstances (i.e., accidental or intentional) and the lack of symptoms (i.e., asymptomatic) should be clearly specified in the verbatim.
 - The patient should be monitored if necessary.

Local injection site reaction (See [Section 10.6.1](#))

- Local injection site reactions that are considered as non-allergic events should be further characterized by evaluation of the related symptoms comprising injection site reactions such as but not limited to redness, pain, etc. (See [Section 17](#), Appendix H). Special e-CRF screens will need to be completed. If such AEs do not occur, then do not report the individual components of the reaction but rather the term “local injection site reactions”, the individual components being described in the specific e-CRF screen.
- General allergic reactions or local injection site reactions deemed to be allergic or with allergic component not referred for consultation with another physician.
 - All allergic events will need to have allergy specific e-CRF screens completed (see [Section 10.6.2](#)), regardless of requirements for immediate reporting.

- Skeletal muscle-related events:
 - Any AEs related to skeletal muscle abnormalities, including myalgia, muscle spasms and stiffness, musculoskeletal discomfort and stiffness, back pain, muscular weakness, and muscle fatigue.
- Neurological (and Neurocognitive) events:
 - Any AEs related to neurologic (and neurocognitive) abnormalities with the exception of those requiring additional examinations/procedures and/or referral to a specialist (see [Section 10.4.4.1](#)).
- Ophthalmologic events:
 - Any AEs related to ophthalmologic abnormalities with the exception of those requiring additional examinations/procedures and/or referral to a specialist should be reported

10.4.5 Guidelines for management of specific laboratory abnormalities

Laboratory abnormalities with pre-specified monitoring should be monitored, documented, and managed according to the flowchart shown in [Section 17](#), Appendix E and Appendix F.

The following laboratory abnormalities should be monitored, documented, and managed according to the related flow chart in protocol appendices:

- Neutropenia.
- Thrombocytopenia.
- Increase in ALT.
- Acute renal insufficiency.
- Increase in CPK and suspicion of rhabdomyolysis.

Decrease in hemoglobin (defined as ≥ 1.5 g/dL) (see [Section 10.4.5.1](#), Hemoglobin decrease).

10.4.5.1 Hemoglobin decrease

See [Section 17](#), Appendix F.

At the first post-randomization occurrence of a hemoglobin (Hb) measurement decrease by ≥ 1.5 g/dL as compared to the randomization visit Hb measurement, then the Central Lab will reflexively measure haptoglobin using specimens already obtained at the same time point for which the hemoglobin and reticulocyte decrease has been detected. The Central Lab will then provide the results of the reticulocyte count, haptoglobin, LDH, and indirect bilirubin (reflexively measured only if the total bilirubin >ULN) to the Investigator.

- If the following patterns of abnormalities are noted:
 - Reticulocyte count >Central Lab's upper limit of the reference range (also referred to as ULN)

AND,

- Haptoglobin <Central Lab's lower limit of the reference range (also referred to as LLN)

AND,

- LDH >ULN

AND,

- Indirect bilirubin >ULN (only if the total bilirubin >ULN)

The patient should be referred to a hematologist. The hematologist should obtain a peripheral blood smear and anti-erythrocyte antibodies (direct and indirect) by Coombs test. Further investigations are at the discretion of the hematologist.

- If the results are normal or the pattern of abnormality is something other than that described above, then Investigator should exercise his/her medical judgement in the interpretation of the results, necessity of workup of the decrease in hemoglobin or referral to a hematologist.
- If as second hemoglobin measurement demonstrating a further decrease ≥ 1 g/dL from the last available value is observed, even if the previous work-up was negative, the same investigations can be repeated and a hematology consultation can be requested at the discretion of the Investigator or at the Sponsor's request.

10.4.6 Summary of adverse event reporting instructions

Section 17 Appendix D shows the summary of the reporting instructions of adverse events described above.

10.5 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner all SAEs that are both unexpected and at least reasonably related to the IMP (Suspected unexpected serious adverse reaction, SUSAR), to the Health Authorities, independent ethics committees (IECs) / institutional review boards (IRBs) as appropriate and to the Investigators.

In addition, the Sponsor will report in an expedited manner all SAEs that are expected and at least reasonably related to the IMP to the Authorities, according to local regulations.

In this study, some AEs are considered related to the underlying condition and thus will not be considered unexpected as given in the IB.

Any other AE not listed as an expected event in the IB will be considered as unexpected. Unblinding may also be performed by the Sponsor for some SAEs that are both related and unexpected in order to conform to regulatory reporting requirements.

The Sponsor will report all safety observations made during the conduct of the trial in the CSR.

10.6 SAFETY INSTRUCTIONS

10.6.1 Local tolerability (Local Injection Site Reactions)

In case the Investigator or the patient recognizes any signs of local intolerability, then this should be treated and followed up as per the Investigator's medical judgement. See [Section 17](#), Appendix H for further information.

AEs that are obviously not of allergic origin (e.g., local injection site reactions) should only be recorded on the Local Injection Site Reaction Complementary Form. However, injection site reactions which progress/expand/worsen/etc., should be evaluated and General Allergic Reaction Complementary Form should be completed.

10.6.2 Allergic adverse events

Specific e-CRF screens are to be filled in to assess allergic reactions or allergic-like reactions that may occur during the clinical studies conducted with alirocumab. Sometimes transient injection site reactions, irritant in nature, may occur, requiring no intervention and being of dubious significance. These reactions would not be considered to be allergic reactions. Adverse events that may constitute an allergic reaction (e.g., generalized itch, nasal itch, swelling at injection site, flushing, hives, swelling at lips, eyes, face, tongue, hands, feet, lump in throat, difficulty to swallow, hoarseness, change in pitch of voice, incapacity to speak, wheezing, chest tightness, stridor, etc.) should be considered to be reported on the General Allergic Reaction and/or Local Injection Site Reaction Complementary Form.

Adverse events that are obviously not of allergic origin (e.g., local injection site reactions related to mechanics of injection) should only be recorded on the Local Injection Site Reaction Complementary Form. However, injection site reactions that progress/expand/worsen/etc. should be evaluated as recommended in [Section 10.6.2.1](#) and the General Allergic Reaction Complementary Form should be completed.

The IMP should be immediately interrupted (temporarily discontinued) if there is a suspicion of an allergic event related to IMP. See [Section 10.3.1](#) for further information on treatment interruption and [Section 10.3.3](#) for criteria for permanent treatment discontinuation.

10.6.2.1 Allergic adverse events with cutaneous involvement

AEs with cutaneous involvement which are obviously of allergic origin or injection site reactions which progress/expand/worse/etc., should be evaluated by dermatologist as soon as possible, and preferably within one week of the study site first becoming aware of the event.

The Investigator should evaluate the patient for possible etiologies (new medications, etc.) and extra-cutaneous symptoms and signs. An unscheduled Central Laboratory assessment for hematology, chemistry, Liver panel, PK, and anti-alirocumab antibodies should be obtained. If

possible, the investigator will take pictures of the skin lesions in order to provide the patient with the abnormal skin images for the dermatologist's visit. If the photographs of skin lesions are obtained, then the photocopies should be kept as source documents with may later be collected by the Sponsor. The Investigator will provide summary of the patient's case, reason for consultation, and information being requested to the consulting dermatologist.

A full consultation report should be sent by the dermatologist to the Investigator. The full report should contain, at a minimum, the following information; 1) a detailed description of the rash (such as the morphology [lesion type], shape of individual lesions, arrangement of multiple lesions [e.g., scattered, grouped, linear, etc.], distribution, color, consistency, presence of pruritus or pain, and other clinical signs); 2) Findings of the skin biopsy (including histopathology and immunofluorescence) if it was deemed necessary as per the dermatologist's or Investigator's medical judgement; and 3) the results of this investigation with, if applicable, a specific diagnosis of the AE. The Investigator will fax the full report and the corrected AE form if necessary, to the Sponsor within 24 hours.

10.6.2.2 Acute allergic reactions of IMP injection

See also [Section 10.4](#).

Acute allergic reactions of IMP injection (which are considered under the category of general allergic reactions) is defined as any AE that occurs during or shortly after injection of the IMP (characterized by but not limited to hypotension, bronchoconstriction, urticaria, edema, angioedema, nausea, vomiting). Emergency equipment and medication for the treatment of these potential adverse effects (e.g., antihistamines, bronchodilators, saline, corticosteroids, acetaminophen, and epinephrine) must be available for immediate use for the injections at the study site.

Patients will be observed at the investigational site for at least 30 minutes following the injection that takes place at the randomization visit. Patients should be treated symptomatically if any AE is observed. Patients are to remain at the study site until any acute injection reaction is assessed as stable, per the Investigator's discretion.

General Allergic Reaction and/or Local Injection Site Reaction Complementary Form will have to be completed.

10.6.3 Cardiovascular events and all deaths

The following suspected or confirmed CV events that occur from randomization until end of the study should have a corresponding specific e-CRF page +/- adjudication package prepared (as per the study site manual) and will be submitted to the CEC:

- Myocardial infarction.
- Congestive heart failure requiring hospitalization.
- Cerebrovascular events (e.g., stroke, transient ischemic attack, intracranial hemorrhage, ischemia or bleeding of spine or retina).

- Unstable angina requiring an emergency room visit or requiring / prolonging hospitalization.
- All coronary revascularization procedures (e.g., PCI and CABG).
- All deaths (including CHD death).

All suspected or confirmed CV events should also be reported as SAEs. For coronary revascularization procedures, please note that a medical or surgical procedure should not be reported as an adverse event, but rather, the reason for the procedure should be reported as the adverse event term (e.g., unstable angina leading to PCI should be reported as 'unstable angina' instead of 'PCI').

10.6.4 Laboratory alert related to two consecutive calculated LDL-C <25 mg/dL (0.65 mmol/L)

The process described in this section and Appendix I includes specific assessment and monitoring in all patients, who achieve two consecutive calculated LDL-C values <25 mg/dL (0.65 mmol/L) (any time after randomization). The safety and benefit below this level has not yet been established. An independent external academic physician(s) (also known as independent physician) and a dedicated DMC member will be the coordinators of this specific monitoring.

Please see Appendix I for an outline of the process.

Sites may receive an alert related to 2 consecutive calculated LDL-C <25 mg/dL (0.65 mmol/L) during the study. These alerts may pertain to true alerts or sham alerts. A sham alert is one in which the patients does not meet the criteria related to 2 consecutive calculated LDL-C <25 mg/dL (0.65 mmol/L) (see Appendix I for criteria for an alert). Sham alert are necessary in order to maintain the integrity of the blind (See [Section 8.3.1.1](#)).

Once an alert is received, the Investigator should follow the recommended steps as outlined below:

- Call the patient as soon as possible to inquire about interval occurrence of AEs.
- Decide whether the patient should be requested to rapidly have an unscheduled site visit, or assessment could be done at the next scheduled visit.
- At the site visit, plan for the following, based on Investigator's medical judgment:
 - Assess the need for conducting clinical investigations, arranging specialist consultation(s) as needed, and any relevant additional work-up.
 - Assess the need for study treatment temporary or permanent discontinuation, or continuation.
 - Regardless of action taken regarding study treatment, the patient should continue the study as per Section 10.3.

10.7 ADVERSE EVENTS MONITORING

All events will be managed and reported in compliance with all applicable regulations, and included in the final CSR.

11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

The study is expected to enroll approximately 159 patients.

Two pairwise comparisons will be performed (alirocumab 150 mg Q4W versus placebo and alirocumab 150 mg Q2W vs. placebo). In order to handle multiple comparisons Bonferroni adjustment will be used, i.e., the alpha level for each comparison is 0.025 to obtain an overall study alpha level of 0.05.

A sample size of 38 patients in the ITT population (19 in alirocumab group and 19 in placebo group) will have 90% power to detect a difference of 30% in mean percentage change in calculated LDL-C in any pairwise comparison with a 0.025 two-sided significance level and assuming a common standard deviation of 25%.

As a result, the total sample size needed for efficacy will be 57 patients (19 in each of the two alirocumab arms and 19 in the placebo arm).

The sample size is also considered in order to obtain long-term safety data. A sample size of 159 patients (randomization ratio 1: 1: 1, i.e., 53 in alirocumab 150 mg Q4W, 53 in alirocumab 150 mg Q2W, and 53 in placebo) will allow having long-term open-label safety data. With this sample size, 100 patients are expected to be exposed to alirocumab for a minimum of 12 months providing that the proportion of drop out in the entire study duration (from randomization to Week 64) is 36%, which is obtained using exponential distribution with the same hazard as that of 30% dropout rate within 12 months. Moreover, with 100 patients treated with alirocumab for at least 12 months, AEs with a rate ≥ 0.03 will be detected with 95% probability.

Therefore, 159 patients (53 in alirocumab 150 mg Q4W, 53 in alirocumab 150 mg Q2W, and 53 in placebo) will be needed to evaluate both efficacy and safety.

11.2 DISPOSITION OF PATIENTS

Screened patients are defined as any patient who met the inclusion criteria and signed the informed consent.

Randomized patients consist of all patients, with a treatment kit number allocated and recorded in IWRS database, and regardless of whether the treatment kit was used or not.

Patients treated without being randomized or treated with a double-blind or open-label treatment kit before the randomization will not be considered as randomized and will not be included in any analysis population.

For any patient randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be assessed separately.

The safety experience of patients treated and not randomized will be reported separately.

11.3 ANALYSIS POPULATIONS

Randomized population includes any patients who have been allocated to a randomized treatment regardless of whether the treatment kit was used or not.

11.3.1 Efficacy populations

The primary efficacy analysis population will be the intent-to-treat (ITT population, as defined below.

11.3.1.1 Intent-to-treat (ITT) population

The ITT population is defined as the randomized population who has an evaluable primary endpoint. The primary efficacy endpoint is evaluable when both of the following conditions are met:

- Availability of at least 1 value for calculated LDL-C before the first dose of double-blind IMP (i.e., baseline).
- Availability of at least 1 value for calculated LDL-C within one of the following analysis windows: Week 4, Week 8, Week 10, and Week 12.

Patients in the ITT population will be analyzed according to the treatment group allocated by randomization.

11.3.1.2 Modified intent-to-treat (mITT) population

The mITT population is defined as the randomized population who took at least one dose or part of dose of the double-blind IMP injection and has an evaluable primary efficacy endpoint during the efficacy double-blind treatment period. The primary efficacy endpoint will be considered evaluable when both of the following conditions are met:

- Availability of at least 1 value for calculated LDL-C before the first dose of double-blind IMP (i.e., baseline).
- Availability of at least 1 value for calculated LDL-C within one of the following analysis window: Week 4, Week 8, Week 10, and Week 12 during the efficacy double-blind treatment period.

The efficacy double-blind treatment period will be defined as:

- The time period from the first double-blind IMP injection up to 21 days after the last double-blind IMP injection (i.e., up to Week 12).

Patients in the mITT population will be analyzed according to the treatment group allocated by randomization.

11.3.2 Safety population

The safety population consists of the randomized population who actually received at least one dose or partial dose of IMP. The safety population will be analyzed according to the treatment actually received.

In addition:

- Non-randomized but treated patients will not be part of the safety population, but their safety data will be presented separately.
- Randomized patients for whom it is unclear whether they took the study medication will be included in the safety population as randomized.
- For patients receiving IMP from more than one treatment group during the trial, the treatment group allocation for as-treated analysis will be the one to which the patient was treated with the longest duration.

11.3.3 Other analysis population

The anti-alirocumab antibody analysis will be performed on all treated patients (safety population) with a blood sample on Week 0 (baseline) and at least one evaluable blood sample for antibodies post first double-blind IMP injection.

The PK analysis will be performed on all treated patients (safety population) with at least one evaluable blood sample for PK post the first double-blind IMP injection.



11.4 STATISTICAL METHODS

Statistical methods are briefly described here and will be detailed in the SAP of the study.

11.4.1 Extent of study treatment exposure and compliance

The extent of study treatment exposure and compliance will be assessed and summarized by actual treatment received within the safety population.

11.4.1.1 Extent of investigational medicinal product exposure

The total exposure will be assessed by:

- Duration of IMP exposure in weeks defined as: (last dose of double-blind IMP injection date – first dose of double-blind IMP injection date + 14 days) / 7, regardless of unplanned intermittent discontinuations.
- The number (n) and percentage (%) of patients with an up-titration from alirocumab 150 mg Q4W to alirocumab 150 mg Q2W.

11.4.1.2 Compliance

Compliance will be assessed using the injection frequency defined for each patient as the average number of days between 2 injections, that is: (last injection date - first injection date) / (number of injections - 1) and will be summarized descriptively (N, Mean, SD, Median, Min and Max).

11.4.2 Analyses of efficacy endpoints

The analysis of the primary efficacy endpoint and the secondary efficacy endpoints up to Week 12 will have been conducted at the time of first analysis only. [REDACTED]

11.4.2.1 Analysis of primary efficacy endpoint(s)

See also [Section 9.1.1](#).

The primary efficacy endpoints, percentage change in calculated LDL-C from baseline to Week 12 will be analyzed in the ITT population using mixed-effect model with repeated measures (MMRM) approach. All post-baseline data available within Week 4, Week 8, Week 10, and Week 12 analysis windows will be used (on-treatment and off-treatment through Week 12) and missing data will be accounted for by the MMRM model.

The model will include the fixed categorical effects of treatment group (placebo, alirocumab 150 mg Q4W, and alirocumab 150 mg Q2W), time point (Week 4, Week 8, Week 10, and Week 12), stratification factor of statin (Yes/No), treatment-by-time point interaction and statin-by-time point interaction, as well as the continuous fixed covariates of baseline calculated LDL-C value, and baseline value-by-time point interaction.

This model will be run using SAS Mixed procedure with an unstructured correlation matrix to model the within-patient errors. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Denominator degrees of freedom will be estimated using Satterthwaite's approximation. This model will provide baseline adjusted least-squares means (LS means) estimates at Week 12 for each treatment group with their corresponding standard errors (SEs). Let μ_0 and μ_1 be the population means of the percentage change from the baseline in calculated LDL-C at Week 12 under placebo and alirocumab, respectively. The

hypothesis that will be tested is “ $H_0: \mu_0 = \mu_1$ ” versus $H_1: \mu_0 \neq \mu_1$ ”. Each alirocumab arm will be compared to placebo group (at significance level of 2.5%) using appropriate contrasts, and the 97.5% confidence interval (CI) of the difference will be provided.

Subgroup analyses will be performed in order to assess the consistency of the treatment effect within stratification factor of statin (Yes/No).

11.4.2.2 Analyses of secondary efficacy endpoints

See also [Section 9.1.2](#).

For the key secondary efficacy endpoints (defined in [Section 9.1.2.1](#)) and the other secondary efficacy endpoints (described in [Section 9.1.2.2](#)), [REDACTED] and analyses will be performed in the ITT population or mITT population, depending on the specified estimand.

A hierarchical procedure will be used for each pairwise comparison to control the type I error and to handle for multiple endpoints. If the primary endpoint analysis is significant at the 2.5% alpha level, the key secondary endpoints will be tested sequentially at the 0.025 level, using the order defined in [Section 9.1.2.1](#). Comparisons of alirocumab 150 mg Q2W versus placebo, and alirocumab 150 mg Q4W versus placebo will be processed in parallel.

Continuous endpoints anticipated to have a normal distribution

Continuous secondary endpoints anticipated to have a normal distribution [i.e., lipids other than Lp(a) and TG], will be analyzed using the same MMRM model as for the primary endpoint with the continuous fixed covariates of corresponding baseline value and baseline value-by-time point interaction.

The percentage change in calculated LDL-C from baseline to averaged Week 10 - 12 will be analyzed using an appropriate contrast statement (assigning a weight of 0.5 for the two time points) from the MMRM model.

Continuous endpoints anticipated to have non-normal distribution

Continuous secondary endpoints anticipated to have a non-normal distribution [i.e., Lp(a) and TG] will be analyzed using multiple imputation approach for handling of missing values followed by robust regression model(38) (i.e., ROBUSTREG SAS procedure with M-estimation option) with treatment group and stratification factor of statin as main effect and corresponding baseline value(s) as covariate. Missing values will be addressed using a multiple imputation approach which will be described in the SAP. The variables in a multiple imputation model will at least include the same variables as used in the robust regression model. The treatment group combined means will be provided with respective SE estimates. The combined mean difference between each alirocumab group and placebo group will be provided with the SE, 97.5% confidence interval and p-value.

Binary endpoints

Binary secondary endpoints will be analyzed using multiple imputation approach for handling of missing values followed by logistic regression. In the data dependent case that the logistic regression method is not applicable (e.g., the response rate is zero in 1 treatment arm and thus the maximum likelihood estimate may not exist), the Last Observation Carried Forward (LOCF) approach would be used for handling of missing values and a stratified exact conditional logistic regression would be performed to compare treatment effects between each alirocumab group and placebo group.

Comparison of alirocumab 150 mg Q4W vs. alirocumab 150 mg Q2W

For a descriptive purpose, the difference of percentage change of calculated LDL-C between baseline and Week 12, and between the two alirocumab arms Q4W and Q2W will also be derived, with a 95% CI.

11.4.2.3 Multiplicity considerations

The multiplicity appears in two kinds in this study, due to the presence of the 2 arms of alirocumab 150 mg Q4W and 150 mg Q2W that are compared with placebo, and due to the multiple key secondary efficacy endpoints.

The overall type I error will be controlled at 0.05 by performing each pairwise test (alirocumab 150 mg Q4W vs. placebo, and alirocumab 150 mg Q2W vs. placebo) for the main efficacy endpoint at the 0.025 level.

Then, a hierarchical procedure will be used for each pairwise comparison to control the type I error and to handle multiple endpoints. If the primary endpoint analysis is significant at the 2.5% alpha level, the key secondary efficacy endpoints will be tested sequentially at the 0.025 level, using the order defined in [Section 9.1.2.1](#). Hierarchical procedure for comparisons of alirocumab 150 mg Q4W versus placebo, and alirocumab 150 mg Q2W versus placebo will be processed separately.

No further adjustments will be made for other secondary endpoints for which p-values will be provided for descriptive purpose only (no claim).

In addition, no further adjustment will be made for multiple analyses (i.e., first and second analyses), since the primary efficacy endpoint and the key secondary efficacy endpoints up to Week 12 will have been conducted at the time of first analysis only. [REDACTED]

11.4.3 Analyses of safety data

See also [Section 9.2](#).

The summary of safety results will be presented by treatment group. No formal inferential testing will be performed. Summaries will be descriptive in nature.

All safety analyses will be performed on the Safety population using the following common rule:

- The baseline value is defined generally as the last available value before the first double-blind IMP injection. For analyses of changes from baseline for laboratory and vital signs parameters, baseline of the last available value before double-blind or open-label IMP injection may be considered.

Safety analyses will be conducted using data of the DBTP. Besides, safety analyses using data of the DBTP and the OLTP (from the first double-blind IMP injection for alirocumab 150 mg Q4W group and alirocumab 150 mg Q2W group, and from the first open-label IMP injection for placebo group) will be conducted to evaluate long-term safety.

The following definitions will be applied to laboratory parameters and vital signs:

- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests and vital signs.
- The PCSA criteria will determine which patients had at least 1 PCSA during the TEAE period, taking into account all evaluations performed during the TEAE period, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the PCSA percentage.

Adverse events (AE) definition:

- **Pre-treatment AEs** are AEs that develop, worsen, or become serious during the PRE-TREATMENT period.
- **Treatment-emergent AEs (TEAEs)** are AEs that develop, worsen, or become serious during TEAE period.
- **Post-treatment AEs** are AEs that develop, worsen, or become serious during the POST-TREATMENT period.

Drug-induced liver injury:

Liver function tests, namely ALT, AST, ALP, and total bilirubin, are used to assess possible drug induced liver toxicity. The proportion of patients with PCSA values at any post-baseline visit by baseline status will be displayed by treatment group for each parameter. A graph of distribution of peak values of ALT versus peak values of total bilirubin will also be presented. Note that the ALT and total bilirubin values will be presented on a logarithmic scale. The graph will be divided into 4 quadrants with a vertical line corresponding to 3 x ULN for ALT and a horizontal line corresponding to 2 x ULN for total bilirubin.

The incidence of liver-related AEs will be summarized by treatment group. The selection of preferred terms will be based on standardized MedDRA query (SMQ) Hepatic disorder.

11.4.3.1 Adverse events

See also [Section 9.2.1](#).

Adverse event incidence tables will present by SOC (sorted by internationally agreed order), HLGT, HLT, and PT sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of patients experiencing an AE. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group.

Adverse event incidence table will be provided by treatment group for all types of TEAEs: all TEAEs, all treatment emergent AESI (defined with a PT or a prespecified grouping), all treatment emerged SAEs, and all TEAEs leading to permanent treatment discontinuation.

If any clinically significant signal is detected and requires further characterization, or AE of clinical interest, exploration of time to onset will be performed for these selected TEAEs.

Death:

The following deaths summaries will be generated:

- Number (%) of patients who died by the study period (TEAE, on-study, post-study) summarized on the safety population by treatment received.
- Death in non-randomized patients, or randomized and not treated patients.
- TEAE leading to death (death as an outcome on the AE CRF page as reported by the Investigator) by primary SOC, HLGT, HLT, and PT showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT.

Adjudicated CV events:

The number and percentage of patients experiencing a positively adjudicated CV event will be presented by treatment group overall and by category of adjudication.

11.4.3.2 Laboratory data and vital signs

See also [Section 9.2.2](#) and [Section 9.2.3](#).

The summary statistics (including mean, median, Q1, Q3, SE, minimum and maximum) of all laboratory variables and all vital signs parameters (raw data and changes from baseline) will be calculated for each time point, last and worst value assessed during the treatment period and presented by treatment group. For selected parameters, mean changes from baseline with the corresponding SE will be plotted over time (at same time points) in each treatment group.

The incidence of PCSAs at any time during the TEAE period (on-treatment PCSAs) will be summarized by treatment group whatever the baseline level and/or according to the following baseline categories:

- Normal / missing.
- Abnormal according to PCSA criterion or criteria.

For laboratory parameters for which PCSA criterion is not defined, similar table(s) using the normal range could be provided.

Hepatitis C test:

The number and percentage of patients with an observed seroconversion for Hepatitis C test will be provided by treatment group.

11.4.3.3 Analyses of other endpoints

See also [Section 9.3](#).

All analyses for other endpoints will be performed on the Safety population unless otherwise specified. The baseline value is defined as the last available value before the first double-blind IMP.

The number and percentage of patients with 2 consecutive calculated LDL-C <25 mg/dL [REDACTED] will be provided by treatment group.

The antibody status (positive / negative), antibody titers, and neutralizing antibody status will be summarized by treatment group and time point using descriptive statistics. [REDACTED]

Further details will be provided in SAP.

11.4.4 Analyses of pharmacokinetic and pharmacodynamic variables

See also [Section 9.3.3](#).

Serum total alirocumab concentrations, total and free PCSK9 concentrations will be summarized by treatment group and time point using descriptive statistics. Serum concentration time profiles will be provided by treatment group. [REDACTED]

Further details will be provided in SAP.

11.5 TIMING OF ANALYSES

The analysis will be conducted in two steps. In Japan, data up to 24 weeks are required for the drug application.

11.5.1 First step: Efficacy and safety analyses using data up to 24 weeks after randomization (including 12 weeks double-blind).

The first analysis will be conducted when all patients have been randomized and have at least all their data up to Week 24 (including 12 weeks DBTP and 12 weeks OLTP) collected and validated, and will consist in the final analysis of the primary and secondary efficacy endpoints up to Week 12 ([Section 9.1](#)). [REDACTED]

[REDACTED] The safety analysis will be performed on all safety data up to Week 24 collected and validated.

The results of the first analysis will not be used to change the conduct of the ongoing study in any aspect. Since primary and key secondary efficacy endpoints analysis up to Week 12 will have been analyzed concluded in all patients at the time of this first analysis, the significance level will be 0.025 for each comparison between the alirocumab group and placebo group.

11.5.2 Second step: Long-term safety and efficacy exploratory analysis

The second analysis will be conducted at the end of the study with all data including the data of the OLTP, and will consist in the final analysis of the safety endpoints and exploratory efficacy assessment during the OLTP.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, delegated Investigator staff and sub-Investigator, in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, and the ICH guidelines for good clinical practice (GCP), all applicable laws, rules and regulations.

This clinical trial will be recorded in a free, publicly accessible, internet-based registry, no later than 21 days after the first patient enrollment, in compliance with applicable regulatory requirements and with Sanofi public disclosure commitments.

12.2 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the patient of all pertinent aspects of the clinical trial including the written information giving approval/favorable opinion by the Ethics Committee (IRB / IEC). All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient's participation in the clinical trial, the written ICF should be signed, name filled in and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written ICF will be provided to the patient.

If genotyping is conducted, patient's consent for genotyping is required and signed written informed consent for genotyping must be obtained prior to genotyping.

The ICF and the optional written ICF for pharmacogenetics used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate Ethics Committee (IRB / IEC) for approval/favorable opinion.

Prior to collection of blood for pharmacogenetics, the optional pharmacogenetic ICF (written) should be signed, name filled in, and personally dated by the patient or by the subject's legally acceptable representative, and by person who conducted the informed consent discussion. A copy of the signed and dated written optional ICF will be provided to the subject.

12.3 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

As required by local regulation, the Investigator or the Sponsor must submit this clinical trial protocol to the appropriate Ethics Committee (IRB / IEC), and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the Chairman with IRB / IEC composition.

The clinical trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, informed consent form, Investigator's Brochure, Investigator's curriculum vitae [CV], etc.) and the date of the review should be clearly stated on the written (IRB / IEC) approval/favorable opinion.

IMP will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the Sponsor.

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the IRB / IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB / IEC should be informed as soon as possible. It should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the Investigator's Brochure will be sent to the IRB / IEC.

A progress report is sent to the IRB / IEC at least annually and a summary of the clinical trial's outcome at the end of the clinical trial.

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator(s) and delegated Investigator staff undertake(s) to perform the Clinical Trial in accordance with this Clinical Trial Protocol, ICH guidelines for GCP and the applicable regulatory requirements.

The Investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the CRF, Discrepancy Resolution Form [DRF] or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

If any circuit includes transfer of data particular attention should be paid to the confidentiality of the patient's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as sub-Investigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All sub-Investigators shall be appointed and listed in a timely manner. The sub-Investigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

13.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this clinical trial is responsible to regulatory health authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the CRFs. Thus, the main duty of the monitoring team is helping the Investigator and the Sponsor to maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial.

At regular intervals during the clinical trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review study progress, Investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AESI documentation and reporting, AE documentation, IMP allocation, patient compliance with the IMP regimen, IMP accountability, concomitant therapy use and quality of data.

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH guidelines for GCP, the monitoring team must check the CRF entries against the source documents, except for the pre-identified source data directly recorded in the CRF. The ICF will include a statement by which the patient allows the Sponsor's duly authorized personnel, the Ethics Committee (IRB / IEC), and the regulatory authorities to have direct access to original medical records which support the data on the CRFs (e.g., patient's medical file, appointment books, original laboratory records, etc.). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

13.4 USE AND COMPLETION OF CASE REPORT FORMS (CRFS) AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate CRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the e-CRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the Sponsor as soon as they are entered in the e-CRF.

The computerized handling of the data by the Sponsor when available in the e-CRF may generate additional requests (DRF) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the e-CRF.

13.5 USE OF COMPUTERIZED SYSTEMS

The complete list of computerized system used for the study is provided in a separate document which is maintained as the Sponsor and Investigator study files.

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

The latest copy of the curriculum vitae describing the experience, qualification and training of each Investigator and sub-Investigator will be dated and provided to the Sponsor prior to the beginning of the clinical trial.

14.2 RECORD RETENTION IN STUDY SITES

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The Investigator should retain the study documents at least 15 years after the completion or discontinuation of the clinical trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the clinical trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

14.3 CONFIDENTIALITY

[REDACTED]

[REDACTED]

14.4 PROPERTY RIGHTS

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

14.5 DATA PROTECTION

The patient's personal data, which are included in the Sponsor database, shall be treated in compliance with all applicable laws and regulations.

When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

The Sponsor also collects specific data regarding Investigator as well as personal data from any person involved in the study which may be included in the Sponsor's databases, shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations.

14.6 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IECs / IRBs or regulatory authorities in countries requiring this document.

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, GCP and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors / inspectors to have direct access to his/her study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all issues / problems found during the audit or inspections.

14.8 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

14.8.1 By the Sponsor

Premature discontinuation of the study is decided by the Sponsor in the following case:

- If the information on the product leads to doubt as to the benefit/risk ratio.

Premature close-out of a site is decided by the Sponsor in the following cases:

- If the Investigator has received all IMP, means and information necessary to perform the clinical trial from the Sponsor and has not included any patient after a reasonable period of time mutually agreed upon.
- In the event of breach by the Investigator of a fundamental obligation under this agreement, including but not limited to breach of the clinical trial protocol, breach of the applicable laws and regulations, or breach of the ICH guidelines on GCP.
- If the total number of patients are included earlier than expected.

In any case the Sponsor will notify the Investigator of its decision by written notice.

14.8.2 By the Investigator

The Investigator must notify 30 days in advance the Sponsor of his/her decision to prematurely close-out her/his site and give the reason in writing.

In all cases (decided by the Sponsor or by the Investigator), the appropriate Ethics Committee(s) (IRB / IEC) and Health Authorities should be informed according to applicable regulatory requirements.

14.9 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a CSR and to provide a summary of study results to the Investigator.

14.10 PUBLICATIONS AND COMMUNICATIONS

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made parts of this clinical trial protocol.

The Investigator should not implement any deviation from, or changes of the clinical trial protocol without agreement by the Sponsor and prior review and documented approval / favorable opinion from the IRB / IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to clinical trial patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this clinical trial protocol.

Any amendment to the clinical trial protocol requires written approval / favorable opinion by the IRB / IEC prior to its implementation, unless there are overriding safety reasons.

In some instances, an amendment may require a change to the informed consent form. The Investigator must receive an IRB / IEC approval/favorable opinion concerning the revised informed consent form prior to implementation of the change and patient signature should be re-collected if necessary.

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