



CLINICAL TRIAL PROTOCOL

TITLE: A Randomized, Open-Label, Parallel Group Study to Evaluate the Efficacy and Safety of Alirocumab versus Usual Care in Patients with Type 2 Diabetes and Mixed Dyslipidemia at High Cardiovascular Risk with Non-HDL-C Not Adequately Controlled with Maximally Tolerated Statin Therapy

Praluent/Alirocumab/SAR236553

STUDY NUMBER: LPS14354

STUDY NAME: ODYSSEY DM - DYSLIPIDEMIA

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CLINICAL TRIAL SUMMARY

COMPOUND: SAR236553 (Praluent/Alirocumab)	STUDY No: LPS14354 STUDY NAME: ODYSSEY DM-Dyslipidemia
TITLE	A Randomized, Open-Label, Parallel Group Study to Evaluate the Efficacy and Safety of Alirocumab versus Usual Care in Patients with Type 2 Diabetes and Mixed Dyslipidemia at High Cardiovascular Risk with Non-HDL-C Not Adequately Controlled with Maximally Tolerated Statin Therapy
INVESTIGATOR/TRIAL LOCATION	Multinational-Multicenter
PHASE OF DEVELOPMENT	3b/4
STUDY OBJECTIVE(S)	<p>Primary objective:</p> <ul style="list-style-type: none"> To demonstrate the superiority of alirocumab in comparison with usual care in the reduction of non-high-density lipoprotein cholesterol (non-HDL-C) after 24 weeks of treatment in patients with Type 2 diabetes and mixed dyslipidemia at high cardiovascular (CV) risk with non-HDL-C not adequately controlled with maximally tolerated statin therapy. <p>Secondary objective(s):</p> <ul style="list-style-type: none"> To demonstrate whether alirocumab is superior in comparison with usual care in its effects on other lipid parameters at Weeks 12 and 24 (ie, low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), total cholesterol (Total -C), lipoprotein a (Lp[a]), high-density lipoprotein cholesterol (HDL-C), triglycerides (TGs), triglyceride rich lipoproteins (TGRLs), apolipoprotein A-1 (Apo A-1), apolipoprotein C-III (Apo C-III), lipid subfractions by nuclear magnetic resonance (NMR) spectroscopy (ie, LDL particle size and LDL, very low-density lipoprotein (VLDL), HDL, intermediate-density lipoprotein (IDL) particle number) To demonstrate the superiority of alirocumab in comparison with usual care in the reduction of non-HDL-C at Week 12. To assess changes in diabetes related parameters in patients randomized to alirocumab vs. usual care treatment over a period of 24 weeks To demonstrate the safety and tolerability of alirocumab  To evaluate changes in proprotein convertase subtilisin kexin type 9 (PCSK9) concentrations at Weeks 12 and 24 To evaluate the development of anti-alirocumab antibodies To demonstrate the superiority of alirocumab versus fenofibrate therapy on non-HDL-C and other lipid parameters
STUDY DESIGN	<p>This is a Phase 3b/4 randomized, open-label, parallel group study to assess the efficacy and safety of alirocumab administered by subcutaneous (SC) injection versus usual care in patients with Type 2 diabetes and mixed dyslipidemia at high CV risk with non-HDL-C not adequately controlled with maximally tolerated statin therapy.</p> <p>Patients will be taking a stable, maximum dose/regimen of statin that is</p>

	<p>tolerated by the patient without other lipid modifying therapies at baseline. Patients may be on no statin if unable to tolerate statin therapy as judged by the investigator.</p> <p>Randomization will be unbalanced (2:1, alirocumab:usual care). The study will be a multinational, multicenter study.</p> <p>Usual care includes the option to continue on the maximum dose of statin that is tolerated by the patient without the addition of a new lipid modifying therapy (LMT) at randomization, or the initiation of either ezetimibe, fenofibrate, omega-3 fatty acids, or nicotinic acid at randomization for the remainder of the 24-week treatment period. Initiation of usual care treatment investigational medicinal product (IMP) should start as soon as possible after randomization, but no later than 7 days from the day of randomization.</p> <p>The Investigator will select the most appropriate LMT for the patient prior to randomization (consisting of either no additional LMT but continuing on maximum tolerated statin, ezetimibe, fenofibrate, omega-3 fatty acids or nicotinic acid) and enter this information into the interactive voice response system (IVRS). If the patient is randomized to open label alirocumab, the Investigator will not institute the LMT option that was selected and entered into IVRS but instead treat the patient with open label alirocumab. If the patient is randomized to usual care (non-alirocumab), the Investigator will initiate treatment with the LMT option that was selected and entered into IVRS, as applicable, in addition to continuing the patient on the maximum tolerated dose of statin.</p> <p>Randomization will be stratified by the Investigator's selection of usual care therapy prior to randomization (for example, the intent to prescribe fenofibrate, intent to prescribe ezetimibe, etc). This will help ensure balanced treatment groups with patients' characteristics as homogenous as possible. Recruitment of patients will complete when ~420 patients have been randomized.</p> <p>Patients randomized to open label alirocumab will continue on the maximum dose of statin that is tolerated by the patient and will administer alirocumab SC with a starting dose of 75 mg every 2 weeks (Q2W) for 12 weeks with a blinded uptitration to alirocumab 150 mg Q2W at week 12 if the non-HDL-C at the week 8 visit is ≥ 100 mg/dL (2.59 mmol/L). Patients who have a non-HDL-C < 100 mg/dL (2.59 mmol/L) at the Week 8 visit will continue with alirocumab 75 mg Q2W until the end of the treatment period.</p> <p>No changes during the course of the study will be made to the dose of LMT administered as part of the usual care arm except for nicotinic acid for which the Investigator may prescribe at randomization a scheduled/gradual dose titration in order to allow for the maximum dose to be achieved based on patient tolerability or except if needed for any usual care LMT for the safety of the patient, based on the Investigator's judgment.</p> <p>The study consists of:</p> <ul style="list-style-type: none">• A screening period of up to 3 weeks;• An open-label treatment period (OLTP) of 24 weeks;• A safety observation period of 8 weeks. <p>A phone visit will take place at Week 32 in order to document any adverse event(s) that might occur between Weeks 24 to 32.</p> <p>Patients should have been previously instructed on a cholesterol lowering diet prior to screening. During the study, the Investigator may reinforce diet</p>
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	<p>recommendations according to local/regional guidelines. Patients should be receiving antihyperglycemic treatment in accordance with local/ regional standards of care. Changes to antihyperglycemics should be limited and made only in circumstances where it is clinically needed.</p> <p>Statin dose and dose regimen should be stable throughout the entire study duration including for 4 weeks prior to the screening period and from screening to the end of the open label treatment period.</p> <p>The data on lipid parameters from blood samples will be masked after randomization. No attempts should be made by the Investigator or patient to have the patient's lipid values independently evaluated after randomization until after the Week 24 visit, except for the safety of the patient as per the Investigator's judgment. At the end of the OLTP (Week 24 visit), the Investigator will continue to manage the patient's lipids in accordance with standard practice. Any lipid values after randomization (eg, if done for patient safety) should be redacted in the source documents and not shared with the Sponsor.</p> <p>Duration of study treatment will be 24 weeks with the last injection of open label alirocumab administered at Week 22. The treatments prescribed in the usual care arm will be administered for 24 weeks. From the Week 24 visit onward, the Investigator will continue to manage the patient's lipids in accordance with standard practice.</p> <p>Patients will visit the study site at Weeks -3, 0, 8, 12, 20, and 24 with lab work at each visit; in addition a phone visit is scheduled at Weeks 4 and 32. Week 8 is a critical visit because it will be the only scheduled visit where a non-HDL-C value for up-titration will be available.</p>
<p>STUDY POPULATION</p> <p>Main selection criteria</p>	<p>Inclusion criteria:</p> <p>I 01. Patients with Type 2 diabetes and mixed dyslipidemia not adequately controlled with a stable, maximum dose/regimen of statin that is tolerated by the patient* for at least 4 weeks prior to the screening visit (Week -3) without other LMT.</p> <p>*Note: The maximum dose/regimen of statin that is tolerated by the patient is the highest registered dose/regimen tolerated by the patient based on the judgment of the Investigator. Patients not able to be on a maximum dose/regimen of statin should be treated with the dose of statin which is considered appropriate for the patient as per the Investigator's judgment or concerns. Some examples of acceptable reasons for a patient taking a lower statin dose include, but are not limited to: adverse effects on higher doses, advanced age, low body mass index (BMI), regional practices, local prescribing information, concomitant medications. Patients may be on alternate day dosing of statin as long as the dose is consistently taken (eg, dose every Monday, Wednesday, Friday, etc). Concomitant treatment with more than 1 statin is not permitted. Patients who have documented statin intolerance, as judged by the Investigator, and who are no longer on statin therapy as a result will also be eligible for the study. The reason(s) for not being on a maximum dose/regimen of statin (including statin intolerance) will need to be documented in the case report form.</p> <p>I 02. Patients ≥ 18 years of age or legal age of majority at screening visit whichever is greater.</p> <p>I 03. Documented history of atherosclerotic cardiovascular disease (ASCVD) or at least one additional CV risk factor.</p> <p>Notes:</p>

	<p>Atherosclerotic cardiovascular disease (ASCVD) includes: coronary heart disease (CHD) and CHD risk equivalents (PAD, ischemic stroke)</p> <p>History of CHD includes at least one of the following:</p> <ul style="list-style-type: none"> • acute myocardial infarction (MI), • silent MI, • unstable angina, • coronary revascularization procedure (eg, percutaneous coronary intervention [PCI] or coronary artery bypass graft surgery [CABG]) • clinically significant CHD diagnosed by invasive or noninvasive testing (such as coronary angiography, stress test using treadmill, stress echocardiography, or nuclear imaging). <p>CHD risk equivalents include at least one of the following:</p> <ul style="list-style-type: none"> • Documented peripheral arterial disease (PAD) (one of the following criteria [a, b, or c] must be satisfied): <ol style="list-style-type: none"> a) Current intermittent claudication (muscle discomfort in the lower limb that is both reproducible and produced by exercise and relieved by rest within 10 minutes) of presumed atherosclerotic origin TOGETHER WITH ankle-brachial index ≤ 0.90 in either leg at rest, OR b) History of intermittent claudication (muscle discomfort in the lower limb that is both reproducible and produced by exercise 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. • Documented previous ischemic stroke with a focal ischemic neurological deficit that persisted more than 24 hours, considered as being of atherothrombotic origin. Computed tomography or magnetic resonance imaging must have been performed to rule out hemorrhage and non-ischemic neurological disease. <p>Cardiovascular risk factors include at least one of the following:</p> <ul style="list-style-type: none"> • hypertension (established on antihypertensive medicine) • current cigarette smoker • age ≥ 45 years for men and ≥ 55 years for women • history of micro/macroalbuminuria • history of diabetic retinopathy (preproliferative or proliferative) • family history of premature CHD (in father or brother before 55 years of age; in mother or sister before 65 years of age) • low HDL-C (male < 40 mg/dL [1.0 mmol/L] and female < 50 mg/dL [1.3 mmol/L]) • documented chronic kidney disease (CKD) as defined by $15 \leq$ estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² for 3 months or more, including the screening visit). <p>I 04. Non-HDL-C at screening ≥ 100 mg/dL (2.59 mmol/L).</p> <p>I 05. Triglycerides at the screening visit ≥ 150 mg/dL (1.70 mmol/L) and</p>
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	<p><500 mg/dL (5.65 mmol/L).</p> <p>I 06. Stable anti-hyperglycemic agents for at least 3 months prior to the screening visit and between screening and randomization (including stable insulin dose defined as no variation more than 30% in daily insulin dose within the preceding 3 months, as judged by the Investigator).</p> <p>I 07. No variation of weight more than 5 kg within 3 months prior to the screening visit or between screening and randomization, as judged by the Investigator.</p> <p>I 08. On stable dose of medications that are known to influence weight and/or lipids (other than LMTs) within 3 months prior to the screening visit or during the screening period (eg, estrogen replacement, oral steroids, antipsychotics known to impact weight).</p> <p>I 09. Signed written informed consent.</p> <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • Use of any LMTs other than statins within 4 weeks prior to the screening visit or during the screening period (eg, ezetimibe, fenofibrate, nicotinic acid, omega-3 fatty acids, etc) or use of over the counter products/nutraceuticals known to impact lipids (eg, red yeast rice) within 4 weeks prior to the screening visit or during the screening period. • Currently drinking more than 2 standard alcoholic drinks/day (Note: A standard drink is considered as 1 pint/bottle of beer, 1 glass of wine, or 1 shot of hard liquor). • Body Mass Index (BMI) >45 kg/m² at screening or currently enrolled in a weight loss program and still in active phase of weight loss, as judged by Investigator. • HbA1c at screening ≥9%
Total expected number of patients	A total of ~420 patients are expected (~280 patients will be randomized to alirocumab and ~140 randomized to usual care).
STUDY TREATMENT(s)	
Investigational medicinal product(s)	Alirocumab (open label).
Formulation:	Prefilled pen; Sterile alirocumab drug product supplied at a concentration of 75 mg/mL or 150 mg/mL in histidine, pH 6.0, polysorbate 20, and sucrose.
Route(s) of administration:	Subcutaneous (SC); 1 injection of 1 mL SC in the abdomen, thigh, or outer area of upper arm (ie, deltoid region)
Dose regimen:	Alirocumab 75 mg Q2W with possible uptitration at Week 12 to 150 mg Q2W. The last planned injection of alirocumab IMP is to be administered at Week 22. Note: A placebo injection for training purposes will be administered to the patient at screening, with the option of a second training injection prior to randomization. If the person who is designated to administer alirocumab to the patient changes during the course of the study, the new designated person will be trained with a placebo.
Investigational medicinal product(s)	Usual Care (open label). There are five options available in the usual care arm including the option to

<p>Formulation:</p> <p>Route(s) of administration:</p> <p>Dose regimen:</p>	<p>add no additional LMT on top of the maximum dose/regimen of statin that is tolerated by the patient or to start one of the following treatments: ezetimibe, fenofibrate, omega-3 fatty acids or nicotinic acid. All patients, regardless of the usual care option that has been selected, should continue on the maximum dose/regimen of statin (non-IMP) that is tolerated by the patient.</p> <p>The following drugs are identified as IMP:</p> <p>Ezetimibe, or Nicotinic acid, or Fenofibrate, or Omega-3 fatty acids</p> <p>Oral</p> <p>As applicable and in accordance with Investigator prescription/local labeling.</p>
<p>Noninvestigational medicinal product(s) (if applicable)</p> <p>Formulation:</p> <p>Route(s) of administration:</p> <p>Dose regimen:</p>	<p>No non-investigational products will be provided by the Sponsor. The following non-investigational products may be taken by the patient, as applicable, and in accordance with the eligibility criteria: statins (HMG CoA reductase inhibitors).</p> <p>As applicable and in accordance with local labeling.</p> <p>As applicable and in accordance with local labeling.</p>
<p>ENDPOINT(S)</p>	<p>Primary endpoint:</p> <ul style="list-style-type: none"> • Percent change in non-HDL-C from baseline to Week 24 in the intent-to-treat (ITT) population, using all non-HDL-C values regardless of adherence to treatment (ITT estimand). <p>Key Secondary Efficacy endpoints (ITT estimand)</p> <ul style="list-style-type: none"> • Percent change in measured LDL-C from baseline to Week 24. • Percent change in non-HDL-C from baseline to Week 12. • Percent change in measured LDL-C from baseline to Week 12. • Percent change in Apo B from baseline to Week 24. • Percent change in Total-C from baseline to Week 24. • Percent change in Lp(a) from baseline to Week 24. • Percent change in TGs from baseline to Week 24. • Percent change in HDL-C from baseline to Week 24. • Percent change in LDL particle number from baseline to Week 24. <p>Diabetes-related endpoints (ITT estimand)</p> <ul style="list-style-type: none"> • Absolute change in HbA1c from baseline to Weeks 12 and 24. • Absolute change in fasting plasma glucose (FPG) from baseline to Weeks 12 and 24. • Absolute change in number of glucose-lowering treatments from baseline to Weeks 12 and 24. <p>Safety endpoints</p> <ul style="list-style-type: none"> • Treatment emergent adverse events (TEAEs), adverse events of special interest (AESIs), product complaints, laboratory data

	<p>(including microalbuminuria), vital signs (including change in body weight and BMI).</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>Other endpoints</p> <ul style="list-style-type: none"> • Anti-alirocumab antibodies assessed throughout the study. • Serum PCSK9 levels assessed throughout the study. <p>Other Efficacy Endpoints (ITT estimand)</p> <ul style="list-style-type: none"> • Percent change in calculated LDL-C from baseline to Weeks 12 and 24. • Percent change in Apo B, Total-C, Lp(a), TGs, and HDL-C from baseline to Week 12. • Proportion of patients reaching measured LDL-C <50 mg/dL (1.30 mmol/L), <70 mg/dL (1.81 mmol/L) and < 100 mg/dL (2.59 mmol/L) at Weeks 12 and 24. • Percent change in measured LDL-C according to baseline TGs of <median TG or ≥median TG at Weeks 12 and 24. • Proportion of patients reaching non-HDL-C <130 mg/dL (3.37 mmol/L), <100 mg/dL (2.59 mmol/L) and <80 mg/dL (2.07 mmol/L) at Weeks 12 and 24. • Percent change in TGs from baseline to Weeks 12 and 24 according to baseline TGs of <median TG or ≥median TG. • Percent change in LDL particle number from baseline to Week 12. • Percent change in LDL particle size from baseline to Weeks 12 and 24. • Percent change in VLDL, HDL and intermediate-density lipoprotein (IDL) particle number from baseline to Weeks 12 and 24. • Percent change in Apo A-1 and Apo-C-III from baseline to Weeks 12 and 24. • Absolute change in TGRLs (ie, non-HDL-C minus LDL-C) from baseline to Weeks 12 and 24. • Proportion of patients with 50% or greater reduction from baseline in measured LDL-C at Weeks 12 and 24. • The proportion of patients reaching Apo B <80 mg/dL at Weeks 12 and 24. • Absolute change in ratio Apo B/Apo A-1, Total-C/HDL-C and LDL-C/HDL-C from baseline to Weeks 12 and 24
<p>ASSESSMENT SCHEDULE</p>	<p>V1: (Week -3, [Day -21 to -8]): screening, alirocumab (placebo IMP) injection training*, safety.</p> <p>V2: (Week 0 [Day 1 + 3]): baseline, randomization, first administration with open label alirocumab (if the patient is randomized to alirocumab) or initiation of usual care (if the patient is randomized to the usual care (non-alirocumab) arm), and as per the prescription of the Investigator), safety. Patients will have the option to self-inject/inject a second time with placebo after the first screening injection training and before randomization. For patients randomized to alirocumab, additional training can be performed with open</p>

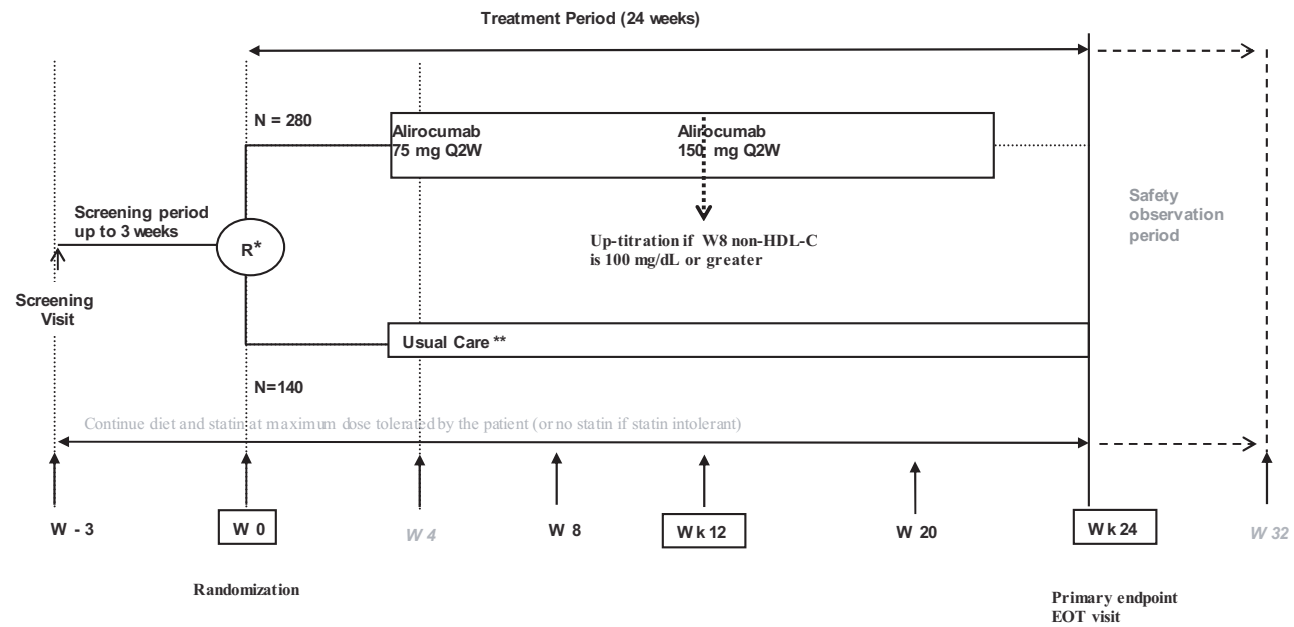
	<p>label alirocumab at this visit.</p> <p>V3: (Week 4[Day 29 ±7 days]): telephone contact.</p> <p>V4: (Week 8 [Day 57 ±3 days]); V6: (Week 20 [Day 141 ±7 days]): Efficacy and safety assessment parameters.</p> <p>V5: (Week 12 [Day 85 ±3 days]): Second allocation of open label alirocumab if randomized to alirocumab or prescription for usual care treatment (IMP) if randomized to usual care (as applicable), efficacy, and safety assessment parameters.</p> <p>V7: (Week 24 [Day 169 ±3 days]): End of open label treatment visit, efficacy, and safety assessment parameters.</p> <p>V8: (Week 32 [Day 225 ±7 days]): telephone contact, safety assessment.</p> <p>*In case a designated person plans to inject the patient but is not present at the time of the screening visit, a dedicated training visit may be scheduled during the screening period prior to the randomization visit or training can be performed at the randomization visit prior to study drug administration.</p> <p>Note: If one visit is changed, the next visit should take place according to the original schedule.</p> <p>Patients who prematurely discontinue treatment should be followed as scheduled.</p>
<p>STATISTICAL CONSIDERATIONS</p>	<p>Sample size determination:</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>Analysis population:</p> <p>Randomized population includes any patients who have been allocated to a randomized treatment arm, regardless of whether they received the planned treatment or not.</p> <p>The primary efficacy analysis population will be the ITT population, defined as all randomized patients who had an evaluable primary efficacy endpoint.</p> <p>The primary efficacy endpoint will be considered evaluable when both of the following conditions are met:</p> <ul style="list-style-type: none"> • The baseline non-HDL-C value is available • A least 1 non-HDL-C value is available within one of the analysis windows up to Week 24.

	<p>Patients in the ITT population will be analyzed according to the treatment group allocated by randomization.</p> <p>The safety population considered for safety analyses will be the randomized population who received at least one dose or part of a dose of the open-label alirocumab and all patients randomized to usual care. The safety population will be analyzed according to the treatment actually received.</p> <p>Primary analysis:</p> <p>The percent change in non-HDL-C from baseline to Week 24 will be analyzed in the ITT population using a Mixed-effect Model with Repeated Measures (MMRM) approach. Non-HDL-C is defined as Total Cholesterol (Total-C) minus HDL-C. All post-baseline data available within Week 8 to Week 24 analysis windows will be used and missing data are accounted for by the MMRM model.</p> <p>The model will include the fixed categorical effects of treatment group (usual care versus alirocumab), time point (Week 8, Week 12, Week 20, Week 24), randomization strata, treatment-by-time point interaction, strata-by-time point interaction as well as the continuous fixed covariates of baseline non-HDL-C value and baseline value-by-time point interaction. Alirocumab will be compared to usual care using appropriate contrasts, and the 97.5% confidence interval (CI) of the difference will be provided.</p> <p>Analysis of key secondary endpoints and other efficacy endpoints:</p> <p>A hierarchical procedure (concerning key secondary efficacy endpoints only) will be used to control the type I error and handle multiple endpoints. If the primary endpoint analysis is significant at the 2.5% alpha level, secondary endpoints will be tested sequentially, using the order defined in section “Key Secondary efficacy endpoints”.</p> <p>Continuous secondary endpoints anticipated to have a normal distribution (eg, lipids other than Lp[a] and TGs), 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. Continuous secondary endpoints anticipated to have a non-normal distribution (eg, Lp[a] and TGs) will be analyzed using multiple imputation approach for handling of missing values followed by robust regression. Binary secondary endpoints will be analyzed using multiple imputation approach for handling of missing values followed by logistic regression.</p> <p>All the efficacy endpoints (primary, key secondary and other efficacy endpoints) will also be analyzed for the patients intended to receive fenofibrate in order to compare the efficacy of alirocumab versus fenofibrate; for this subgroup, significance will be claimed at the 2.5% alpha level and the hierarchical procedure will be used as well. The comparison of alirocumab versus the other options of the usual care will be performed via exploratory subgroup analyses.</p> <p>Analysis of other endpoints:</p> <p>Descriptive analyses will be performed concerning questionnaire and diabetes related endpoints.</p> <p>Safety analysis:</p> <p>Safety analysis (TEAEs, AESIs, product complaints, laboratory parameters, vital signs) will be descriptive, based on the safety population. The safety</p>
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	<p>analysis will be performed at the end of the study. If an advanced analysis at Week 24 is needed for scientific communication purposes, safety analyses would be performed at the same time as efficacy analysis, with all safety data available until the cut-off date, and an update would be performed at Week 32.</p> <p>Advanced analysis:</p> <p>All the efficacy data will be available for the final analysis at a cut-off date corresponding to the Week 24 visit of the last patient. All the safety data will be available at the end of the study (Week 32). If needed for scientific communication purposes, both the efficacy and safety analyses will be performed at the Week 24 cut-off date, with an update for safety at the end of the study. If not needed, the 2 analyses will be performed at the same time, at the end of the study (Week 32).</p>
<p>DURATION OF STUDY PERIOD (per patient)</p>	<p>The duration of the study is up to 9 months to include a 3-week screening period, a 24-week treatment period, and an 8-week period of safety observation.</p> <p>Patients with a serious adverse event (SAE) or an adverse event of special interest should be followed until resolution, stabilization, or death.</p>

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



R : Randomization : As a principle, it should occur after signature of the informed consent form and just before the first dosing of the study drug (ie, IMP or usual care). The Randomization Day is always Day 1. The randomization is stratified by intent to prescribe usual care (eg, intent to prescribe ezetimibe, intent to prescribe fenofibrate).
 *First study drug administration.
 **Usual care includes continuing on maximum dose of statin tolerated by the patient (or no statin if statin intolerant) and one of the following: no additional LMT or initiation of either ezetimibe, fenofibrate, omega-3 fatty acids or nicotinic acid.
Phone call visits are indicated in italics.

1.2 STUDY FLOW CHART

	Screening	Open-Label Treatment Period (OLTP)						Safety Observation Period
VISIT	1 (Week -3)	2 (Week 0)	3 (Week 4) ^a	4 (Week 8)	5 (Week 12)	6 (Week 20)	7 (Week 24) End of OLTP	8 (Week 32) ^a
DAY	-21	1	29	57	85	141	169	225
Visit Window (Days)	(-21 to -8)	+3	±7	±3	±3	±7	±3	±7
Informed consent	X							
Review of Inclusion/Exclusion Criteria	X	X						
Patient demography	X							
Medical/surgical history, alcohol habits, smoking habits	X							
Prior medication history	X							
Physical examination ^b	X	X			X		X	
Vital signs^b:								
Heart rate (HR), blood pressure (BP)	X	X		X	X	X	X	
Body weight	X	X		X	X	X	X	
Measured height	X							
Randomization		X						
Patient diary dispensation		X		X	X	X		

	Screening	Open-Label Treatment Period (OLTP)						Safety Observation Period
VISIT	1 (Week -3)	2 (Week 0)	3 (Week 4) ^a	4 (Week 8)	5 (Week 12)	6 (Week 20)	7 (Week 24) End of OLTP	8 (Week 32) ^a
DAY	-21	1	29	57	85	141	169	225
Visit Window (Days)	(-21 to -8)	+3	±7	±3	±3	±7	±3	±7
Patient Diary Collection/Review (for Compliance check of IMP and data collection on IMP administration)			X	X	X	X	X	
interactive voice response system/interactive web response system (IVRS/IWRS) contact	X	X			X		X	
Injection training ^c	X	X						
alirocumab dispensation (if randomized to alirocumab) or provision of prescription for usual care (IMP) if randomized to usual care (if applicable) ^d		X			X			
IMP administration ^e		X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X
Adverse Event (AE)/SAE recording / product technical complaints ^f	X	X	X	X	X	X	X	X
Reinforce diet recommendations, if needed		X	X	X	X	X	X	

	Screening	Open-Label Treatment Period (OLTP)						Safety Observation Period
VISIT	1 (Week -3)	2 (Week 0)	3 (Week 4) ^a	4 (Week 8)	5 (Week 12)	6 (Week 20)	7 (Week 24) End of OLTP	8 (Week 32) ^a
DAY	-21	1	29	57	85	141	169	225
Visit Window (Days)	(-21 to -8)	+3	±7	±3	±3	±7	±3	±7
Fasting laboratory testing-Efficacy:								
Lipid panel (Total-C, calculated LDL-C, HDL-C, TGs, non-HDL-C)	X	X		X	X	X	X	
Measured LDL-C (via beta quantification)	X	X		X	X	X	X	
Apo B, Apo A-1, Apo C-III, lipid subfractions by NMR ^g , Lp(a)		X		X	X	X	X	
Fasting laboratory testing-Safety:								
Hematology and chemistry (including plasma glucose) ^h	X	X ⁱ		X	X		X	
Creatine phosphokinase	X	X ⁱ		X	X		X	
Liver panel ⁱ	X	X ⁱ		X	X		X	
Pregnancy test (for women of childbearing potential) ^j	X	X					X	
Standard urinalysis and spot urine albumin:creatinine ^k	X						X	
HbA1c	X	X			X		X	

	Screening	Open-Label Treatment Period (OLTP)						Safety Observation Period
VISIT	1 (Week -3)	2 (Week 0)	3 (Week 4) ^a	4 (Week 8)	5 (Week 12)	6 (Week 20)	7 (Week 24) End of OLTP	8 (Week 32) ^a
DAY	-21	1	29	57	85	141	169	225
Visit Window (Days)	(-21 to -8)	+3	±7	±3	±3	±7	±3	±7
Hepatitis B surface antigen ^h	X							
Hepatitis C antibody ^h	X						X	
Thyroid stimulating hormone (TSH) ^h	X							
Anti-alirocumab antibodies		X			X		X	
Serum PCSK9 levels		X			X		X	
				X			X	

- a Weeks 4 and 32 are telephone visits only
- b Physical examination and vital signs: height, weight, HR, and BP. Abnormal vital signs are to be recorded as adverse events only if they are medically relevant: symptomatic, requiring corrective treatment, leading to discontinuation and/or fulfilling a seriousness criterion.
- c Injection-training is performed with placebo. Investigators will have the option of providing a second placebo for alirocumab for patients who require additional self-injection training. The first open label injection is administered at the site by the patient or a trained designated person with open label treatment kit allocated by IVRS. Further training with open label treatment can be done for patient's randomized to alirocumab at an additional unscheduled visit(s) at the time of a planned injection per protocol, as per patient or Investigator's judgment. Only patients who are randomized to alirocumab will receive an injection of alirocumab at the randomization visit.
- d For kit dispensation: along with kit dispensation, the treatment administration package should be given as well as the patient diary and injection instruction manual, as needed.
- e Duration of study treatment will be 24 weeks. Alirocumab will be administered every two weeks with the last injection of open label alirocumab administered at Week 22. The treatments prescribed in the usual care arm will be administered for 24 weeks. At the end of the open-label treatment period (Week 24 visit), the Investigator will continue to manage the patient's lipids in accordance with standard practice.
- f Safety evaluation: adverse events (AEs), and product complaints regardless of seriousness or relationship to alirocumab treatment, will be collected from the time the patient signs the informed consent form (ICF) until the end of the post-open-label treatment safety observation period. If the patient discontinues the study, AEs would need to be reported up to 70 days after the last dose of open-label investigational medicinal product (IMP) or 70 days after the last on-site study visit if randomized to usual care and the Investigator has not prescribed an additional LMT, or Study Day 225, whichever comes first.

- g* Lipid subfractions by nuclear magnetic resonance (NMR) spectroscopy corresponds to the following: LDL particle size; LDL, VLDL, HDL, and IDL particle number.
- h* Hematology includes: complete blood cell count (CBC) including hematocrit, hemoglobin, red blood cell (RBC) count, red blood cell distribution width (RDW), white blood cell (WBC) count with differential count, and platelets. Chemistry includes: plasma glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, uric acid, lactate dehydrogenase (LDH), total protein, albumin, and gamma-glutamyl transpeptidase (GGT). Hepatitis C antibody (at screening, end of OLTP, and in case of transaminases elevation), Hepatitis B antigen (screening only). Note that any Hepatitis C antibody that returns abnormal during the study will need to be followed by confirmatory testing. TSH values should be performed at screening for patients who are on thyroid hormone replacement only.
- i* Liver panel: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin.
- j* Pregnancy status should be checked by serum pregnancy test at screening in women of childbearing potential only. Pregnancy status shall be assessed at Week 0 and Week 24 by urine pregnancy test.
- k* Urinalysis (UA) and spot urine albumin: creatinine ratio: To be performed at screening and Week 24. Additional UA to be repeated if needed based on Investigator judgment.
- l* To be obtained at the randomization visit only in case of clinically relevant abnormal values for these parameters at the screening visit as determined by the Investigator, with the exception of fasting plasma glucose, which should be obtained in all cases at the randomization visit.

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3 LIST OF ABBREVIATIONS

ADR:	adverse drug reaction
AE:	adverse event
AESI:	adverse event of special interest
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
Apo A-1:	apolipoprotein A-1
Apo B:	apolipoprotein B
Apo C-III:	apolipoprotein C-III
ASCVD:	atherosclerotic cardiovascular disease
AST:	aspartate aminotransferase
BMI:	body mass index
BP:	blood pressure
CABG:	coronary artery bypass graft
CHD:	coronary heart disease
CI:	confidence interval
CKD:	chronic kidney disease
CPK:	creatine phosphokinase
CV:	cardiovascular
CVD:	cardiovascular disease
DM:	diabetes mellitus
DRF:	discrepancy resolution form
eGFR:	estimated glomerular filtration rate
FPG:	fasting plasma glucose
GGT:	gamma-glutamyl transpeptidase
HDL-C:	high-density lipoprotein cholesterol
heFH:	heterozygous familial hypercholesterolemia
HIV:	human immunodeficiency virus
HLGT:	high level group term
HLT:	high level term
HR:	heart rate
IDL:	intermediate-density lipoprotein
IMP:	investigational medicinal product
█	█
ITT:	intent-to-treat
IUD:	intrauterine device
IVRS:	interactive voice response system
IWRS:	interactive web response system
LDH:	lactate dehydrogenase
LDL-C:	low-density lipoprotein cholesterol
LDL-R:	low-density lipoprotein receptor
LLT:	lowest level term

LMT:	lipid 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
NMR:	nuclear magnetic resonance
non-HDL-C:	non-high-density lipoprotein cholesterol
NYHA:	New York Heart Association
OLTP:	open-label treatment period
PAD:	peripheral arterial disease
PCI:	percutaneous coronary intervention
PCSA:	potentially clinically significant abnormality
PCSK9:	proprotein convertase subtilisin kexin type 9
PK:	pharmacokinetics
PRO:	patient reported outcome
PT:	preferred term
Q2W:	every 2 weeks
Q4W:	every 4 weeks
RBC:	red blood cell
RDW:	red blood cell distribution width
SAE:	serious adverse event
SAP:	statistical analysis plan
SC:	subcutaneous
SD:	standard deviation
SE:	standard error
SMQ:	standardized MedDRA query
SOC:	system organ class
SUSAR:	suspected unexpected serious adverse reaction
TEAE:	treatment emergent adverse event
TG:	triglyceride
TGRLs:	triglyceride rich lipoproteins
Total-C:	total cholesterol
TSH:	thyroid stimulating hormone
UA:	urinalysis
ULN:	upper limit of normal range
VLDL:	very low-density lipoprotein cholesterol
WBC:	white blood cell

4 INTRODUCTION AND RATIONALE

Background on patient populations:

More than 380 million people worldwide have diabetes (1), most of whom will die from cardiovascular disease (CVD) (2, 3, 4). Compared to people without diabetes, those with diabetes are at higher risk of developing CVD, develop associated clinical complications and at an earlier age, and have shortened life expectancy by about 6-7 years (5, 6, 7). In addition to the high human cost of disease, CVD contributes greatly to the overall healthcare expenditure in these patients (4).

Individuals with diabetes often have mixed dyslipidemia characterized by elevated non-high-density lipoprotein cholesterol (non-HDL-C), triglycerides (TGs), and low-density lipoprotein cholesterol (LDL-C), and low HDL-C, leading to higher coronary heart disease (CHD) risk than raised LDL-C alone (8, 9). Management of mixed dyslipidemia is a persistent challenge in clinical practice and these patients are less likely to achieve recommended lipid levels following lipid modifying therapy (LMT) (10).

Non-HDL-C:

Non-HDL-C has been proposed as a therapeutic target for mixed dyslipidemia since it encompasses all of the circulating atherogenic triglyceride-rich lipoproteins, including very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), LDL, and lipoprotein a (Lp[a]). It has been shown to be superior to LDL-C in predicting CVD risk in individuals with diabetes (11). It is simply assessed by subtracting HDL-C from total cholesterol (Total-C). The specific non-HDL-cholesterol target differs depending on the guidelines consulted and the severity of risk experienced by the patient, but they generally recommend a target of <100 mg/dL in patients with diabetes at high cardiovascular (CV) risk (with documented CVD, severe chronic kidney disease (CKD), or with 1 or more CV risk factors and/or target organ damage) (5, 12, 13).

Lipid modifying therapy for management of mixed dyslipidemia:

Statins

Statins significantly lower LDL-C and non-HDL-C and, to a lesser extent, also lower TGs and raise HDL-C. Multiple clinical trials with statins and subgroup analyses in patients with diabetes have demonstrated significant reductions in CV events (14, 15, 16, 17, 18, 19). Greater reductions in LDL-C produce greater reduction in CV events, and comparative data of intensive versus standard statin treatment suggest that the lower the LDL-C level, the greater the benefit in patients at high CV risk (20, 21, 22, 23). Data from a meta-analysis including over 18 000 patients with diabetes suggest that, for each 1 mmol/L (39 mg/dL) decrease in LDL-C patients with diabetes experienced a 9% reduction in all-cause mortality and a 13% reduction in vascular mortality over a mean follow up period of 4.3 years (19).

Despite the widespread use of statin therapies, many patients with diabetes and dyslipidemia remain sub-optimally treated (20, 21, 24) or may be intolerant to statin therapy, due to troubling

side effects, and many go on to experience CV events. Additional therapies are used to manage mixed dyslipidemia, including ezetimibe, fibrates, nicotinic acid and omega-3 fatty acids. Currently, it remains unknown which is the best treatment strategy to address lipid abnormalities in these patients and to reduce CV burden.

Ezetimibe

Ezetimibe inhibits cholesterol absorption from the intestine, and lowers apolipoprotein B (Apo B), non-HDL-C, LDL-C, and TGs. The CV benefits of adding ezetimibe to a statin in patients post-acute coronary syndrome were recently demonstrated (25). Individuals with diabetes may have even higher benefit from this combination therapy (25).

Fibrates

Fibrates are the most effective drugs for lowering TGs. They also may lower LDL-C and raise HDL-C. The potential CV outcome benefit of fenofibrate and statin combination therapy compared with statin monotherapy was evaluated in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid trial (26). In the overall study cohort of patients with type 2 diabetes, there was no significant difference in the primary end point of the first occurrence of nonfatal myocardial infarction (MI), nonfatal stroke, or death from CV causes. A pre-specified subgroup analysis suggested a possible interaction according to the lipid subgroup, with a possible benefit for patients with both high baseline TGs and low HDL-C ($p = 0.057$ for interaction) (26).

Omega-3 fatty acids

Omega-3 fatty acids lower TGs but have little effect on LDL-C and HDL-C. Despite having multiple effects on surrogate cardioprotective markers (attenuate inflammation, improve endothelial function and reduce thrombus formation), omega-3 fatty acids have not been shown to improve CV outcomes in individuals with diabetes (27).

Nicotinic acid

Nicotinic acid is currently the most effective drug in raising HDL-C with a moderate effect on lowering of LDL-C, TGs and Lp(a). However, the combination of nicotinic acid and statin has not been shown to provide additional CV benefits when compared with statin monotherapy in 2 outcome studies (28, 29).

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

The investigational medicinal product (IMP) in this study is alirocumab, a monoclonal antibody to proprotein convertase subtilisin kexin type 9 (PCSK9). Proprotein convertase subtilisin kexin type 9 (PCSK9) is involved in regulating the levels of the low-density lipoprotein receptor (LDL-R) protein. Once PCSK9 is secreted into plasma it directly binds to the LDL-R and promotes its degradation. The increased degradation of LDL-Rs leads to a reduced LDL particle removal and, therefore higher LDL-C circulating levels. Blocking PCSK9 binding to the LDL-R can potentially benefit patients with hypercholesterolemia by decreasing their plasma LDL-C levels and reducing non-HDL-C (30, 31, 32, 33, 34).

Summary of select clinical studies with alirocumab:

As of 31 December 2014, 12 Phase 3 studies were completed or had a first step analysis completed, with 10 evaluating alirocumab administered every 2 weeks (Q2W regimen) and 2 evaluating alirocumab administered every 4 weeks (Q4W regimen). These studies evaluated heterozygous familial hypercholesterolemia (heFH) patients, patients with a range of CV risk but predominately high and very high risk, and patients not taking statins including statin intolerant patients.

Phase 3 studies that evaluated Q2W regimen – efficacy results:

Ten studies that were completed or had a 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 /dose regimen were performed. Averaged across the various studies, alirocumab use resulted in a mean -45.6 to -48.9% reduction in LDL-C from baseline to week 24 in studies that investigated the up-titration regimen and -60.4% in studies that solely investigated 150 mg Q2W dosing, whereas control rates were 0.5 to 4.2% (placebo) and -19.3 to -22.3% (ezetimibe). 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. Overall, absolute reductions in LDL-C in the range of -40 to -90 mg/dL (-1.03 to -2.33 mmol/L) were observed in the alirocumab treatment arms.

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.

Significant and clinically meaningful reductions were also observed in pro-atherogenic biomarkers, including non-HDL-C, Apo B, and Total-C. Alirocumab was also superior to placebo, and to ezetimibe in most studies, for the reduction in Lp(a). Modest but consistent reductions in fasting TGs and increases in HDL-C were also observed with alirocumab treatment.

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. ■

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 no evidence of a pattern in the type of AEs observed. The percentages of patients who experienced at least 1 treatment emergent adverse events (TEAE), at least 1 treatment-emergent serious adverse event (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 aminotransferase (ALT) increase and hepatic disorders, adjudicated CV events, diabetes mellitus, and ophthalmologic disorders in the alirocumab-treated group overall, but more cataracts (2.1%) were noted in patients treated with alirocumab who achieved 2 consecutive LDL-C values <25 mg/dL compared to those treated with alirocumab who did not meet this criterion (0.6%).

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 (upper respiratory symptoms), and pruritus were identified as adverse drug reactions (ADR). Rare and sometimes serious allergic adverse reactions (eg, hypersensitivity, eczema nummular, urticaria, and hypersensitivity vasculitis) have been reported from clinical studies in patients receiving alirocumab.

The analysis of the safety data with Q2W dosing did not suggest a safety signal as of 31 December 2014.

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

SELECTION OF THE DOSE

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 their individual target LDL-C goal, with up-titration to 150 mg Q2W in patients not achieving their LDL-C goal. Two main doses of alirocumab with the Q2W dosing regimen are evaluated in the on-going ODYSSEY Phase 3 program and assess both an initiation with 75 mg, with up-titration to 150 mg in patients who do not reach pre-defined LDL-C levels, based on their CV risk, and initiating treatment directly with the 150 mg Q2W dose.

Rationale for protocol design:

The objective of the present study is to assess the efficacy and safety of alirocumab in patients with Type 2 diabetes and mixed dyslipidemia with established CVD or otherwise at high CV risk whose non-HDL-C is not adequately controlled with maximally tolerated statin therapy. Patients will also be included if they are statin intolerant or are on alternate day dosing of statin. Although statins serve as the foundation for LDL-C lowering many patients are not optimally managed and a second therapy to bring non-HDL-C to within the target range is frequently used in patients with diabetes and mixed dyslipidemia. There is no single preferred second line treatment for patients with elevated non-HDL-C as guidelines suggest an individualized approach. Alirocumab will be

compared to the physician's usual care that will include the option to continue on maximally tolerated statin monotherapy with no additional LMT, or to add either ezetimibe, fenofibrate, omega-3 fatty acids, or nicotinic acid. Numerous clinical trials have demonstrated beneficial effects of these therapies on the multiple lipid abnormalities that characterize mixed dyslipidemia. It is important to note that all patients will continue their maximally tolerated statin therapy. Physician's choice of next step therapy (ie, usual care) will be made at randomization and implemented in patients who are not randomized to alirocumab. The treatment strategy implemented post-randomization will remain unchanged throughout the study.

Alirocumab will be evaluated at a dose of 75 mg Q2W with a blinded increase of dose to 150 mg Q2W if non-HDL-C values at Week 8 are ≥ 100 mg/dL (2.59 mmol/L).

It is possible that some patients in alirocumab arm may attain LDL-C levels well below 70 mg/dL. Persons with genetic mutations such as heterozygous form of hypobetalipoproteinemia linked to Apo B mutations or loss of function PCSK9 mutations have very low LDL-C levels throughout life and have low vascular risk, and no apparent adverse effects (33, 35, 36, 37). [REDACTED]

The sample size of 420 patients with treatment duration of 24 weeks is intended to provide a broad safety experience in this patient population and to assess the impact of uptitration of alirocumab on efficacy and safety parameters. The control group is composed of patients receiving usual care and is appropriate for the objectives of this study.

Conclusion on the benefit risk assessment with alirocumab:

Based on the clinical data available to date, treatment with alirocumab has demonstrated a significant LDL-C and non-HDL-C lowering effect and was generally well tolerated in a population of patients with non-familial hypercholesterolemia (non-FH) or with heFH, including patients with a history of intolerance to statins. The efficacy on LDL-C was associated with consistent results in Total-C, apolipoprotein B (Apo B), and Apo B/apolipoprotein A-1 (Apo A-1) ratio. Reductions in lipoprotein (a) and TGs and increases in HDL-C were also observed with alirocumab treatment. There was no safety signal observed with neurologic events and neurocognitive disorders, ALT increase and hepatic disorders, adjudicated CV events, diabetes mellitus, and ophthalmologic disorders.

Injection site reactions, influenza (upper respiratory symptoms), and pruritus were identified as ADRs. Rare and sometimes serious allergic adverse reactions (eg, hypersensitivity, eczema nummular, urticaria, and hypersensitivity vasculitis) have been reported from clinical studies in patients receiving alirocumab. Alirocumab lowered LDL-C below 25 mg/dL in some patients. [REDACTED]

The benefit of alirocumab on CV morbidity and mortality has not yet been determined and is under investigation in the on-going ODYSSEY OUTCOMES trial.

This study is being undertaken to evaluate the risk benefit profile of alirocumab in patients with diabetes and mixed dyslipidemia. In the ODYSSEY* program, the effect of alirocumab in patients with diabetes and mixed dyslipidemia has not been assessed in a dedicated study. The important clinical question is which therapy to add as the next lipid lowering agent when a patient with mixed dyslipidemia is not at non-HDL-C target despite taking maximally tolerated statin therapy. Therefore, a head to head study with alirocumab versus usual care in this patient population would be needed to address this question in an evidence based manner. This study design allows the physician to make the therapeutic choice for his/her patient with diabetes and mixed dyslipidemia and elevated non-HDL-C despite maximally tolerated statin therapy. Superiority of alirocumab versus fenofibrate on non-HDL-C and other lipid parameters will also be assessed.

*ODYSSEY program refers to the alirocumab clinical trial program.

5 STUDY OBJECTIVES


5.1 PRIMARY

The primary objective is:

- To demonstrate the superiority of alirocumab in comparison with usual care in the reduction of non-HDL-C after 24 weeks of treatment in patients with Type 2 diabetes and mixed dyslipidemia at high CV risk with non-HDL-C not adequately controlled with maximally tolerated statin therapy.

5.2 SECONDARY

The secondary objectives are:

- To demonstrate whether alirocumab is superior in comparison with usual care in its effects on other lipid parameters at Weeks 12 and 24 (ie, LDL-C, apolipoprotein B (Apo B), Total-C, Lp(a), high-density lipoprotein cholesterol (HDL-C), TGs, triglyceride rich lipoproteins (TGRLs), Apo A-1, apolipoprotein C-III (Apo C-III), lipid subfractions by nuclear magnetic resonance (NMR) spectroscopy (ie, LDL particle size and LDL, VLDL, HDL and IDL particle number)
- To demonstrate the superiority of alirocumab in comparison with usual care in the reduction of non-HDL-C at Week 12.
- To assess changes in diabetes related parameters in patients randomized to alirocumab versus usual care treatment over a period of 24 weeks
- To demonstrate the safety and tolerability of alirocumab
- 
- To evaluate changes in PCSK9 concentrations at Weeks 12 and 24
- To evaluate the development of anti-alirocumab antibodies
- To demonstrate the superiority of alirocumab versus fenofibrate therapy on non-HDL-C and other lipid parameters

6 STUDY DESIGN

6.1 DESCRIPTION OF THE PROTOCOL

This is a Phase 3b/4 randomized, open-label, parallel group study to assess the efficacy and safety of alirocumab administered by subcutaneous (SC) injection versus usual care in patients with Type 2 diabetes and mixed dyslipidemia at high CV risk with non-HDL-C not adequately controlled with maximally tolerated statin therapy. The study will be multinational and multicenter. The study consists of a screening period of up to 3 weeks, an open-label treatment period (OLTP) of 24 weeks, and a safety observation period of 8 weeks.

Patients, unless they are statin intolerant, will be taking a stable, maximally tolerated dose of statin therapy without other lipid modifying therapies (LMT). Statin dose and dose regimen should be stable throughout the entire study duration including for 4 weeks prior to the screening period and from screening to the end of the open label treatment period. Patients should continue to follow a cholesterol lowering diet during the study, however, the Investigator may reinforce diet recommendations according to local/regional guidelines. Patients should be receiving treatment for diabetes in accordance with local/regional standards of care. Changes to antihyperglycemics should be limited and made only in circumstances where it is clinically needed.

Randomization will be unbalanced (2:1, alirocumab:usual care).

The usual care arm includes the option to continue on the maximum dose of statin that is tolerated by the patient without the addition of a new LMT at randomization, or may initiate either ezetimibe, fenofibrate, omega-3 fatty acids, or nicotinic acid at randomization for the remainder of the 24-week treatment period. Initiation of usual care treatment (IMP) should start as soon as possible after randomization, but no later than 7 days from the day of randomization.

The Investigator will select the most appropriate LMT for the patient prior to randomization (consisting of either no additional LMT but continuing on maximum tolerated statin, ezetimibe, fenofibrate, omega-3 fatty acids or nicotinic acid) and enter this information into the interactive voice response system (IVRS). If the patient is randomized to open label alirocumab, the Investigator will not institute the LMT option that was selected and entered into IVRS but instead treat the patient with open label alirocumab. If the patient is randomized to usual care (non-alirocumab), the Investigator will initiate treatment with the LMT option that was selected and entered into IVRS, as applicable, in addition to continuing the patient on the maximum tolerated dose of statin.

Patients randomized to open label alirocumab will continue on the maximum dose of statin that is tolerated by the patient and will administer alirocumab SC with a starting dose of 75 mg Q2W for 12 weeks with a blinded uptitration to alirocumab 150 mg Q2W at week 12 if the non-HDL-C at the week 8 visit is ≥ 100 mg/dL (2.59 mmol/L). Patients who have a non-HDL-C < 100 mg/dL (2.59 mmol/L) at the Week 8 visit will continue with alirocumab 75 mg Q2W until the end of the

treatment period. No changes during the course of the study will be made to the dose of LMT administered as part of the usual care arm except for nicotinic acid for which the Investigator may prescribe at randomization a scheduled/gradual dose titration in order to allow for the maximum dose to be achieved based on patient tolerability or except if needed for any usual care LMT for the safety of the patient, based on the Investigator's judgment.

The study consists of:

- A screening period of up to 3 weeks;
- An OLTP of 24 weeks
- A safety observation period of 8 weeks.

A phone visit will take place at Week 32 in order to document any adverse event(s) that might occur between Weeks 24 to 32.

Patients should have been previously instructed on a cholesterol lowering diet prior to screening. During the study, the Investigator may reinforce diet recommendations according to local/regional guidelines. Patients should be receiving antihyperglycemic treatment in accordance with local/regional standards of care.

Statin dose and dose regimen should be stable throughout the entire study duration including for 4 weeks prior to the screening period and from screening to the end of the open label treatment period.

The data on lipid parameters from blood samples will be masked after randomization. No attempts should be made by the Investigator or patient to have the patient's lipid values independently evaluated after randomization until after the Week 24 visit, except for the safety of the patient as per the Investigator's judgment. At the end of the OLTP (Week 24 visit), the Investigator will continue to manage the patient's lipids in accordance with standard practice. Any lipid values after randomization (eg, if done for patient safety) should be redacted in the source documents and not shared with the Sponsor.

Duration of study treatment will be 24 weeks with the last injection of open label alirocumab administered at Week 22. The treatments prescribed in the usual care arm will be administered for 24 weeks. From the Week 24 visit onward, the Investigator will continue to manage the patient's lipids in accordance with standard practice.

Patients will visit the study site at Weeks -3, 0, 8, 12, 20, and 24 with lab work at each visit; in addition a phone visit is scheduled at Weeks 4 and 32. Week 8 is a critical visit because it will be the only scheduled visit where a non-HDL-C value for uptitration will be available.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

The duration of the study is approximately 9 months to include:

- a 3-week screening period from signed informed consent form (ICF) to randomization
- a 24-week OLTP
- a safety observation period of 8 weeks after the end of the OLTP

Note, the Investigator will need to document in the CRF any AEs that have occurred up to Study Day 225. A phone visit will take place at Week 32 in order to ensure documentation of any AEs that might occur during this period. If the patient prematurely discontinues the study:

- if treated with IMP, AEs would need to be reported up to 70 days after the last dose of IMP or Study Day 225, whichever comes first (even if patient continues on the usual care treatment that was added at randomization after discontinuing the study).
- if randomized to usual care without additional LMT, AEs would need to be reported up to 70 days after the last on-site study visit, or Study Day 225, whichever comes first.

Patients with an SAE or an adverse event of special interest (AESI) should be followed until resolution, stabilization, or death.

6.2.2 Determination of end of clinical trial (all patients)

The end of study is defined as being the last patient last visit/contact.

6.3 INTERIM ANALYSIS

If needed for the purpose of scientific communication, an analysis of efficacy and safety may be conducted after the last patient has completed the Week 24 visit. At that time, all the efficacy data will be available for final analysis. Since safety data are being collected until the end of the study (Week 32), if the analysis with Week 24 data is performed, an update of the safety analysis will be performed at the end of the study. If analyses are not needed at Week 24, then there will be only a one time analysis at the end of the study (Week 32).

6.4 STUDY COMMITTEES

Steering committee

The Steering Committee is composed of university-based scientists (experts in lipids field, and/or Endocrinology/Diabetology) with clinical and study conduct expertise, working in collaboration with Sponsor based scientists. The committee will provide guidance on designing and conducting a scientifically sound study and ensure accurate reporting of the study. The Steering Committee will address and resolve scientific issues if encountered during the study. They will also help with the study recruitment, as needed. The Steering Committee members and Sponsor based scientists will participate in face-to-face meetings at regular intervals throughout the study and in regularly scheduled teleconferences. Detailed activities and responsibilities of the Steering Committee will be described in the Steering Committee Charter.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

- I 01. Patients with Type 2 diabetes and mixed dyslipidemia not adequately controlled with a stable maximum dose/regimen of statin that is tolerated by the patient* for at least 4 weeks prior to the screening visit (Week -3) without other LMT.

*Note: The maximum dose/regimen of statin that is tolerated by the patient is the highest registered dose/regimen tolerated by the patient based on the judgment of the Investigator. Patients not able to be on a maximum dose/regimen of statin, should be treated with the dose of statin which is considered appropriate for the patient as per the Investigator's judgment or concerns. Some examples of acceptable reasons for a patient taking a lower statin dose include, but are not limited to: adverse effects on higher doses, advanced age, low body mass index (BMI), regional practices, local prescribing information, concomitant medications. Patients may be on an alternate day dose of statin as long as the dose is consistently taken (eg, dose every Monday, Wednesday, Friday, etc). Concomitant treatment with more than 1 statin is not permitted. Patients who have documented statin intolerance, as judged by the Investigator, and who are no longer on statin therapy as a result will also be eligible for the study. The reason(s) for not being on a maximum dose/regimen of statin (including statin intolerance) will need to be documented in the case report form.

- I 02. Patient ≥ 18 years of age or legal age of majority at screening visit whichever is greater.
- I 03. Documented history of atherosclerotic cardiovascular disease (ASCVD) or at least one additional CV risk factor.

Notes:

Atherosclerotic cardiovascular disease (ASCVD) includes: CHD and CHD risk equivalents (peripheral arterial disease (PAD), ischemic stroke)

History of CHD includes at least one of the following:

- acute MI,
- silent MI,
- unstable angina,
- coronary revascularization procedure (eg, percutaneous coronary intervention [PCI] or coronary artery bypass graft surgery [CABG]),
- clinically significant CHD diagnosed by invasive or noninvasive testing (such as coronary angiography, stress test using treadmill, stress echocardiography, or nuclear imaging).

CHD risk equivalents include at least one of the following:

- Documented PAD (one of the following criteria [a, b, or c] must be satisfied):
 - a) Current intermittent claudication (muscle discomfort in the lower limb that is both reproducible and produced by exercise and relieved by rest within 10 minutes) of presumed atherosclerotic origin TOGETHER WITH ankle-brachial index ≤ 0.90 in either leg at rest, OR
 - b) History of intermittent claudication (muscle discomfort in the lower limb that is both reproducible and produced by exercise 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.
- Documented previous ischemic stroke with a focal ischemic neurological deficit that persisted more than 24 hours, considered as being of atherothrombotic origin. Computed tomography or magnetic resonance imaging must have been performed to rule out hemorrhage and non-ischemic neurological disease.

Cardiovascular risk factors include at least one of the following:

- hypertension (established on antihypertensive medicine)
- current cigarette smoker
- age ≥ 45 years for men and ≥ 55 years for women
- history of micro/macroalbuminuria
- history of diabetic retinopathy (preproliferative or proliferative)
- family history of premature CHD (in father or brother before 55 years of age; in mother or sister before 65 years of age)
- low HDL-C (male < 40 mg/dL [1.0 mmol/L] and female < 50 mg/dL [1.3 mmol/L])
- documented CKD as defined by $15 \leq$ estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² for 3 months or more, including the screening visit.

I 04. Non-HDL-C at screening ≥ 100 mg/dL (2.59 mmol/L)

I 05. Triglycerides at the screening visit ≥ 150 mg/dL (1.70 mmol/L) and < 500 mg/dL (5.65 mmol/L)

I 06. Stable anti-hyperglycemic agents for at least 3 months prior to the screening visit and between screening and randomization (including stable insulin dose defined as no variation more than 30% in daily insulin dose within the preceding 3 months, as judged by the Investigator)

I 07. No variation of weight more than 5 kg within 3 months prior to the screening visit or between screening and randomization, as judged by the Investigator

- I 08. On stable dose of medications that are known to influence weight and/or lipids (other than LMTs) within 3 months prior to the screening visit or during the screening period (eg, estrogen replacement, oral steroids, antipsychotics known to impact weight).
- I 09. 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. Not on a stable dose/regimen of statin for at least 4 weeks prior to the screening visit (Week -3) or from screening to randomization, unless statin intolerant in which case there will be no statin for 4 weeks prior to the screening visit/during the screening period.
- E 02. Use of any LMTs other than statins within 4 weeks prior to the screening visit or during the screening period (eg, ezetimibe, fenofibrate, nicotinic acid, omega-3 fatty acids, etc) or use of over the counter products/nutraceuticals known to impact lipids (eg, red yeast rice) within 4 weeks prior to the screening visit or during the screening period.
- E 03. Patients who are on insulin at baseline and not treated with insulin for at least 6 months prior to the screening visit and not on a stable insulin regimen (ie, a change in type of insulin, general timing/frequency of injections, mode or pattern of administration such as basal only, basal-prandial, etc) for at least 3 months prior to the screening visit, or likelihood of requiring a change in insulin type/frequency or mode of injection during the study period.
- E 04. Likelihood of requiring a change of antihyperglycemic regimen during the course of the study, as judged by the Investigator (eg, addition of new agent, plans for titration of insulin dose, etc).
- E 05. Recent (within 3 months prior to the screening visit [Week -3] or between screening and randomization visits) MI, unstable angina leading to hospitalization, uncontrolled cardiac arrhythmia, CABG, PCI, carotid surgery or stenting, cerebrovascular accident, transient ischemic attack (TIA), endovascular procedure or surgical intervention for peripheral vascular disease.
- E 06. Planned to undergo scheduled PCI, CABG, carotid or peripheral revascularization during the study.
- E 07. History of New York Heart Association (NYHA) Class III or IV heart failure within the past 12 months (See [Appendix A](#)).
- E 08. Systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg at screening or randomization visit.

- E 09. Patient who has received plasmapheresis treatment within 2 months prior to the screening visit (Week -3), or who has plans to receive it.
- E 10. Known history of hemorrhagic stroke.
- E 11. Known history of loss of function of PCSK9 (ie, genetic mutation or sequence variation) or known history of homozygous familial hypercholesterolemia.
- E 12. New cancer or active progression of cancer within the past 5 years, except for adequately treated basal cell skin cancer, squamous cell skin cancer, or in situ cervical cancer.
- E 13. Known history of positive human immunodeficiency virus (HIV) test.
- E 14. Patient who has taken any active investigational drugs within 1 month or 5 half-lives, whichever is longer.
- E 15. Patients not previously instructed on a cholesterol lowering diet prior to the screening visit (Week -3).
- E 16. BMI $>45 \text{ kg/m}^2$ at screening or currently enrolled in a weight loss program and still in active phase of weight loss, as judged by Investigator.
- E 17. Recent initiation of weight loss drugs (ie, within 3 months prior to the screening visit) or recent bariatric surgery (within the last 6 months) and in an active weight loss phase, as judged by the Investigator or plans to undergo bariatric surgery or to initiate weight loss drugs during the course of the study.
- E 18. Currently drinking more than 2 standard alcoholic drinks/day (Note: A standard drink is considered as 1 pint/bottle of beer, 1 glass of wine, or 1 shot of hard liquor).
- E 19. Currently receiving or plans to receive renal replacement therapy during the study (eg, hemodialysis, renal transplant).
- E 20. 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 of thyroxin has been stable for at least 3 months prior to screening and the patient's sensitive thyroid stimulating hormone (s-TSH) levels are within $\pm 10\%$ of the normal range of the laboratory at the screening visit.

- E 21. Known familial hypertriglyceridemia (Fredrickson classification 1 and 5) ([Appendix B](#)).
- E 22. Laboratory findings during the screening period (not including randomization labs, except for pregnancy test):
 - Serum TGs $>500 \text{ mg/dL}$ (5.65 mmol/L) (1 repeat lab is allowed)
 - Positive serum or urine pregnancy test in women of childbearing potential

- Positive test for Hepatitis B surface antigen or Hepatitis C antibody (confirmed by reflexive testing)
- Estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m² according to 4-variable Modification of Diet in Renal Disease (MDRD) equation
- ALT or Aspartate Aminotransferase (AST) >3 x upper limit of normal range (ULN) (1 repeat lab is allowed)
- Creatine Phosphokinase (CPK) >3 x ULN (1 repeat lab is allowed)
- HbA1c ≥ 9%

E 23. Conditions/situations such as:

- Patients with short life expectancy.
- Requirement for concomitant treatment that could bias primary evaluation.
- Impossibility to meet specific protocol requirements (eg, need for hospitalization, ability to make study visits).
- Patient is the Investigator or any Sub-Investigator, research assistant, pharmacist, study coordinator, other staff, or relative thereof directly involved in the conduct of the study.
- Uncooperative or any condition that could make the patient potentially non-compliant to the study procedures.
- Any technical/administrative reason that makes it impossible to randomize the patient in the study.
- Any clinically significant abnormality identified at the time of screening 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, for example, history of acute pancreatitis, etc.

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

E 24. Any contraindications to the background therapy(ies) or warning/precaution of use (when appropriate) as displayed in the respective National Product Labeling.

7.2.3 Exclusion criteria related to the current knowledge of Sanofi compound

E 25. Hypersensitivity to alirocumab or to any of the ingredients of alirocumab.

E 26. Pregnant or breastfeeding woman.

E 27. Women of childbearing potential not protected by highly-effective method(s) of birth control (as defined in the informed consent form and/or in a local protocol addendum) 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 inclusion visits. They must use an effective contraceptive method throughout the entire duration of the study treatment and for at least 10 weeks after the last injection of alirocumab/last usual care treatment. The applied methods of contraception have to meet the criteria for a highly effective method of birth control according to the “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 ICH.2009 Jun: 1-25”.

Postmenopausal women must be amenorrhic 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 28. Patient who has withdrawn consent before enrollment/randomization (starting from signed informed consent form).
- E 29. Despite screening of the patient, enrollment/randomization is stopped at the study level.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

8.1.1 Alirocumab

Sterile alirocumab drug product will be supplied at a concentration of 75 mg/mL and 150 mg/mL in histidine, pH 6.0, polysorbate 20, and sucrose, both as 1 mL volume, in an auto-injector (also known as prefilled pen).

Sterile placebo for alirocumab will be prepared in the same formulation as alirocumab without the addition of protein as 1 mL volume in a prefilled pen, for the patients to perform injection training.

During the screening period, the patient (or another designated person) will have to perform a placebo self-injection training, using a prefilled pen, before randomization and the first administration of alirocumab IMP.

For those patients randomized to alirocumab, the initial dose is 75 mg administered SC once Q2W. The dose will be increased in a blinded fashion to 150 mg Q2W at Week 12 for patients randomized to alirocumab if the Week 8 non-HDL-C value is ≥ 100 mg/dL (2.59 mmol/L).

NOTE: in order to ensure the continuity of the study treatment without interruption (only in the event the manufacturer faces any performance or supply issues of the prefilled pen), contingency alternatives are:

- in case of disruption of the 150 mg prefilled pen only, if the use of 75 mg prefilled pens is maintained, patients will need to administer 2 injections as follows:
 - 2 injections of 75 mg as 1 mL each in a prefilled pen for patients receiving the 150 mg dose
 - 1 injection of 75 mg as 1 mL in a prefilled pen plus 1 injection of placebo as 1 mL in a prefilled pen for patients receiving the 75 mg dose

OR

- in case of disruption of either 75 mg or 150 mg or both prefilled pens, patients will be switched to the use of prefilled syringes of 75 mg or 150 mg, with one injection of 1 mL for each of these doses.

Should this occur, the alternative alirocumab IMP will be maintained until the end of the study.

8.1.1.1 Route and method of administration

A prefilled pen training guide (auto-injector training guide) will be provided to the sites and instructions for use (auto-injector for use) will be provided to the patient. Each administration of alirocumab will consist of 1mL SC injection in the abdomen, thigh, or outer area of upper arm (ie, deltoid region). If another concomitant drug is being injected at the same site planned for the alirocumab injection, then the patient should be advised to use an alternate location for administration of alirocumab.

Alirocumab could be administered by self-injection or by another designated person (such as a spouse, relative, etc). In case a designated person is due to inject alirocumab to a patient during the study, it must be ensured that this person has been adequately trained prior to administering the injection. Anyone that plans to administer alirocumab must be trained by the study staff.

Instructions should be provided to the patient (or another designated person [such as spouse, relative, etc] that will administer the injections) at training and as needed during the course of the study. Close supervision and feedback should be given at the first visit, and other visits as needed.

The used prefilled pen will be discarded in a sharps container which will be provided to patients.

It is recommended that the SC alirocumab injections be rotated within an anatomical area (eg, right thigh, then left thigh or right abdomen, then left abdomen). Patients also have the option to inject in a different anatomical area (eg, thigh then abdomen or the outer area of upper arm, etc) during the study.

Patients will be asked to store alirocumab in a refrigerator. Prior to administration, alirocumab should be set outside in a safe location at room temperature for about 30 to 40 minutes. Thereafter, alirocumab should be administered as soon as possible.

8.1.1.2 Timing of administration

During the screening period, patients or the designated person will have to perform a placebo self-injection training using a prefilled pen, before randomization and the first alirocumab injection.

At the randomization visit, the first alirocumab injection will be done at the site by the patient or another designated person (such as spouse, relative, etc) under direct site staff supervision. Patients will be monitored at the investigational site for at least 30 minutes after this first injection in this study. If the designated person changes during the course of the study, the new designated person will need to be trained with placebo prior to administering alirocumab to the patient.

Alirocumab SC injections will then be performed outside of the clinic, Q2W up to the last injection. If the injection is scheduled to take place on the same date as the site visit, then alirocumab should be administered after the blood sampling has been completed. In exceptional cases, if a patient prefers to have the injection performed at the study site and provisions are able to be made to accommodate the administration of injections at the site, it may also be allowed.

Alirocumab should be administered SC Q2W, ideally at approximately the same time of the day; however, it is acceptable to have a window period of ± 3 days. The time of the day is based upon the patient's preference.

If by mistake or due to other circumstances an injection is delayed by:

- more than 7 days from the missed date or completely missed, then the patient should return to the original schedule of alirocumab administration without administering delayed injections.
- less than or equal to 7 days from the missed date, then the patient should administer the delayed injection and then resume the original schedule of alirocumab administration.

Please note that injections should not be administered within less than 7 calendar days. Please refer to [Section 10.4.1.3](#) for the definition of overdose with alirocumab.

8.1.2 Usual care treatment

There are five options available in the usual care arm including the option to add no additional LMT on top of the maximum dose/regimen of statin that is tolerated by the patient or to start one of the following treatments: ezetimibe, fenofibrate, omega-3 fatty acids or nicotinic acid. All patients, regardless of the usual care option that has been selected, should continue on the maximum dose/regimen of statin (non-IMP) that is tolerated by the patient.

The following drugs are identified as IMP:

- Ezetimibe,
- Nicotinic acid,
- Fenofibrate,
- Omega-3 fatty acids

The pharmaceutical form, dose and number of units per administration and timing of dosing of usual care treatment will be determined by the Investigator, and prescribed as per the Investigator's usual practice in accordance with local standard of care.

The usual care IMP will be financially supported by Sanofi. The Investigator will provide the patient with a prescription for usual care IMP at randomization and at Week 12 to cover the treatment period. The commercially available products will be delivered to the patient by the Investigator or other authorized persons (eg, pharmacist) according to the prescription.

8.1.2.1 Route and method of administration

LMT administered as part of the usual care treatment will be taken orally.

8.1.2.2 Timing of administration

LMT administered as part of the usual care treatment will be taken at approximately the same time of the day each day in accordance with Investigator's prescription and local prescribing information.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCT(S)

The following classes of drugs are identified as non-IMP because the medication is a background therapy:

- Statins

Background statin treatment will not be provided by the Sponsor. Patients will obtain these medications in compliance with local regulations.

8.3 BLINDING PROCEDURES

While allocation to treatment will be open-label, once a patient is randomized to alirocumab, data on the dose of alirocumab from Week 12 will be blinded. As such, alirocumab 75 mg and 150 mg will be provided in identically matched prefilled pens and will be packaged identically, which includes labeling to protect the blind. Each 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 IVRS/interactive web response (IWRs) that will be available 24 hours-a-day, 7 days-a-week.

Refer to [Section 10.5](#) for suspected unexpected ADR unblinding by the Sponsor.

8.3.1 Adverse event

Information on dose of alirocumab may be unblinded by the Pharmacovigilance Department for reporting to the Health Authority of any Suspected Unexpected Serious Adverse Reaction (SUSAR), ie, any Serious Adverse Event that is both unexpected (per the specific section of the Clinical Investigator's brochure and reasonably associated with the use of alirocumab according to either the judgment of the Investigator and /or the Sponsor.

Refer to [Section 10.5](#) on suspected unexpected ADR unblinding by the Sponsor.

8.3.2 Lipid parameters

Lipid parameter values from blood samples obtained after the randomization visit, run by the central lab, will not be communicated to the sites so that they cannot deduce the treatment effect based on non-HDL-C level attained. The sponsor's operational team will not have access to lipid parameters associated with patient identification until after the final database lock has occurred. For safety purposes, TG alerts for TG values ≥ 500 mg/dL any time after randomization will be sent to the Investigator ([Section 8.8.1](#) and [Section 9](#)).

At the end of the OLTP (Week 24 visit) the Investigator will continue to manage the patient's lipids in accordance with standard practice. Any lipid values after randomization should be redacted in the source documents and not shared with the Sponsor.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

The randomized list of treatment kit numbers will be generated centrally by Sanofi. Alirocumab (alirocumab 75 or 150 mg kits, or placebo training 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 centralized treatment allocation system provider. Then, this centralized treatment allocation system provider will generate the patient randomization list according to which it will allocate the treatments to the patients.

Patients will be randomized to receive either usual care or alirocumab during the OLTP. The randomization ratio alirocumab:usual care will be 2:1. For each patient randomized to alirocumab, there will be several corresponding treatment kit numbers (resupply visits), which will be allocated through the centralized treatment allocation system. The randomization is stratified by intent to prescribe usual care (eg, intent to prescribe ezetimibe, intent to prescribe fenofibrate).

The treatment kit numbers will be allocated using the centralized treatment allocation system on randomization visit (Day 1, Week 0), and then at Week 12 as re-supply visits, and at unscheduled visits if needed.

For patients in the alirocumab treatment arm, the treatment kit allocated at Week 12 will be based on their Week 8 non-HDL-C level following the up-titration rules ([Section 6.1](#)). Regular transfer of data will be planned between the central laboratory and the centralized treatment allocation system provider in order to proceed in a blinded manner for study sites and sponsor.

Before randomizing a patient, the Investigator or designee will have to contact the centralized treatment allocation system (eg, IVRS/IWRS).

A randomized patient is defined as a patient who is registered and, if randomized to alirocumab, 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, then the patient will be considered as not randomized and withdrawn from the study.

Two types of centralized treatment allocation systems will be used, the IVRS and the IWRS depending on the choice of the site.

8.5 PACKAGING AND LABELING

8.5.1 Alirocumab

For the OLTP, each open-label treatment kit will be prepared to contain 6 prefilled pens.

In order to protect the blinding of dose information, treatment kit boxes for injection provided at Week 12 will have the same look and feel and therefore will be labeled with the same label.

In addition to the open-label treatment kits for injection, a training kit containing 1 placebo for alirocumab prefilled pen will be prepared for the purpose of instructing patients on injection administration which is to be performed prior to randomization. If deemed necessary, a second injection training with placebo for alirocumab can be performed using an additional training kit prior to randomization. Injection training with placebo will be performed and documented in the source data and the CRF, including if the designated person who administers alirocumab to the patient changes during the course of the study.

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

8.5.2 Usual Care (IMP)

Packaging and labeling will be as per the manufactured product.

For the purpose of the study, labeling may be added in accordance with the local regulatory specifications and requirements.

8.6 STORAGE CONDITIONS AND SHELF LIFE

8.6.1 Alirocumab

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

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

Alirocumab will be stored in a refrigerator between +2°C and +8°C (36°F to 46°F) at the site. The temperature of the site refrigerator should be checked daily and recorded on a log sheet.

Alirocumab stored at the investigational site should be kept in an appropriate locked room, under the responsibility of the Investigator or designee or other authorized person in accordance with the storage conditions indicated on the label.

After the supply of alirocumab kits to patients at the study site visits, appropriate provisions will be in place for transportation of the alirocumab kits from the study site to the patient's refrigerator.

8.6.2 Usual Care

Usual care treatments (IMP) will be stored in accordance with manufacturer's instructions.

8.7 RESPONSIBILITIES

The Investigator, the hospital pharmacist, or other personnel 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 IMP 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 will the Investigator 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 (alirocumab or usual care) compliance and accountability are described below:

- The Investigator or designee will obtain via IVRS/IWRS the treatment kit number(s) and he/she will dispense the treatment kit(s) to the patient if the patient is randomized to alirocumab.
- The Investigator or designee will enter the treatment kit packaging number(s) and the kit numbers in the e-CRF, if applicable.
- Alirocumab administration data will be recorded by the patients onto a Patient diary. If the patient is randomized to usual care, a diary to collect information on treatment compliance will also be completed by the patient and data recorded into the CRF.
- For alirocumab:
 - Used pens (sharps container) and the treatment kit dispensed at the previous dispensation visit are brought back by the patient at Weeks 12 and 24, as applicable

- The Investigator or designee counts the number of remaining unused prefilled pens in the returned packs, checks the patient diary and fills in the Treatment Log Form at Weeks 12 and 24
- The monitor will check the data consistency between e-CRF pages and treatment log forms using the patient diary and returned, unused prefilled pens of a corresponding kit, as applicable.
- For usual care IMP:
 - Used treatment packaging (eg, blister packs, pill container) dispensed at the previous dispensation visit are brought back by the patient at Weeks 12 and 24, as applicable
 - The Investigator or designee counts the number of remaining treatments in the returned packs, checks the patient diary and fills in the Treatment Log Form at Weeks 12 and 24
 - The monitor will check the data consistency between e-CRF pages and treatment log forms using the patient diary and returned treatment packaging, as applicable.

The patient will be instructed on the importance to take the study treatment as planned for the remainder of the treatment duration.

8.7.2 Return and/or destruction of treatments

A detailed treatment log of the destroyed 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 before the Sponsor provides written authorization.

Sharp containers containing all used prefilled pens will be brought back to the site by the patient for the purpose of destruction, as applicable.

If the site is not able to destroy or destruction is not allowed in the country, all treatments kits will be retrieved by the Sponsor. A detailed treatment log of the returned IMP will be established with the Investigator or designee and countersigned by the Investigator and the Monitoring Team.

8.8 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient concomitantly to any IMP(s) during the study, until Week 32. This medication is not provided by the Sponsor.

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.

8.8.1 Management of background statin therapy

For background statin use, and for LMT used as part of the usual care treatment arm, sites must follow the national product label for the safety monitoring and management of patients.

Patients will be on stable, maximum dose/regimen of statin therapy that is tolerated by the patient without other LMT during the study as indicated in [Section 7](#).

Lipid profile values will be blinded from samples obtained after randomization. Nevertheless, for safety reasons, sites will be made aware of TG alerts ([Section 9](#)).

From the screening visit (Week -3) until the Week 24 visit, the background statin therapy should not be changed. No dose adjustment, discontinuation or initiation of other statins or other LMT (except as initiated as part of the usual care arm) should take place during this time, barring exceptional circumstances whereby overriding concerns (including but not limited to a TG alert posted by the central lab) warrant such changes, as per the Investigator's judgment. For a TG alert that has been confirmed by repeat testing, the Investigator should perform investigations, manage the patient, and modify the LMT as per his/her medical judgment. Please note that the only fibrate that is allowed is fenofibrate.

8.8.2 Contraception

Women of childbearing potential must use an effective contraceptive method throughout the entire duration of the study treatment and for at least 10 weeks after the last injection of alirocumab/last usual care treatment. The applied methods of contraception have to meet the criteria for a highly effective method of birth control according to the "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. ICH. 2009 Jun: 1-25.*"

*Note: Highly effective methods of birth control are defined as those, alone or in combination, that result in a low failure rate (ie, less than 1% per year) when used consistently and correctly. Please refer to [Appendix C](#).

8.8.3 Prohibited concomitant medications

The following therapies are not allowed during the study (including the screening period until the end of treatment visit):

- Red yeast rice products
- Other PCSK9 inhibitors
- Bile acid sequestrants
- Fibrates other than fenofibrate
- Over the counter products/nutraceuticals known to impact lipids (eg, plant stanols such as found in Benecol, flax seed oil, and psyllium) except for omega-3 fatty acids which may be used as part of the usual care arm.

Note: while red yeast rice is considered a dietary supplement/nutraceutical, it contains HMG CoA reductase inhibitor activity (mechanism of action of statins), along with other active ingredients. Because such products lack standardization, varying amounts of the active substance could lead to alterations in lipids during the study and potentially confound endpoint assessment.

8.8.4 Lifestyle and dietary habits

Lifestyle and dietary habits should be maintained if possible throughout the entire study duration, as medically feasible. During the study, the Investigator may reinforce diet recommendations according to local/regional guidelines.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

Lipid parameters

Blood sampling to determine lipid parameters (ie, Total-C, LDL-C, HDL-C, TGs, non-HDL-C, Apo B, Apo A-1, ratio Apo B/Apo A-1, Apo C-III, lipid subfractions by NMR spectroscopy (ie, LDL particle size and LDL, VLDL, HDL, IDL particle number), and Lp [a]) should be performed 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.

Total-C, HDL-C, TGs, Apo B, Apo A-1, Apo C-III and Lp(a) will be directly measured by the Central Laboratory as per the schedule in [Section 10](#). LDL-C will be directly measured via beta quantification method by the Central Laboratory as per the schedule in [Section 1.2](#). LDL-C will be calculated using the Friedewald formula at all visits (except Weeks 4 and 32) (39). If TG values exceed 400 mg/dL (4.52 mmol/L) then the central lab will reflexively measure (via the beta quantification method) the LDL-C rather than calculating it. Non-HDL-C will be calculated by subtracting HDL-C from the Total-C. Ratio Apo B/Apo A-1 will be calculated. Triglyceride rich lipoprotein will be calculated by total cholesterol minus HDL cholesterol minus LDL cholesterol (40). Detailed procedures of sample preparation, storage and shipment will be described in the specific laboratory manual which will be provided to sites. [REDACTED]

All patients will qualify for randomization based on the non-HDL-C value obtained at Week -3 visit. If the patient is not fasting at this or any other visit requiring fasting, then he/she will be asked to come the day after or as close as possible to this date for the blood sampling.

Communication of lipid results by central lab

The lipid results from blood samples obtained after the randomization visit will not be communicated to the Investigators. However, sites will be notified in the event of a TG level ≥ 500 mg/dL (5.65 mmol/L) obtained any time after randomization (ie, TG alert). Repeat testing should be done as soon as possible after a TG alert. For a confirmed TG alert, please refer to relevant information in [Section 8.8.1](#).

Efficacy endpoints will not be considered as AEs, such as those involving abnormalities in lipid levels, unless meeting the criteria in [Section 10.4.2](#).

9.1 PRIMARY ENDPOINT

9.1.1 Primary endpoint

The primary endpoint is the percent change in non-HDL-C from baseline to Week 24 in the intent-to-treat (ITT) population, using all non-HDL-C values regardless of adherence to treatment (ITT estimand).

The percent change is defined as:

$100 \times (\text{non-HDL-C value at Week 24} - \text{non-HDL-C value at baseline}) / \text{non-HDL-C value at baseline}$.

The baseline non-HDL-C value will be the last non-HDL-C level obtained before randomization for all patients. The non-HDL-C at Week 24 will be the non-HDL-C level obtained within the Week 24 analysis window.

All non-HDL-C values (scheduled or unscheduled, fasting or not fasting) between Weeks 8 to 24 may be used to provide a value for the primary endpoint, if appropriate, according to above definition.

The analysis window used to allocate a time point to a measurement will be defined in the statistical analysis plan (SAP).

9.2 SECONDARY ENDPOINTS

9.2.1 Key secondary efficacy endpoints (ITT estimand)

- Percent change in measured LDL-C from baseline to Week 24.
- Percent change in non-HDL-C from baseline to Week 12.
- Percent change in measured LDL-C from baseline to Week 12.
- Percent change in Apo B from baseline to Week 24.
- Percent change in Total-C from baseline to Week 24.
- Percent change in Lp(a) from baseline to Week 24.
- Percent change in TGs from baseline to Week 24.
- Percent change in HDL-C from baseline to Week 24.
- Percent change in LDL particle number from baseline to Week 24.

9.2.2 Diabetes-related endpoints (ITT estimand)

- Absolute change in HbA1c from baseline to Weeks 12 and 24.
- Absolute change in fasting plasma glucose (FPG) from baseline to Weeks 12 and 24.

- Absolute change in number of glucose-lowering treatments from baseline to Weeks 12 and 24.

9.2.3 Safety endpoints

Safety parameters (AEs, laboratory parameters, vital signs) will be assessed throughout the study.

The observation of safety data will be as follows:

- Pre-treatment period is defined from the signed informed consent up to the first dose of open-label alirocumab injection/first dose of usual care treatment for those prescribed another LMT if allocated to the usual care arm. For those allocated to the usual care arm for whom another LMT is not prescribed, the pre-treatment period will end on Day 1 at the time of randomization.
- Treatment Emergent Adverse Event period is defined as the time from the first dose of open-label alirocumab injection to the last dose of open-label treatment + 70 days (10 weeks) as residual effect of treatment could be expected until 10 weeks after the stop of alirocumab. For patients randomized to usual care, this will be considered as 70 days after the last usual care treatment (IMP) has been administered, or Study Day 225, whichever comes first. For patients who are randomized to usual care and the Investigator has not prescribed an additional LMT, the “date of last dose of usual care” is defined as the date of the last on-site visit.
- Post-treatment period is defined as the time starting the day after the end of the TEAE period up to resolution/stabilization of all SAE and AESI, whichever comes last.

9.2.3.1 Adverse events

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

All AEs diagnosed by the Investigator 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.

Adverse events/AESIs, SAEs, and product complaints will be collected from the time the patient signs the ICF to the last scheduled study visit.

Definitions for AEs, SAEs, and AESI, as well as obligation for reporting are further defined in [Section 10.4.1](#) and [Section 10.5](#).

Adverse events of special interest

For this study, the following AEs are AESI:

- Increase in ALT

- Allergic events
- Local injection site reactions that are allergic in nature
- Pregnancy
- Symptomatic overdose with alirocumab
- Neurologic events
- Neurocognitive events

Additional information can be found in [Section 10.4.1.3](#) and [Appendix D](#).

9.2.3.2 Laboratory safety variables

The clinical laboratory data consist of blood analysis (including hematology, clinical chemistry and urinalysis [UA]). Clinical laboratory values will be analyzed after conversion into standard international units. International units will be used in all listings and tables.

9.2.3.3 Vital signs

Vital signs include: height at baseline, weight, BMI, heart rate (HR), systolic and diastolic blood pressure (BP).

9.2.4

9.2.5 Other endpoints

9.2.5.1 Pharmacokinetics

Total and Free PCSK9 concentrations will be measured at baseline, Week 12 and Week 24.

9.2.5.1.1 Sampling time

Serum samples for PCSK9 measurement will be collected in accordance with the study flowchart ([Section 1.2](#)). Exact date and time of sampling is to be recorded.

9.2.5.1.2 Sampling procedure

Detailed procedure of sample preparation, storage and shipment will be described in the specific laboratory manual which will be provided to sites.

9.2.5.1.3 *Bioanalytical method*

9.2.5.2 *Anti-alirocumab antibody assessments*

Anti-alirocumab antibodies include the antibody status (positive/negative) and antibody titers. Further details will be provided in SAP.

9.2.5.2.1 *Sampling time*

Serum samples for anti-alirocumab antibodies determination will be drawn periodically throughout the study as per schedule noted in the study flowchart ([Section 1.2](#)). All samples will be obtained before alirocumab injection (pre-dose) for patients randomized to alirocumab.

9.2.5.2.2 *Sampling procedure*

Detailed procedure of sample preparation, storage and shipment will be described in a specific laboratory manual which will be provided to sites.

9.2.5.2.3 *Bioanalytical method*

9.2.6 *Other efficacy endpoints (ITT estimand)*

- Percent change in calculated LDL-C from baseline to Weeks 12 and 24.
- Percent change in Apo B, Total-C, Lp(a), TGs, HDL-C from baseline to Week 12.
- Proportion of patients reaching measured LDL-C <50 mg/dL (1.30 mmol/L), <70 mg/dL (1.81 mmol/L) and < 100 mg/dL (2.59 mmol/L) at Weeks 12 and 24.
- Percent change in measured LDL-C according to baseline TGs of <median TG or \geq median TG at Weeks 12 and 24.
- Proportion of patients reaching non-HDL-C <130 mg/dL (3.37 mmol/L), <100 mg/dL (2.59 mmol/L) and <80 mg/dL (2.07 mmol/L) at Weeks 12 and 24.

- Percent change in TGs from baseline to Weeks 12 and 24 according to baseline TGs of <median TG or ≥median TG.
- Percent change in LDL particle number from baseline to Week 12.
- Percent change in LDL particle size from baseline to Weeks 12 and 24.
- Percent change in VLDL, HDL and IDL particle number from baseline to Weeks 12 and 24.
- Percent change in Apo A-1 and Apo-C-III from baseline to Weeks 12 and 24.
- Absolute change in TGRLs (ie, non-HDL-C minus LDL-C) from baseline to Weeks 12 and 24.
- Proportion of patients with 50% or greater reduction from baseline in measured LDL-C at Weeks 12 and 24.
- The proportion of patients reaching Apo B < 80 mg/dL at Weeks 12 and 24.
- Absolute change in ratio Apo B/Apo A-1, Total-C/HDL-C and LDL-C/HDL-C from baseline to Weeks 12 and 24.

9.3 FUTURE USE OF SAMPLES

Not applicable.

9.4 APPROPRIATENESS OF MEASUREMENTS

The primary endpoint of the change in non-HDL-C from baseline is a valid measure to determine CV risk, as explained in [Section 4](#).

10 STUDY PROCEDURES

The window period for Week 0 is + 3 days. The window period for Weeks 8, 12 and 24 is ± 3 days. The window period for Weeks 4, 20, and 32 is ± 7 days.

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

Blood sampling

All blood sampling, including the blood sampling for determination of lipid parameters (eg, Total-C, LDL-C, HDL-C, TGs, non-HDL-C, Apo A, Apo B, Apo C-III, Lp(a), lipid subfractions by NMR spectroscopy) and also for plasma glucose should be performed in the morning, in fasting condition (ie, overnight, at least 10 to 12 hours fast and refrain from smoking), and before IMP/statin administration 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 the patient is not in fasting conditions, the blood sample will not be collected and a new appointment will be given to the patient for the day after (or as close as possible to this date), with instructions to fast (see above conditions).

Laboratory tests

The laboratory data are collected in accordance with the study schedule and the details provided in the Study Flow Chart ([Section 1.2](#)).

- Hematology: all visits except Weeks 4 and 20; may be performed at Week 0 as applicable and based on the clinical discretion of the Investigator
- Chemistry: all visits except Weeks 4 and 20; may be performed at Week 0 as applicable and based on the clinical discretion of the Investigator, except for plasma glucose which should be performed at Week 0 for all patients
- HbA1c: screening and Weeks 0, 12, and 24
- Lipid panel: screening and Weeks 0, 8, 12, 20, and 24
- Measured LDL-C via beta quantification: screening and Weeks 0, 8, 12, 20, and 24
- Other lipid assessments (Apo B, Apo A-1, Apo C-III, lipid subfractions by NMR spectroscopy, Lp[a]): Weeks 0, 8, 12, 20, and 24
- Liver panel: all visits except Weeks 4 and 20; may be performed at Week 0 as applicable and based on the clinical discretion of the Investigator. In case of total bilirubin values above the normal range, differentiation into conjugated and non-conjugated bilirubin will occur automatically
- CPK: all visits except Weeks 4 and 20; may be performed at Week 0 as applicable and based on the clinical discretion of the Investigator.

- Hepatitis B surface antigen: screening only.
- Hepatitis C antibody: at screening and Week 24; in case of ALT increase during the study, hepatitis C antibody should be determined. If Hepatitis C antibody is positive during the study, reflexive testing should be performed.
- Pregnancy testing (in women of childbearing potential only): serum pregnancy test at screening only. Urine pregnancy test at Weeks 0 and 24.
- Thyroid stimulating hormone: screening only for patients who are taking thyroid hormone replacement.
- PCSK9 levels will be measured at Weeks 0, Week 12, and Week 24.
- Anti-alirocumab antibodies: Weeks 0, Week 12, and Week 24.

Urine samplings

Urinalysis will be performed at screening and Week 24 visits. Dipstick will be performed and will assess for pH, specific gravity, and for the presence of blood, protein, glucose, ketones, nitrates, leukocyte esterase, uro-bilinogen and bilirubin. If the dipstick is abnormal then standard microscopy will be conducted. Microscopy will evaluate for the presence of red blood cells (RBC), RBC clumps, white blood cells (WBC), WBC clumps, epithelial cells (transitional, renal tubular, and squamous), casts (hyaline, epithelial, WBC, RBC, granular, fatty, cellular, broad, waxy), crystals (triple phosphate, calcium oxalate, calcium phosphate, calcium carbonate, uric acid, amorphous, ammonium biurate, bilirubin, leucine, tyrosine, cystine), bacteria, yeast-budding, yeast-hyphae, trichomonas, oval fat body, fat, mucous, and sperm.

Spot urine testing will be performed for albumin and creatinine to calculate the albumin: creatinine ratio at the screening and Week 24 visits.

Notes: Any clinically relevant abnormal laboratory value should be immediately rechecked for confirmation before making any decision for the concerned patient. It should be documented as an AE/AESI/SAE if one or more criteria in [Section 10.4.2](#) are met.

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in [Appendix E](#) and should be followed by Investigators.

Physical examination

A general physical examination should be performed at the time points indicated in the study schedule flowchart ([Section 1.2](#)). If a new clinically significant abnormality or worsening from baseline is detected after inclusion, 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 judgment.

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 comfortably in sitting position for at least 5 minutes). Values are to be recorded in the e-CRF; both systolic BP and diastolic BP should be recorded. At the first screening visit, BP should be measured in both arms. The arm with the highest diastolic pressure will be determined at this visit, and BP should be measured on this arm throughout the study. This highest value will be recorded in the e-CRF.

Heart rate will be measured at the time of the measurement of BP.

Notes: in case of high BP values, the Investigator is responsible for the optimization of the patient's treatment to achieve BP targets as defined by local guidelines/regional standards of care.

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.

Height needs to be measured, as self-reported heights are not acceptable.

[REDACTED]

[REDACTED]

10.1 VISIT SCHEDULE

10.1.1 Screening period

Only patients who meet the inclusion criteria as noted in [Section 7.1](#) should be screened. The screening period will take place up to 3 weeks prior to randomization/Day 1 visit. Please note that every effort should be made to ensure that the screening window is as short as possible. If it is planned to have another designated person administer the injections to the patient during the study, then this person should be present for injection training.

Screening visit (Week -3/ Day -21 up to Day -8)

- Complete informed consent - the patient will receive complete information about the study both verbally and in writing. Written informed consent for the study must be obtained prior to any investigations.
- Assess inclusion/exclusion criteria
- Obtain patient demography – age, gender, race, and ethnicity
- Obtain medical history (including menopausal status), diabetes history, 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 of age in a female, first degree relative], and family history of allergy)
- Take prior medication history within the previous 12 weeks, especially for LMT and nutraceutical products that may affect lipids (eg, omega-3 fatty acids at doses <1000 mg, plant stanols such as found in Benecol, flax seed oil, psyllium)
- Record concomitant medication
- Record statin treatment, as applicable
- Perform physical examination
- Get body weight and height measurements.
- Take vital signs including HR and BP
- 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 (the 3-digit patient chronological number is 001 for the first patient screened at a center, 002 for the second patient screened at the same center...).
- Collect AEs from this point onward
- Collect UA/spot urine albumin: creatinine
- Obtain fasting blood samples for:
 - Lipids: total-C, calculated LDL-C, measured LDL-C, HDL-C, TGs, non-HDL-C
 - Hematology: blood cell count including hematocrit, hemoglobin, RBC count, red blood cell distribution width (RDW), WBC count with differential count and platelets
 - Chemistry: plasma glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, uric acid, total protein, albumin, lactate dehydrogenase (LDH), and gamma-glutamyl transpeptidase (GGT)
 - HbA1c
 - Liver panel (ALT, AST, alkaline phosphatase (ALP), and total bilirubin)
 - CPK
 - Hepatitis B surface antigen and Hepatitis C antibody tests.
 - Serum pregnancy test (women of childbearing potential only).
 - TSH (for patients on thyroid hormone replacement therapy)

Note: if the 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 patient with instruction to be fasted (at least 10 to 12 hours fasting). Alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the blood sampling are discouraged.

- Perform injection training

- Injection training should be provided as outlined in [Section 8.1.1](#). The training injection (placebo) should be administered by the patient or another designated person (such as spouse, relative, etc) at the study site under supervision of site staff with appropriate feedback.
- If patient will undergo the second optional injection training, then the following steps are needed. However, if patient does not need a second optional training injection with placebo then do not perform these steps.
 - Recontact IVRS/IWRS for allocation of a second new packaging number for a second training kit.
 - Record the second packaging number allocated in e-CRF.
 - Dispense the second training injection kit to the patient for self-administration.

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

- Give an appointment for the next visit.
- If it is planned to have another designated person administer the injections to the patient during the study, and the designated person did not perform injection training at the screening visit, then the designated person should also be present at the next visit (Week 0).

10.1.2 Open-label treatment period (study visits)

10.1.2.1 Randomization visit (Week 0/Day 1)

- Assess Inclusion/Exclusion Criteria
- Collect AEs
- Record concomitant medication
- Record statin treatment, as applicable
- Get body weight measurement
- Reinforce diet recommendations according to local/regional guidelines, if needed
- Perform physical examination
- Take vital signs including HR and BP
- If the patient is confirmed eligible, the Investigator will start the next study procedures:
- Urine pregnancy test (women of childbearing potential only).
- Obtain fasting blood sample for:
 - Lipids: total-C, LDL-C (calculated via Friedewald and measured via beta quantification), HDL-C, TGs, non-HDL-C, Apo B, Apo A-1, Apo C-III, ratio Apo B/Apo A-1, lipid subfractions by NMR spectroscopy (ie, LDL particle size and LDL, VLDL, HDL, IDL particle number) and Lp(a)

- HbA1c
- Anti-alirocumab antibodies
- Serum PCSK9 levels
- Plasma glucose
- Obtain blood samples for the following only if clinically relevant abnormal values at the screening visit, based on the judgment of the Investigator:
 - Hematology: blood cell count including hematocrit, hemoglobin, RBC count, RDW, WBC count with differential count and platelets
 - Chemistry: sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, uric acid, total protein, albumin, LDH and GGT
 - Liver panel (ALT, AST, ALP, and total bilirubin)
 - CPK


Note: if the 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 patient with instruction to be fasted (at least 10 to 12 hours fasting). Alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the blood sampling are discouraged.

- IVRS procedures:
 - Investigator to enter the selection of usual care treatment into IVRS/IWRS
 - IVRS/IWRS contact for randomization and if randomized to alirocumab, allocation of a 7-digit treatment kit number according to the randomization list. Investigators should never allocate a treatment kit number to a patient without contacting IVRS/IWRS.
- Provide open-label alirocumab IMP kit if randomized to alirocumab
 - The first alirocumab IMP administration will take place at the study site, but only after the collection of the fasting blood samples. Close supervision, feedback and further training to be provided for alirocumab administration. The patient should be observed for at least 30 minutes after the injection.
- If randomized to usual care, provide prescription based on treatment entered into IVRS, as applicable, see [Section 8.1.2](#)
- Provide the Patient diary and instruct the patient to complete it
- Reminders to be communicated to the patient
 - An appointment will be given for the next phone call and study site visit.
 - Remind patient to be in fasting conditions (ie, overnight, at least 10-12 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.

10.1.2.2 Week 4 (phone call)

- Record concomitant medication
- Record statin treatment, as applicable
- Collect information on IMP administration (alirocumab or usual care) (Patient diary)
- Collect information on AEs/product complaints (if any)
- Reinforce diet recommendations according to local/regional guidelines, if needed
- Reminders to be communicated to the patient:
 - Alirocumab administration should be Q2W, for patients randomized to alirocumab
 - Reinforce adherence to usual care treatment, for patients randomized to usual care.
 - Next study site visit appointment.
 - Fasting conditions (ie, overnight, at least 10-12 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.
 - Bring the Patient diary completed since randomization to the next study site visit

10.1.2.3 Week 8, Week 12, and Week 20

- Collect AEs/product complaints
- Record concomitant medication
- Record statin treatment, as applicable
- Get body weight measurement
- Reinforce diet recommendations according to local/regional guidelines, if needed
- Take vital signs including HR and BP
- Perform physical examination (Week 12 only)
- IVRS/IWRS contact if randomized to alirocumab (Week 12 only)
- Data collection on IMP administration and check by review of Patient diary
- Provide (Week 12 only):
 - Open-label alirocumab IMP kit, if randomized to alirocumab and instruction for use
 - Prescription for usual care treatment (IMP) if randomized to usual care, as applicable, see [Section 8.1.2](#)
 - Patient diary
- 
- Obtain fasting blood sample for:
 - total-C, LDL-C, HDL-C, TGs, non-HDL-C,
 - measured LDL-C (beta quantification)

- Apo B, Apo A-1, ratio Apo B/Apo A-1, Apo C-III, lipid subfractions by NMR spectroscopy and Lp(a)
- Obtain blood samples for
 - Hematology: blood cell count including hematocrit, hemoglobin, RBC count, RDW, WBC count with differential count and platelets (Weeks 8 and 12 only)
 - Chemistry: plasma glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, uric acid, total protein, albumin, LDH, and GGT (Weeks 8 and 12 only)
 - HbA1c (Week 12 only)
 - Liver panel (ALT, AST, ALP, and total bilirubin) (Weeks 8 and 12 only)
 - CPK (Weeks 8 and 12 only)
 - Anti-alirocumab antibodies (Week 12 only)
 - Serum PCSK9 levels (Week 12 only)

Note: if the 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 patient with instruction to be fasted (at least 10 to 12 hours fasting). Alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the blood sampling are discouraged.

- Reminders to be communicated to the patient
 - An appointment will be given for the next study site visit.
 - Remind patient to be in fasting conditions (ie, overnight, at least 10-12 hours fast and refrain from smoking) for next study site visit. Alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the next study site visit are discouraged.
 - Bring used pens (sharps container) and the treatment kit dispensed at the previous dispensation visits (Weeks 12 and 24) if randomized to alirocumab
 - Bring used treatment packaging (eg, blister packs, pill container) dispensed at the previous dispensation visits (Weeks 12 and 24) if randomized to usual care, as applicable

10.1.2.4 Week 24 / end of treatment visit

- Collect AEs/product complaints
- Record concomitant medication
- Record statin treatment, as applicable
- Get body weight measurement
- Reinforce diet recommendations according to local/regional guidelines, if needed
- Take vital signs including HR and BP

- Perform physical examination
- IVRS/IWRS contact
- Data collection on IMP administration and compliance by review of Patient diary and treatment kit
- [REDACTED]
- Urinalysis and spot albumin: creatinine
- Urine pregnancy test (women of childbearing potential only).
- Obtain fasting blood sample for lipids:
 - total-C, LDL-C, HDL-C, TGs, non-HDL-C, Apo B, Apo A-1, ratio Apo B/Apo A-1, Apo C-III, lipid subfractions by NMR spectroscopy and Lp(a)
 - measured LDL-C (beta quantification)
- Obtain blood samples for
 - Hematology: blood cell count including hematocrit, hemoglobin, RBC count, RDW, WBC count with differential count and platelets
 - Chemistry: plasma glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, uric acid, total protein, albumin, LDH, and GGT
 - Hepatitis C Antibody Test
 - HbA1c
 - Liver panel (ALT, AST, ALP, and total bilirubin)
 - CPK
 - Anti-alirocumab antibodies
 - Serum PCSK9 levels
- Reminder to report any AEs up to Study Day 225.

Specific cases if patient prematurely discontinues the study:


- if treated with IMP, AEs would need to be reported up to 70 days after the last dose of IMP or Study Day 225, whichever comes first (even if patient continues on the usual care treatment that was added at randomization after discontinuing the study).
- if randomized to usual care without additional LMT, AEs would need to be reported up to 70 days after the last on-site study visit, or Study Day 225, whichever comes first.

10.1.2.5 Week 32 / 10 weeks after last alirocumab injection (phone call)

- Record concomitant medication, noting also whether the patient has started a commercially available PCSK9 inhibitor
- Record statin treatment, as applicable

- Collect information on AEs (if any)

10.2 DEFINITION OF SOURCE DATA

- Agreement, date, and signature of informed consent mentioning the study identification.
- Patient identification, last participation in a clinical trial, medical history, associated diseases, and data related to the studied pathology.
- Contraception methods for women of childbearing potential.
- Previous and concomitant medications (including insulin use [eg, type of insulin, frequency, and dose], other antihyperglycemics, and the use of LMT, especially statins used, with doses, or to document statin intolerance).
- Study identification.
- Treatment number, dates of administration.
- Dates of visits and assessments including the examination report.
- Vital signs (HR, BP), height, body weight.
- Faxed lab reports (dated and signed by the Principal Investigator or Sub-Investigator documenting timeliness of review).
- IVRS/IWRS confirmation fax.
- 
- Patient diary
- Adverse events and follow-up:
 - In case of SAE/AESI, 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/AESI. The site should make every effort to obtain details of all consultations, hospital records, etc to document the event. All attempts to obtain information should be noted in the source documents.
- Date of premature study discontinuation (if any) and reason.
- Source documentation may be found in the following:
 - Patient's identity
 - Medical history
 - Hospital records
 - Nursing notes
 - Physician's notes
 - Laboratory and procedure reports.

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

The IMP should be continued whenever possible. In case the IMP is stopped, it should be determined whether the stop can be made temporarily; permanent IMP discontinuation should be a 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 [Section 7.2](#)).

For all temporary treatment discontinuations, duration should be recorded by the Investigator in the appropriate pages of the CRF.

Temporary treatment discontinuation is defined as one or more scheduled injections (for patients randomized to alirocumab) or one or more missed doses of IMP (if randomized to usual care) that are not administered to the patient as decided by the Investigator.

This section is not applicable for patients who are randomized to usual care for whom no additional LMT is added.

10.3.2 Permanent treatment discontinuation with investigational medicinal product(s)

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator or the patient not to re-expose the patient to the IMP at any time. Patient withdrawal from the study treatment or study should be avoided as much as possible.

This section is not applicable for patients who are randomized to usual care for whom no additional LMT is added.

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. All efforts should be made to document the reasons for treatment discontinuation and this should be documented in the CRF or e-CRF.

Patients should discontinue IMP for the following reasons:

- Pregnancy, intention for pregnancy, or no longer with effective contraceptive method of birth control (females only).
- Acute injection reaction of clinical concern (if randomized to alirocumab).
- Serious adverse event (or non-serious but severe in intensity) of hypersensitivity reaction considered related to IMP.
- At patient request, ie, withdrawal of the consent for treatment.
- 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 (eg, laboratory abnormalities, please refer to decision tree in [Appendix E](#)).
- At the specific request of the Sponsor.
- Patient receives open-label treatment prior to randomization

Any abnormal laboratory value will be immediately rechecked for confirmation (within 24 hours if possible), before making a decision of permanent discontinuation of the IMP for the concerned patient.

This section is not applicable for patients who are randomized to usual care for whom no additional LMT is added.

10.3.4 Handling of patients after permanent treatment discontinuation

Patients will be followed-up according to the study procedures as specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last. This means that patients who prematurely discontinue study treatment (regardless of the reason) should still continue the study and undergo all visits and procedures as described in [Section 1.2](#) with the exception of study treatment administration and its associated procedures. If possible, and after the permanent discontinuation of treatment, the patients will be assessed using the procedure normally planned for the end of open-label treatment visit (this should take place within 5 days of treatment discontinuation, if possible) and then resume the original study schedule until end of study.

If after treatment discontinuation, the patient refuses to resume the original study schedule until the end of the study, then if possible, the patient should undergo an unscheduled visit with assessments normally planned at the end of open-label treatment visit (it should take place within 5 days of treatment discontinuation, if possible). The patient, at a minimum, should then be followed-up for at least 10 weeks from the last administration of IMP or until recovery or stabilization of any AE as specified in this protocol, whichever comes last. A final end of study phone visit will take place 10 weeks after the premature discontinuation.

All cases of permanent treatment discontinuation should be recorded by the Investigator in the appropriate pages of the CRF when considered as confirmed. IVRS/IWRS should be notified when a patient prematurely discontinues study treatment. In the medical record, at least the date of the withdrawal and the reason should be documented.

This section is not applicable for patients who are randomized to usual care for whom no additional LMT is added.

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. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-patient contact follow-up, eg, medical records check. Patients requesting withdrawal should be informed that withdrawal of consent for follow-up may jeopardize the public health value of the study. If possible, the patients should be assessed using the procedures defined above.

Patients who withdraw should be explicitly asked about the contribution of possible AEs to their decision to withdraw consent, and any adverse event information elicited should be documented. Preferably the patient should withdraw consent in writing and, if the patient or the patient's representative refuses or is physically unavailable, the site should document and sign the reason for the patient's failure to withdraw consent in writing.

If possible, the patients are assessed using the procedure normally planned for the end of open-label treatment visit.

For patients who fail to return to the site, unless the patient withdraws the consent for follow-up, the Investigator should make the best effort to recontact the patient (eg, contacting patient's family or private physician, reviewing available registries or health care databases), 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 (eg, times and dates of attempted telephone contact, receipt for sending a registered letter).

The SAP will specify how the primary endpoints of patients who are lost to follow-up will be considered.

Patients who have withdrawn from the study cannot be re-randomized (treated) in the study. Their inclusion and treatment numbers 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 (ie, 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 (ie, 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
- Suspected transmission of an infectious agent: if any suspected transmission of an infectious agent via a medicinal product (eg, product contamination)

10.4.1.3 Adverse event of special interest

An 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. Adverse events of special interest may be added or removed during a study by protocol amendment. Please refer to protocol [Section 10.4.4](#).

For this study, the AESI are:

- Increase in ALT.
 - ALT ≥ 3 x ULN (if baseline ALT <ULN) or ALT ≥ 2 times the baseline value (if baseline ALT \geq ULN) (See [Appendix E](#)).
- Pregnancy:
 - Pregnancy occurring in a female patient or the partner of a male patient (if permitted by the female partner and by local regulatory authorities) during the study or within 70 days following the last dose of study drug (open-label alirocumab) or 70 days following the last dose of usual care treatment (IMP) (as applicable) or Day 225, whichever comes first. If the patient is randomized to usual care and the Investigator has not prescribed an additional LMT, the "date of the last dose of study drug" is defined as the date of the last on-site study visit.
 - Pregnancy will be recorded as AESI in all cases. Pregnancy will be qualified as an SAE only if it fulfils one or more SAE criteria.
 - In the event of pregnancy of a female patient included in the study, study product should be discontinued.
 - The follow-up of the pregnancy will be mandatory until the outcome has been determined.
- Symptomatic overdose with alirocumab:
 - An overdose (accidental or intentional) is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic injection counts) and defined as at least twice of the intended dose within the intended therapeutic interval (ie, 2 or more injections are administered in <7 calendar days), to be reported using the Term "symptomatic OVERDOSE" (accidental or intentional), indicating the circumstance in parentheses (eg, "symptomatic overdose [accidental]" or "symptomatic overdose [intentional]"). The patient should be monitored and appropriate symptomatic treatment instituted.
 - The circumstances of the overdose should be clearly specified in the verbatim and symptoms entered on separate AE/SAE forms.
 - Of note, asymptomatic overdose should be reported as a standard AE.
- Other project specific AESI(s)
- Allergic events (including local injection site reactions that are allergic in nature):

- Allergic drug reactions and/or local injection site reactions deemed to be allergic by the Investigator (or have an allergic component), that require consultation with another physician for further evaluation of hypersensitivity/allergy as per the Investigator's medical judgment should be reported as an AESI.

Note: Other local injection site reactions are non-AESIs. Please see [Section 10.4.1.4](#) for details.

- Neurologic events:
 - Neurologic events that require additional examinations/procedures and/or referral to a specialist should be reported as an AESI. If the event does not require additional examinations/procedures and/or referral to a specialist, it should be reported as a standard adverse event.
- Neurocognitive events
 - All neurocognitive events will be considered as AESI

Note: The definition of AEs and AESIs, the reporting time frame, and the corresponding complementary forms in the e-CRF to be completed are summarized in [Appendix D](#).

10.4.1.4 Local injection site reactions

Local injection site reactions that are considered non-allergic (eg, local injection site reactions related to mechanics of injection) or allergic but not requiring consultation with another physician are not considered as AESIs but should be reported as standard AEs.

Local injection site reactions that are considered by the Investigator as non-allergic events and that are related to the alirocumab injection, as opposed to another injectable agent, should be further characterized by evaluating the related symptoms that comprise an injection site reaction such as but not limited to redness, pain, etc.

Under certain circumstances, no AE of local injection site reactions should be reported as this is not typically considered a clinically important finding:

- The patient has erythema/redness, and/or swelling, and all <2.5 cm, AND
- The swelling does not interfere with activity, AND
- No other signs or symptoms are involved.

Note: if the patient has a reaction of swelling with a diameter <2.5 cm that interferes with activity, it should be considered as a clinically relevant finding and should be reported as an AE with a corresponding intensity of moderate or severe, in accordance with [Appendix G](#).

The definition of local injection site reactions, the reporting time frame, and the corresponding complementary forms in the e-CRF to be filled are summarized in [Appendix D](#).

10.4.1.5 Device deficiency

[REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

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.
- All product complaints associated or not to an AE are to be recorded immediately on the corresponding products (study medical device) complaints pages and reported to the local Complaint Service immediately (within 24 hours).
- 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, or until death, in order to ensure the safety of the patients. 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 (See [Section 10.4.4](#))

10.4.3 Instructions for reporting serious adverse events

In the case of occurrence of an SAE, the Investigator or any designees 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 monitoring team after approval of the Investigator within the e-CRF or after a standard delay.
- SEND (preferably by fax or e-mail) a photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring team whose name, fax number, and email address appear on the clinical trial protocol. Care should 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 results, include the laboratory normal ranges. If for any reason, results of lipid values are indicated on any source documents (done for the safety of a patient in exceptional circumstances only), all such information should be redacted.
- 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 knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life threatening within a week (7 days) of the initial notification.
- A back-up plan (using a paper CRF process) is available and should be used when the e-CRF system does not work

In case of e-CRF back-up:

- SEND (within 24 hours, preferably by fax or e-mail) the signed and dated corresponding page(s) from the CRF to the representative of the monitoring team whose name, fax number and e-mail address appear in the clinical trial protocol.
- ATTACH a photocopy of all examinations carried out and the dates on which these examinations were performed. Care should 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 results, include the laboratory normal ranges.

- All further documentation should be sent to the monitoring team within 24 hours of knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life threatening within a week (7 days) of the initial notification.

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 alirocumab with a reasonable possibility, should be reported to the monitoring team.

10.4.4 Guidelines for reporting adverse events of special interest

For each defined AESI the Investigator must make every attempt to collect additional specific information such as:

- Preexisting related condition or lifestyle of interest for the AE (eg, habits, CV risk factor).
- Expected list of associated signs and symptoms.
- Corrective actions (eg, treatment discontinuation, concomitant treatment).
- Diagnostic actions (eg, test(s) or procedure(s) results).
- Additional descriptive factors.
- Sequelae.

For these AEs, the Sponsor must be informed immediately (ie, 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. Please refer to [Section 10.4.1.3](#) for a listing of AESI and [Appendix D](#) or a summary of reporting AEs.

10.4.5 Guidelines for management of specific laboratory abnormalities

The following laboratory abnormalities should be monitored, documented, and managed according to the related flow chart in [Appendix E](#). Reporting instructions are provided in [Appendix D](#).

- Neutropenia
- Thrombocytopenia
- Increase in ALT
- Acute renal insufficiency
- Increase in CPK (other than cardiac-related) and suspicion of rhabdomyolysis

Investigators are strongly encouraged to follow these algorithms in [Appendix E](#), especially in situations where the abnormality persists or when there is no clear explanation for the observed abnormality. However there may be situations where these algorithms are not entirely applicable; therefore, the Investigator may use his/her best judgment. Also, in some situations, the Sponsor may wish to discuss with the Investigator. Examples where these algorithms may not be applicable include, but are not limited to, the following situations:

- Patients with known stable, low or borderline neutrophil count at baseline
- Patients with known stable, low or borderline platelet count at baseline
- Patients with impaired renal function at baseline

The Investigator should attempt to have a diagnosis for the observed finding and should use his/her best judgment as whether to or not enroll such patients, and if the patient is enrolled, how to best monitor these baseline abnormalities throughout the study.

Additional examples where these algorithms may not be applicable include, but are not limited to, the following situations:

- Patients with ALT increase for which the abnormality resolves following statin dose reduction or statin discontinuation
- Patients with elevated creatinine kinase for which the abnormality resolves following statin dose reduction or statin discontinuation
- Patients with elevated creatinine kinase caused by an MI

In addition, discontinuation caused by a laboratory abnormality can be either permanent or temporary, depending on the particular case. There is no requirement for permanent treatment discontinuation in every case of the general guidance for the follow-up of selected laboratory abnormalities mentioned in [Appendix E](#).

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 alirocumab (SUSAR), to the regulatory authorities, IECs/IRBs as appropriate and to the Investigators.
- All SAEs that are expected and at least reasonably related to alirocumab to the regulatory authorities, according to local regulations.

The AESIs listed in [Section 10.4.1.3](#) will be reported to those regulatory authorities who require such reporting.

In this study, some AEs are considered related to the underlying condition and thus will not be considered unexpected as indicated in the Investigator's Brochure.

Any other AE not listed as an expected event in the Investigator's Brochure or in this protocol will be considered unexpected.

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

10.6 SAFETY INSTRUCTIONS

10.6.1 Local tolerability (local injection site reactions that are non-allergic or allergic and not requiring consultation)

The classification of local injection site reactions, the reporting time frame, and the corresponding complementary forms in the e-CRF to be filled are summarized in [Appendix D](#).

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 judgment.

Specific e-CRF screens are to be filled in. The local symptoms should be reported in the "local injection site reaction" section of the complementary form. If the injection site reaction were to progress/expand/worsen/etc, both "local injection site reaction" and "general allergic reaction" of the complementary form should be completed. Information on classifying the reaction are given in [Section 10.4.1.4](#) and on reporting these reactions is given in [Appendix G](#).

10.6.2 Allergic adverse events requiring consultation and local injection site reactions that are allergic and requiring consultation

Specific e-CRF screens are to be filled in to assess allergic reactions or allergic-like reactions requiring consultation with another physician 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 (eg, 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 if meeting the criteria for an AESI.

Adverse events that are obviously not of allergic origin (eg, 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 [Appendix G](#) 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 10.3.2](#) for criteria for permanent treatment discontinuation.

The Investigator should exercise medical judgment concerning the handling of all background/concomitant medications potentially related to an allergic event.

10.6.2.1 Allergic adverse event with cutaneous involvement

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

The Investigator should evaluate the patient for possible etiologies (new medications, etc) and extracutaneous symptoms and signs. An unscheduled assessment for hematology, chemistry, liver panel should be obtained. An additional blood sample will have to be drawn for pharmacokinetics (PK) and anti-alirocumab antibody analyses (adequate instructions will be provided to the site by the Monitor). If it is possible, the site will take pictures of the skin lesions in order to provide the patient with them for the dermatologist's visit. If the photos are obtained, then copies should be kept as source documents which may later be collected by the sponsor. The Investigator will provide a 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; a detailed description of the rash (such as the morphology [lesion type], shape of individual lesions, arrangement of multiple lesions [eg, scattered, grouped, linear], distribution, color, consistency, presence of pruritus or pain, and other clinical signs) and in case a skin biopsy (including histopathology and immunofluorescence) was done (if it was deemed necessary as per the dermatologist's or Investigator's medical judgment), 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 Monitoring Team Representative within 24 hours.

10.6.2.2 Acute allergic injection reactions

Acute allergic injection reaction (which are considered under the category of general allergic reactions) is defined as any AE that occurs during or shortly after injection of alirocumab (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 (eg, antihistamines, bronchodilators, IV saline, corticosteroids, acetaminophen, and epinephrine) must be available for immediate use for the injections at the training, and inclusion visits.

Patients will be observed at the investigational site for at least 30 minutes following the injection that takes place at the inclusion visit. Patients should be treated symptomatically if any AEs are observed. Patients are to remain at the 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.

10.7 ADVERSE EVENTS MONITORING

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

11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

[REDACTED]

[REDACTED]

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 screened patients who are recorded in the IVRS/IWRS database (if randomized to usual care) and with a treatment kit allocated (if randomized to alirocumab), regardless of whether the treatment kit was used or not. Patients treated without being randomized or treated with a treatment kit before the randomization will not be considered as randomized and will not be included in any analysis population. The safety experience of patients treated and not randomized will be reported separately and these patients will not be in the safety 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.

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy populations

The primary efficacy analysis population will be the ITT population as defined below.

11.3.1.1 Intent-to-treat population

The ITT population is defined as all randomized patients who have an evaluable primary efficacy endpoint.

The primary efficacy endpoint is evaluable when the two following conditions are met:

- The baseline non-HDL-C value is available
- At least one non-HDL-C value is available within one of the analysis windows up to Week 24.

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

11.3.2 Safety population

The safety population considered for safety analyses will be the randomized population who received at least one dose or part of a dose of the open-label alirocumab and all patients randomized to usual care. Patients will be analyzed according to the treatment actually received (usual care or alirocumab).

The safety analysis will focus on the TEAE period defined as the time from the first open-label dose to the last open-label dose of alirocumab + 70 days (10 weeks) (if randomized to alirocumab) or, if randomized to usual care, 70 days after the last usual care treatment (IMP) has been administered or Study Day 225, whichever comes first.

If the patient is randomized to usual care and the Investigator has not prescribed an additional LMT, the date of the “last dose of study drug” is defined as the date of the last on-site study visit.

In addition:

- Nonrandomized 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 more than 1 study treatment 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 at Week 0 (baseline) and at least one evaluable blood sample for antibodies post-open-label treatment administration/post-baseline (for those randomized to usual care).



The analysis population for PCSK9 levels will be defined in the SAP.

11.4 STATISTICAL METHODS

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.

In order to ensure the continuity of the investigational treatment for the patients without interruption (only in case a disruption occurs in the availability of device components or during production of the prefilled pen), back-up plans may be implemented as described in [Section 8.1](#). In that case, exposure to initial device and back-up device will be summarized and impact on study results will be assessed. More details will be provided in the SAP, if applicable.

11.4.1.1 Extent of investigational medicinal product exposure

Alirocumab arm

The total exposure will be assessed by:

Duration of alirocumab exposure in weeks is defined as: (last dose of open-label treatment date - first dose of open-label treatment date + 14 days)/7, regardless of unplanned intermittent discontinuations.

The total number of injections by patient.

The number (n) and percentage (%) of patients with an up-titration in the alirocumab group will be described.

Usual care arm (except when no LMT other than statin is prescribed)

The total duration of exposure in weeks is defined as: (last dose of open-label treatment date - first dose of open-label treatment date + 1 day)/7, regardless of unplanned intermittent discontinuations.

11.4.1.2 Compliance

A given administration will be considered noncompliant if the patient did not take the planned dose of treatment as required by the protocol. No imputation will be made for patients with missing or incomplete data.

Compliance will be assessed using the following parameters:

- For alirocumab:
 - the injection frequency will be defined for each patient as the average number of days between 2 injections, that is: (last dose date – first dose date)/(number of injections -1).
 - The compliance is defined by the actual number of injections/number of planned injections
- For IMPs in usual care:
 - the compliance is defined by the number of days with all intakes as planned / duration of exposure x 100. The number of patients with a compliance $\geq 80\%$ will also be assessed.

These parameters will be summarized descriptively (N, Mean, SD, Median, Min and Max).

11.4.2 Analyses of efficacy endpoints

All the efficacy endpoints (primary, key secondary and other efficacy endpoints) will be analyzed in all patients (ITT population) for the overall comparison (alirocumab versus usual care) and for patients intended to receive fenofibrate in order to compare the efficacy of alirocumab versus fenofibrate. Further details will be provided in the SAP.

11.4.2.1 Analysis of primary endpoint

The percent change in non-HDL-C from baseline to Week 24 as defined in [Section 9.1](#) will be analyzed in the ITT population using a Mixed-effect Model with Repeated Measures (MMRM) approach. All post-baseline data available within Week 8 to Week 24 analysis windows will be used and missing data are accounted for by the MMRM model.

The model will include the fixed categorical effects of treatment group (usual care versus alirocumab), the randomization stratum (as per IVRS), time point (Week 8, Week 12, Week 20 and Week 24), treatment-by-time point interaction, stratum-by-time interaction, as well as the continuous fixed covariates of baseline non-HDL-C value and baseline value-by-time point interaction. Model assumptions for normality will be explored prior to the analysis testing.

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 LS means estimates at Week 24 for both treatment groups with their corresponding standard errors (SEs) and 97.5% confidence intervals (CIs). To compare the alirocumab group to the usual care group, an appropriate contrast statement will be used to test the differences of these estimates, at the 2-sided 0.025 level.

Let μ_0 and μ_1 be the population means of the percent change from baseline in non-HDL-C at Week 24 under usual care and alirocumab, respectively. The null hypothesis that will be tested is:

$$H0 : \mu0 = \mu1$$

versus

$$H1 : \mu0 \neq \mu1$$

Robustness of this statistical method will be assessed via sensitivity analyses detailed in the SAP, including different methodologies. In addition, a sensitivity analysis will be performed on the main analysis excluding non-HDL-C values assessed after the first treatment change compared to the randomized treatment (discontinuation or start of a new drug).

The same methodology will be applied to compare alirocumab versus fenofibrate in the “intent to prescribe fenofibrate” stratum.

11.4.2.2 Analyses of secondary efficacy endpoints

Method for controlling the overall type-I error rate when testing the key secondary efficacy endpoints is described in [Section 11.4.2.3](#).

For key secondary efficacy endpoints (defined in [Section 9.2.1](#)) and other efficacy endpoints (described in [Section 9.2.6](#)), descriptive summaries and analyses will be performed in the ITT population.

For descriptive summaries, percent change from baseline in non-HDL-C, total-C, HDL-C, TGs, and LDL-C will be provided at each time point for each treatment group. All measurements, scheduled or unscheduled will be assigned to analysis windows defined in the SAP in order to provide an assessment for these time points. Laboratory assessments other than the ones provided by the central laboratory will be excluded. The time profile of each parameter will be plotted by treatment group with the corresponding SEs.

Similar tables (with either percent change from baseline or absolute change from baseline for the ratio) and plots will be provided for other efficacy endpoints: Apo B, Apo A-1, ratio Apo B/Apo A-1, Apo C-III, Lp(a), TGRLs, lipid subfractions by NMR spectroscopy (ie, LDL particle size, and LDL, VLDL, HDL, IDL particle number). For TGs and Lp(a), summary statistics will include Q1 and Q3, and medians (instead of means) by time point will be plotted.

Multiple types of measurements are planned to be analyzed during differing time points in the trial, specifically continuous measurements expected to have a normal distribution (eg, percent change in non-HDL-C), continuous measurements expected to have a non-normal distribution (eg, TGs), and binary measurements (eg, proportion of patients reaching non-HDL-C <100 mg/dL).

Continuous endpoints anticipated to have a normal distribution

Continuous secondary variables defined in [Section 9.2](#) anticipated to have a normal distribution (eg, lipids other than TGs and Lp[a]) will be analyzed using the same MMRM model as for the primary endpoint. Specifically, the model will contain fixed categorical effects of treatment group, planned time points to Week 24 and treatment-by-time point interaction, as well as, the

continuous fixed covariates of corresponding baseline value and baseline value-by-time point interaction.

Continuous endpoints anticipated to have a non-normal distribution

Continuous secondary efficacy endpoints defined in [Section 9.2](#), anticipated to have a non-normal distribution (eg, TGs and Lp[a]), will be analyzed using a robust regression model (ie, ROBUSTREG SAS procedure with M-estimation option) with treatment group 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 the 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 the treatment groups will be provided with the SE, 97.5% CI and p-value.

Binary endpoints

Binary secondary efficacy endpoints defined in [Section 9.2.1](#) will be analyzed using logistic regression with treatment group 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 the multiple imputation model will at least include the same variables as used in the logistic regression model. Treatment effects will be compared and the combined odds ratio estimate between the treatment groups, with their corresponding 97.5% CIs and p-value will be provided.

In the data dependent case that the logistic regression method is not applicable (eg, 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 an exact conditional logistic regression would be performed to compare treatment effects. The LOCF imputation method will consist of using the last value obtained up to the Week 24 analysis window (or Week 12 as applicable) to impute the missing Week 24 value (or Week 12 respectively).

The same methodology will be applied to compare alirocumab versus fenofibrate in the “intent to prescribe fenofibrate” stratum.

11.4.2.3 Multiplicity considerations

The following strategy will be applied in both analyses (alirocumab versus usual care and alirocumab versus fenofibrate) in order to keep an overall alpha type I error rate at 0.05:

In order to handle multiple key secondary efficacy endpoints, the type-I error (0.025 for each analysis) will be controlled by the use of a sequential inferential approach. Statistical significance of the primary parameter at the 0.025 alpha level is required before drawing inferential conclusions about first key secondary parameter (refer to order of list in [Section 9.2.1](#)).

Inferential conclusions about successive key secondary parameters require statistical significance of the prior one. This fixed hierarchical approach will ensure a strong control of the overall type-I error rate at the 0.025 level for each analysis (alirocumab versus usual care and alirocumab versus fenofibrate).

No further adjustments will be made for other efficacy endpoints for which p-values will be provided for descriptive purpose only. The comparison of alirocumab versus the other options of the usual care will be performed via exploratory subgroup analyses.

11.4.3 Analyses of safety data

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 rules:

The baseline value is defined generally as the last available value before the first injection of open-label alirocumab/first dose of usual care treatment or before randomization for patient's randomized to usual care and not receiving additional LMT.

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.

Potentially clinically significant abnormality criteria will determine which patients had at least 1 PCSA during the on-treatment period, taking into account all evaluations performed during the on-treatment period, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage.

The following definitions will be applied to AEs:

- Pre-treatment AEs are AEs that developed or worsened or became serious during the PRE-TREATMENT period
- Treatment-emergent AEs (TEAEs) are AEs that developed or worsened or became serious during the TEAE period
- Post-treatment AEs are AEs that developed or worsened or became serious during the POST-TREATMENT period

Liver function tests

The 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 are 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 PTs will be based on standardized MedDRA query (SMQ) Hepatic disorder. Time to liver-related treatment discontinuation and time to liver death may also be provided based on hepatic disorder SMQ.

11.4.3.1 Adverse events

Adverse event incidence tables will present by SOC (sorted by internationally agreed order), HLT, 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-emergent SAEs and all TEAEs leading to permanent treatment discontinuation.

If any clinically significant signal is detected and needs further characterization or for AE of clinical interest, exploration of time to onset will be performed for these selected TEAEs as described below to account for the differential exposure time in all patients.

Selected TEAEs will be also analyzed using time-to-event approach (Kaplan-Meier methodology). Time to the first occurrence of the event will be calculated (only the first event will be counted), with the origin date being the date of the first dose of open-label IMP for patients receiving an additional IMP (alirocumab or usual care) or the date of the randomization for patients not receiving an IMP (statins only). Patients without any event will be censored at the end of the TEAE period. Incidence rates at 6 months will be presented and Kaplan-Meier curves will be provided.

Death: The following deaths summaries will be generated:

- Number (%) of patients who died by 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, HLT, HLT and PT showing number (%) of patients sorted by internationally agreed order of SOC and alphabetical order of HLT, HLT, and PT.

11.4.3.2 Laboratory data and vital signs

The summary statistics (including mean, median, Q1, Q3, SE, minimum and maximum) of all laboratory variables, all vital signs parameters (raw data and changes from baseline) will be calculated for each visit, last and worst value assessed during the treatment period and presented by treatment group.

For selected parameters, mean changes from baseline with the corresponding standard error 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. Further details will be provided in SAP.

11.4.4 Analyses of diabetes-related endpoints

The analyses of diabetes-related endpoints will be performed on the ITT population and will be descriptive only. Summary statistics, including the mean, median, Q1, Q3, SE, minimum, and maximum of the 4 endpoints (HbA1c, FPG, and number of glucose lowering treatment) will be calculated for each visit and presented by treatment group, as well as the change from baseline.

11.4.5

Handling missing data

The algorithm used to calculate the scores accounts for missing items.




11.4.6 Analyses of other endpoints

Analyses of anti-alirocumab antibodies

Analyses of anti-alirocumab antibodies will be described in the SAP.

Analyses of pharmacokinetic variables

Analyses of PCSK9 levels will be described in the SAP.

11.5 INTERIM ANALYSIS

No interim analysis is planned. However, a first-step analysis including the final analysis of the primary endpoint may be needed in order to provide results in a timely manner for a scientific communication.

All the efficacy data will be available for final analysis at a cut-off date corresponding to the Week 24 visit of the last patient. Since safety data are being collected until the end of the study (Week 32), if the analysis with Week 24 data has to be performed, an update of the safety analysis will be performed at the end of the study. If analyses are not needed at Week 24, then there will be only a one time analysis at the end of the study.

The first-step analysis would be conducted as soon as all patients have been randomized and have at least all their data up to Week 24 collected and validated, and will consist of a final analysis of the primary and secondary efficacy endpoints up to Week 24. The safety analysis will be performed on all safety data collected and validated at the time of this first-step analysis.

The second-step analysis will consist of the updated analysis of safety endpoints until Week 32. Even in the case of a two-step analysis, there is no multiplicity issue because all efficacy analyses will be completed at the time of the advanced analysis, so that no adjustment would be performed on the type I error rate.

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 Subinvestigator, 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 informed consent form 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 informed consent form will be provided to the patient.

The informed consent form 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.

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 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.

Alirocumab 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 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 and/or Study Coordinators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All Sub-investigators and Study Coordinators shall be appointed and listed in a timely manner. The Sub-investigators and Study Coordinators 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 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 to help the Investigator and the Sponsor 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, alirocumab allocation, patient compliance with the IMP regimen, IMP accountability, statin/concomitant therapy use and quality of data.

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH 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 informed consent form 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 (eg, 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 written information should be completed 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 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 systems used for the study is provided in a separate document which is maintained in the Sponsor and Investigator study files.

External data loading is planned for this clinical trial.

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification and training of each Investigator and Subinvestigator will be signed, 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.

Subject race or ethnicity (ie, Caucasian/white, Black, Asian/Oriental, others) will be collected in this study because these data are required by several regulatory authorities (eg, on afro American population for FDA, on Japanese population for the PMDA in Japan, or on Chinese population for the CFDA in China).

The data collected in this study will only be used for the purposes of the study and to document the evaluation of the benefit/ risk ratio, efficacy and safety of the product. They may be further processed if they have been anonymized.

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, Good Clinical Practice 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 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

The Sponsor has the right to terminate the participation of either an individual site or the study at any time, for any reason, including but not limited to the following:

- The information on the product leads to doubt as to the benefit/risk ratio;
- Patient enrollment is unsatisfactory;
- The Investigator has received from the Sponsor all IMP, means and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon;

- Non-compliance of the Investigator or Subinvestigator, delegated staff with any provision of the clinical trial protocol, and breach of the applicable laws and regulations or breach of the ICH GCP;
- 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 may terminate his/her participation upon thirty (30) days' prior written notice if the study site or the Investigator for any reason becomes unable to perform or complete the clinical trial.

In the event of premature discontinuation of the study or premature close-out of a site, for any reason whatsoever, the appropriate IRB/IEC and regulatory authorities should be informed according to applicable regulatory requirements.

14.9 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a clinical study report 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 part 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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