CLINICAL TRIAL PROTOCOL

A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Alirocumab in Insulin Treated Patients with Type 1 or Type 2 Diabetes and With Hypercholesterolemia at High Cardiovascular Risk Not Adequately Controlled on Maximally Tolerated LDL-C Lowering Therapy

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COMPOUND: alirocumab (SAR236553)

STUDY NUMBER: LPS14355

STUDY NAME: ODYSSEY DM - Insulin

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CLINICAL TRIAL SUMMARY

COMPOUND: SAR236553 (alirocumab)	**STUDY No: LPS14355**
TITLE	A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Alirocumab in Insulin Treated Patients with Type 1 or Type 2 Diabetes and With Hypercholesterolemia at High Cardiovascular Risk Not Adequately Controlled on Maximally Tolerated LDL-C Lowering Therapy (ODYSSEY DM – Insulin)
INVESTIGATOR/TRIAL LOCATION	Multinational - Multicenter
PHASE OF DEVELOPMENT	3b
STUDY OBJECTIVE(S)	**Primary Objectives** • To demonstrate the superiority of alirocumab in comparison with placebo in the reduction of calculated low-density lipoprotein cholesterol (LDL-C) after 24 weeks of treatment in patients with diabetes treated with insulin and with hypercholesterolemia at high cardiovascular risk not adequately controlled on maximally tolerated LDL-C lowering therapy • To evaluate the safety and tolerability of alirocumab in patients with diabetes treated with insulin **Secondary Objective** • To demonstrate that alirocumab is superior in comparison to placebo in its effects on other lipid parameters at Weeks 12 and 24 (ie, measured LDL-C, non-high-density lipoprotein cholesterol [non-HDL-C], apolipoprotein B [Apo B], total cholesterol [TC], lipoprotein a [Lp(a)]), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG) levels, triglyceride rich lipoproteins (TGRL), apolipoprotein A-1 (Apo A-1), apolipoprotein C-III (Apo C-III), and LDL particle number and size)
STUDY DESIGN	This is a Phase 3b randomized, double-blind, placebo-controlled study to assess the efficacy and safety of alirocumab administered by subcutaneous (SC) injection in insulin treated patients with Type 1 or Type 2 diabetes and with hypercholesterolemia at high cardiovascular risk not adequately controlled on maximally tolerated LDL-C lowering therapy. Patients, unless they are statin intolerant, will be taking a stable, maximum dose/regimen of statin therapy that is tolerated by the patient, based on the Investigator's judgment, with or without other lipid modifying therapies (LMT). Randomization will be unbalanced (2:1, alirocumab:placebo) The study will be a multinational, multicenter study. Patients will be stratified by diabetes type (ie, Type 1 diabetes versus Type 2 diabetes). Recruitment of patients with Type 2 diabetes will complete when approximately 400 patients have been randomized. Recruitment of patients with Type 1 diabetes will continue until approximately 100 patients have been randomized or the end of the targeted recruitment period (summer 2016), whichever comes first.

	Alirocumab will be administered subcutaneously 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 LDL-C at the Week 8 visit is ≥70 mg/dL (1.81 mmol/L). Patients who have an LDL-C <70 mg/dL (1.81 mmol/L) at the Week 8 visit will continue with alirocumab 75 mg every two weeks until the end of the double-blind treatment period. The study consists of: • A screening period of up to 3 weeks; • A double-blind treatment period of 24 weeks; • A safety observation period (off-treatment) of 8 weeks after the end of the double-blind treatment period. Note, the Investigator will need to document in the case report form (CRF) any adverse events (AEs) that have occurred within 70 days of the last dose of IMP that (s)he is aware of. A phone visit will take place at Week 32 in order to ensure documentation of any AEs occurring during this period. Patients should be on a stable diet for glucose and lipid management throughout the entire study duration from screening to the Week 24 visit. There shall be no significant changes in nutritional composition of the diet or in the quantity/pattern of food consumed. Patients must be receiving treatment for diabetes in accordance with local/regional standards of care. Statin dose and dose regimen as well as dose and dose regimen of other lipid modifying treatment(s) (if applicable) should be stable for 4 weeks prior to the screening period and throughout the entire study duration, including from the screening visit to randomization. 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 double-blind treatment period (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 administered at Week 22. Patients will visit the study site at Weeks -3, 0, 8, 12, 20, and 24 with lab work at each visit; in addition phone visits are scheduled at Weeks 4 and 32. Week 8 is a critical visit because it will be the only scheduled visit where an LDL-C value for uptitration will be available.
STUDY POPULATION **Main selection criteria**	**Inclusion criteria** I 01. Patients with Type 1 or Type 2 diabetes treated with insulin with LDL-C ≥70 mg/dL (1.81 mmol/L), not adequately controlled by 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) with or 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 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, or 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. Patients ≥18 years of age or legal age of majority at screening visit, whichever is greater. I 03. Patients diagnosed with Type 1 or Type 2 diabetes at least one year prior to the screening visit (Week -3). Note: Patients diagnosed with Type 1 diabetes need to meet all of the following criteria: • diagnosis prior to the age of 30 years • treated with a multiple daily injection regimen/basal-prandial insulin regimen or insulin pump regimen within 6 months after diagnosis • C-peptide <0.2 pmol/mL at the screening visit I 04. HbA1c <10% at the screening visit (Week -3). Note: Patients with an elevated HbA1c (up to 10%) are eligible provided that there is no plan to target a lower HbA1c during the study, based on the judgment of the Investigator). I 05. Patients with documented history of cardiovascular disease (CVD) (including CHD and/or CHD risk equivalents) and/or at least one additional cardiovascular risk factor. Notes: History of CHD includes at least one of the following: • acute myocardial infarction (MI), • silent MI, • unstable angina, • coronary revascularization procedure (eg, percutaneuous 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). AND/OR CHD risk equivalents include at least one of the following: • Documented peripheral arterial disease (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 radio imaging must have been performed to rule out hemorrhage and non-ischemic neurological disease. AND/OR 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 chronic kidney disease (CKD) as defined by 15 ≤eGFR <60 mL/min/1.73 m^2 for 3 months or more, including the screening visit). I 06. Signed written informed consent **Key Exclusion criteria** • Not on a stable dose of LMT (including statin or other LMT) 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 • Plans to initiate new LMT during the course of the study or to modify the dose of the current LMT • Serum TG >400 mg/dL (4.52 mmol/L) at the screening visit (Week -3). • eGFR<15 ml/min/1.73 m^2 according to 4-variable MDRD equation at the screening visit (Week -3) • Currently receiving or plans to receive renal replacement therapy during the study (eg, hemodialysis, renal transplant, etc) • Unstable weight defined as a variation of >5 kg within 2 months prior to the screening visit, as judged by the Investigator. • BMI >45 kg/m^2 or plans to undergo bariatric surgery, weight loss program, or to initiate weight loss drugs during the course of the study. • Patients not treated with insulin for at least 6 months prior to the screening visit or 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 [Type 2 diabetes]], 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. • Not on a stable insulin dose for at least 3 months prior to screening (ie, more than a 30% variation in total daily insulin dose as judged by the Investigator), or likelihood of requiring intensification of insulin/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). • Other antihyperglycemic medications taken by the patient have not been stable for at least 3 months before the screening visit. • History of recent decompensation of diabetes within 2 months prior to the screening visit (ie, diabetic ketoacidosis, hyperosmolar hyperglycemic state [HHS]).
Total expected number of patients	A total of approximately 500 patients are expected (approximately 400 patients with Type 2 diabetes and up to 100 patients with Type 1 diabetes). The recruitment of patients with Type 2 diabetes will complete when approximately 400 patients have been randomized. Recruitment of patients with Type 1 diabetes will continue until approximately 100 patients have been randomized or the end of the targeted recruitment period (summer 2016), whichever comes first.
STUDY TREATMENT(s)	
Investigational medicinal product(s) **Formulation**	Alirocumab or placebo for alirocumab. 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. Placebo contains histidine, pH 6.0, polysorbate 20, and sucrose.
Route(s) of administration	Subcutaneous (SC); one injection of 1 mL subcutaneously in the abdomen, thigh, or outer area of upper arm (ie, deltoid region)
Dose regimen	Alirocumab 75 mg every two weeks (Q2W) with possible uptitration at Week 12 to 150 Q2W or placebo for alirocumab Q2W. The last planned injection of 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 IMP to the patient changes during the course of the study, the new designated person will be trained with a placebo.
Noninvestigational medicinal product(s) (if applicable) **Formulation**	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: antihyperglycemic medications (eg, insulin, metformin, etc), statins (HMG CoA reductase inhibitors), other LMTs (eg, cholesterol absorption inhibitors, bile acid-binding sequestrants, nicotinic acid, fibrates, omega-3 fatty acids).
Route(s) of administration	As applicable and in accordance with local labeling.
Dose regimen	As applicable and in accordance with local labeling.

ENDPOINT(S)	**Primary efficacy endpoint:** • Percent change in calculated LDL-C from baseline to Week 24 in the intent-to-treat (ITT) population **Primary safety endpoints:** • Safety parameters (treatment emergent adverse events [TEAEs], adverse events of special interest [AESIs], product complaints, laboratory data, vital signs [including change in body weight and BMI]) Note: collection of AESI may be reassessed based on product labeling should alirocumab receive regulatory approval during the study period. **Key secondary efficacy endpoints** • Percent change in calculated LDL-C from baseline to Week 24, using all LDL-C values during the efficacy treatment period (on-treatment estimand) • Percent change in measured LDL-C from baseline to Week 24 (ITT estimand) • Percent change in calculated LDL-C from baseline to Week 12 (ITT estimand) • Percent change in measured LDL-C from baseline to Week 12 (ITT estimand) • Percent change in non-HDL-C from baseline to Week 24 (ITT estimand) • Percent change in Apo B from baseline to Week 24 (ITT estimand) • Percent change in total cholesterol from baseline to Week 24 (ITT estimand) • The proportion of patients reaching calculated LDL-C <70 mg/dL at Week 24 (on-treatment estimand) • The proportion of patients reaching calculated LDL-C <50 mg/dL at Week 24 (on-treatment estimand) • The proportion of patients reaching non-HDL-C <100 mg/dL at Week 24 (on-treatment estimand) • The proportion of patients reaching non-HDL-C <80 mg/dL at Week 24 (on-treatment estimand) • The percent change in Lp(a) from baseline to Week 24 (ITT estimand) • The percent change in HDL-C from baseline to Week 24 (ITT estimand) • The percent change in TG from baseline to Week 24 (ITT estimand) • The percent change in LDL-C particle number from baseline to Week 24 (ITT estimand) • The percent change in LDL-C particle size from baseline to Week 24 (ITT estimand) **Diabetes-related endpoints** • Absolute change in HbA1c from baseline to Weeks 12 and 24 (ITT and on-treatment estimands) • Absolute change in FPG from baseline to Weeks 12 and 24 (ITT

	and on-treatment estimands) • Absolute change in total daily insulin dose from baseline to Weeks 12 and 24 (ITT and on-treatment estimands) • Absolute change in number of glucose-lowering treatments from baseline to Weeks 12 and 24 (ITT and on-treatment estimands) **Other efficacy endpoints** The following endpoints will be evaluated as other efficacy endpoints and will be further detailed in the statistical analysis plan (SAP). • Percent change in calculated LDL-C from baseline to Week 12 (on-treatment estimand) • Percent change in measured LDL-C from baseline to Weeks 12 and 24 (on-treatment estimand) • Percent change in non-HDL, Apo B, total cholesterol, Lp(a), HDL-C, and TG from baseline to Weeks 12 (ITT and on-treatment estimands) and Week 24 (on-treatment estimand) • Proportion of patients reaching calculated LDL-C <50 and also <70 mg/dL at Weeks 12 (ITT and on-treatment estimands) and 24 (ITT estimand) • Proportion of patients with 50% or greater reduction from baseline in calculated LDL-C at Weeks 12 and 24 (ITT estimand) • Proportion of patients reaching non-HDL-C <80 mg/dL and also <100 mg/dL at Weeks 12 (ITT and on treatment estimands) and 24 (ITT estimand) • Proportion of patients reaching Apo B <80 mg/dL at Weeks 12 and 24 (ITT and on-treatment estimands) • Percent change in LDL-C particle number and size from baseline to Week 12 (ITT and on-treatment estimands) and Week 24 (on-treatment estimand) • Percent change in TGRL, Apo A-1, and Apo C-III from baseline to Weeks 12 and 24 (ITT and on treatment estimands) • Absolute change in ratio Apo B/Apo A-1 and TC/HDL-C from baseline to Weeks 12 and 24 (ITT and on-treatment estimands) • Proportion of patients reaching calculated LDL-C <70 and <50 mg/dL at Weeks 12 and 24 according to baseline A1c of <8% or ≥8% (ITT and on-treatment estimands) • Proportion of patients reaching calculated LDL-C <70 mg/dL and <50 mg/dL at Weeks 12 and 24 according to baseline A1c of <median A1c or ≥median A1c (ITT and on-treatment estimands) [redacted] • [redacted] **Other Endpoints** • Anti-alirocumab antibodies assessed throughout the study.

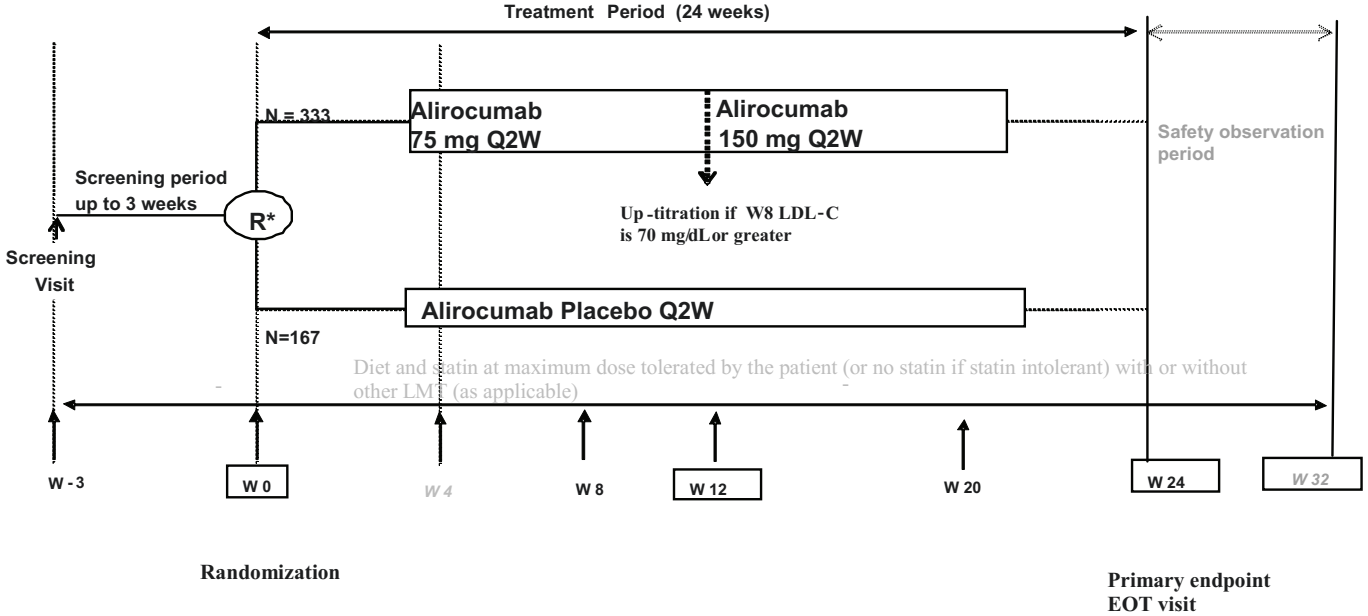
ASSESSMENT SCHEDULE	V1: (Week -3 [Day -21 to -8]): screening, investigational medicinal product (IMP) training, and safety. V2: (Week 0 [Day 1 +3 days]): baseline, randomization, first administration with double-blind IMP, and safety. V3: (Week 4 [Day 29 ±7 days]): telephone contact V4: (Week 8 [Day 57 ±3 days]); V5: (Week 12, [Day 85 ±3 days]); V6: (Week 20 [Day 141 ±7 days]) (efficacy and safety assessments) V5: (Week 12) Second allocation of double-blind IMP V7: (Week 24 [Day 169 ±3 days]): End of treatment (EOT) visit (efficacy and safety assessments) V8: (Week 32 [Day 225 ±7 days]): telephone contact (safety assessment) If one visit is changed, the next visit should take place according to the original schedule. Note: Patients who prematurely discontinue treatment should be followed as scheduled.
STATISTICAL CONSIDERATIONS	**Sample size determination:** [redacted] **Analysis Population:** Randomized population includes any patients who have been allocated to a randomized treatment regardless of whether the treatment kit was used or not. The primary efficacy analysis population will be the ITT population, defined as all randomized patients who had an evaluable primary efficacy endpoint. The primary efficacy endpoint will be considered evaluable when both of the following conditions are met: • The baseline calculated LDL-C value is available • A least one calculated LDL-C value is available within one of the analysis windows up to Week 24. The mITT population (otherwise referred to as the on-treatment population) is defined as all randomized patients who took at least one dose or part of dose of the double-blind IMP injection and had an evaluable primary efficacy endpoint during the efficacy treatment period. The primary efficacy endpoint will be considered evaluable during the efficacy treatment period when both of the following conditions are met: • The baseline calculated LDL-C value is available

	• At least one calculated LDL-C value is available during the efficacy treatment period and within one of the analysis windows up to Week 24. The efficacy treatment period will be defined as: • The time period from the first double-blind IMP injection up to 21 days after the last double-blind IMP injection. Patients in the ITT and mITT populations will be analyzed according to the treatment group allocated by randomization. The safety population consists of the randomized population who actually received at least one dose or partial dose of IMP. The safety population will be analyzed according to the treatment actually received. Separate analyses will be performed for Type 1 diabetes patients on one hand and Type 2 diabetes patients on the other hand. However, some endpoints may also be analyzed on the pooled data (Type 1 and Type 2 diabetes patients together). These analyses will be defined later in the statistical analysis plan. **Primary Analysis:** The percent change in calculated LDL-C from baseline to Week 24 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 (placebo versus alirocumab), time point (Week 8, Week 12, Week 20, Week 24), treatment-by-time point interaction, as well as the continuous fixed covariates of baseline LDL-C value and baseline value-by-time point interaction. Alirocumab will be compared to placebo using appropriate contrasts, and the 95% confidence interval (CI) of the difference will be provided. **Analysis of key secondary endpoints and other efficacy endpoints:** A hierarchical procedure (concerning key secondary endpoints only) will be used to control the type I error and handle multiple endpoints. If the primary endpoint analysis is significant at the 5% alpha level, secondary endpoints will be tested sequentially, using the order defined in section “Key Secondary endpoints”. Continuous secondary endpoints anticipated to have a normal distribution, 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 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. **Analysis of diabetes-related endpoints and other endpoints:** Descriptive analyses will be performed concerning diabetes-related endpoints and other endpoints such as anti-alirocumab antibodies.

	Safety analysis: Safety analysis (TEAEs, AESIs, product complaints, laboratory parameters, vital signs) will be descriptive, based on the safety population. The safety analysis will focus on the TEAE period defined as the time from the first double-blind dose to the last double-blind dose of IMP +70 days (10 weeks). **Timing of the analyses:** 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. All the safety data will be available at the end of the study (Week 32). If needed for the purpose of scientific communication, both the efficacy and safety analyses will be performed at the Week 24 cut-off date and an update of the safety analysis 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.
DURATION OF STUDY PERIOD (per patient)	The duration of the study is approximately 9 months to include a 3-week screening period and 24-week treatment period and an 8 week safety observation period. Patients with an SAE or an AESI should be followed until resolution, stabilization, or death.

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 IMP. The Randomization Day is always Day 1.**
***First IMP administration.**
***Phone call visits are indicated in italics**

1.2 STUDY FLOW CHART

	Screening	Double-blind Treatment Period						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)/ EOT	8 (Week 32)/10 weeks after last injection of IMP [a]
DAY (visit window days)	-21 (-21 to -8)	1 (+ 3)	29 (± 7)	57 (±3)	85 (±3)	141 (±7)	169 (±3)	225 (±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	
Measured body weight	X	X		X	X	X	X	
Measured height	X							
Randomization		X						
Confirm patient diet		X	X	X	X	X	X	
Insulin log								
Dispensation/collection	X	X		X	X	X	X	
Review		X	X	X	X	X	X	
IVRS/IWRS contact	X	X			X		X	
Injection training with placebo[c]	X							
Double-blind IMP dispensation[d]		X			X			
Concomitant medication check[e]	X	X	X	X	X	X	X	X
Patient diary dispensation		X		X	X	X		
Patient diary review (compliance check of IMP and data collection on IMP administration)			X	X	X	X	X	

	Screening	Double-blind Treatment Period						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)/ EOT	8 (Week 32)/10 weeks after last injection of IMP [a]
Safety:								
AE /SAE recording / Product Technical Complaints[f] (if any)	X	X	X	X	X	X	X	X
Fasting Laboratory Testing – Efficacy:								
Lipid Panel (TC, Calculated LDL-C[g], HDL-C, TG, non-HDL-C)	X	X		X	X	X	X	
Measured LDL-C (via beta quantification)		X			X		X	
Apo B, Apo A-1, Apo C-III, LDL particle size and number, Lp(a)		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[j]	X	X[i]		X	X		X	
Pregnancy test (for women of childbearing potential)[k]	X	X					X	
Standard urinalysis and spot urine albumin:creatinine[l]	X						X	
HbA1c	X	X			X		X	
C-peptide	X							
Hepatitis B Surface Antigen[h]	X							
Hepatitis C Antibody[h]	X						X	
Thyroid Stimulating Hormone[h]	X							
Anti-alirocumab antibodies		X			X		X	
Serum PCSK9 levels		X						

	Screening	Double-blind Treatment Period						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)/ EOT	8 (Week 32)/10 weeks after last injection of IMP [a]
[redacted]								
[redacted]				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 AEs only if they are medically relevant: symptomatic, requiring corrective treatment, leading to discontinuation of IMP and/or fulfilling a seriousness criterion.

c Injection-training prior to randomization 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 double-blind injection is administered at the site by the patient or a trained designated person with double-blind study treatment kit allocated by IVRS. Further training with double-blind treatment can be done at an additional unscheduled visit(s), as per patient or Investigator's judgment. If a designated person changes during the course of the study, then the person will be trained using placebo.

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 Patients will be asked to additionally keep a log of the daily insulin dose for 7 days prior to each visit (including daily basal dose and daily prandial dose, as applicable).

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 study (Week 32).

g LDL-C will be calculated using the Friedewald formula. 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.

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 GGT, Hepatitis C antibody (at screening, Week 24 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 Samples to be collected only if required per judgment of the Investigator. The only exception is plasma glucose which must be collected at Week 0.

j Liver panel: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin

k 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.

l Urinalysis and spot urine albumin: creatinine ratio: To be performed at screening and Week 24. Additional urine testing to be repeated if needed based on Investigator judgment.

2 TABLE OF CONTENTS

3 LIST OF ABBREVIATIONS

ADR:	adverse drug reaction
AE:	adverse event(s)
AESI:	adverse event(s) 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
AST:	aspartate aminotransferase
BMI:	body mass index
BP:	blood pressure
CABG:	coronary artery bypass graft surgery
CHD:	coronary heart disease
CI:	confidence interval
CPK:	creatine phosphokinase
CRF:	case report form
CV:	cardiovascular
CVD:	cardiovascular disease
DRF:	discrepancy resolution form
eGFR:	estimated glomerular filtration rate
EOT:	end of treatment
GCP:	good clinical practice
HbA1c:	glycosylated hemoglobin
HDL-C:	high density lipoprotein cholesterol
heFH:	heterozygous familial hypercholesterolemia
HHS:	hyperosmolar hyperglycemic state
HLGT:	high level group term
HLT:	high level term
ICF:	informed consent form
IMP:	investigational medicinal product
[redacted]	[redacted]
ITT:	intent-to-treat
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

LS:	least square
MDRD:	modification in diet of renal disease
MedDRA:	Medical Dictionary for Regulatory Activities
MI:	myocardial infarction
mITT:	modified intent-to-treat
MMRM:	model with repeated measures
non-FH:	non familial hypercholesterolemia
non-HDL-C:	non-high density lipoprotein cholesterol
NYHA:	New York Heart Association
PCI:	perutaneuous coronary intervention
PCSA:	potentially clinically significant abnormality
PCSK9:	proprotein convertase subtilisin kexin type 9
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(s)
SAP:	statistical analysis plan
SC:	subcutaneous
SE:	standard error
SMQ:	standardized MedDRA query
SOC:	system organ class
s-TSH:	sensitive thyroid stimulating hormone
SUSAR:	Suspected Unexpected Serious Adverse Reaction
TC:	total cholesterol
TEAE:	treatment-emergent adverse event(s)
TG:	triglycerides
TGRL:	triglyceride rich lipoproteins
TIA:	transient ischemic attack
WBC:	white blood cell(s)

4 INTRODUCTION AND RATIONALE

Background on Patient Populations

This study will include adult patients with Type 1 or Type 2 diabetes on insulin therapy with hypercholesterolemia at high cardiovascular (CV) risk that is not adequately controlled on a maximally tolerated dose of statin with or without other lipid modifying therapy (LMT).

Type 2 diabetes

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 to 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).

The development of CVD in people with diabetes is a progressive process and insulin requiring patients with Type 2 diabetes are at even higher risk than those at an earlier stage of disease (5).

Dyslipidemia is a major risk factor for macrovascular complications in individuals with diabetes. In Type 2 diabetes, the dyslipidemia includes a range of lipid abnormalities including elevated low density lipoprotein cholesterol (LDL-C), elevated triglycerides (TG), and reduced high density lipoprotein cholesterol (HDL-C) (8).While an elevation of LDL-C may be variable, patients often present with an elevation of small, dense LDL particles which are particularly atherogenic. These disturbances, particularly that of LDL-C elevation, contribute to the greater CV risk observed in those with diabetes compared with those without (8). Low density lipoprotein cholesterol is identified as the primary target of cholesterol lowering therapy (9) and is accepted as a valid surrogate endpoint (10, 11, 12).

Multiple clinical trials with statins and subgroup analyses in patients with diabetes (done primarily in patients with Type 2 diabetes) have demonstrated that significant reductions in CV events can be achieved through lowering of LDL-C (13, 14, 15, 16, 17, 18). The benefits of further intensification of LDL-C lowering, which included patients with diabetes, were recently demonstrated by adding ezetimibe to a statin (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-analyses including over 18000 patients with diabetes suggests 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 (18).

The specific LDL-C target differs depending on the guidelines consulted and the severity of risk experienced by the patient, but they generally recommend a target of <1.8 mmol/L (70 mg/dL) in patients with Type 1 and Type 2 diabetes at high CV risk or at least a ≥50% LDL-C reduction

(4, 5, 6, 9, 24). Despite the widespread use of statin therapies, many patients with diabetes and dyslipidemia remain sub-optimally treated (25, 26, 27), or may be intolerant to statin therapy, due to troubling side effects, and may go on to experience additional CV events. For example, in the latest EUROASPIRE survey, although 79% of those with diabetes were on a statin, 47% had an LDL-C above target (26). Similarly, in the cohort of statin-treated diabetes patients in the DYSIS survey, 41.3% had an LDL-C above target (27).

Type 1 diabetes

Type 1 diabetes is one of the most common chronic autoimmune disorders with age-adjusted incidence from 0.1 per 100 000 people per year in China to 40.9 in Finland. In the US, around 15 000 children and a similar number of adults are diagnosed every year. Aside from the enormous psychological and health burden on the individual patients, the disease costs the health-care system an estimated US $14.9 billion annually (28). Type 1 diabetes is associated with a substantially increased risk of premature death as compared to general population. Among persons with diabetes who are younger than 30 years of age, excess mortality is largely explained by acute complications of diabetes, including diabetic ketoacidosis and hypoglycemia, while CVD is the main cause of death later in life (29). A recent study showed that for Type 1 diabetes patients with on-target glycemic control, the risk of death from CV causes was more than twice the risk in the general population (30). Type 1 diabetes may also be accompanied by dyslipidemia that may predispose an individual to precocious CVD, particularly when renal dysfunction is present. Although the majority of participants in statin trials had Type 2 diabetes, there was no evidence that the effects of statin therapy on LDL-C lowering or major vascular events in people with Type 1 diabetes differed from that in those with Type 2 diabetes; indeed, the reduction in major vascular events in people with Type 1 diabetes was statistically significant (18).

Background to proprotein convertase subtilisin kexin type 9

The investigational medicinal product (IMP) in this study is alirocumab, a monoclonal antibody to proprotein convertase subtilisin kexin type 9 (PCSK9). 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 LDLRs 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 (31, 32, 33, 34, 35).

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 TC. Alirocumab was also superior to placebo, and to ezetimibe in most studies, for the reduction in lipoprotein a (Lp[a]). Modest but consistent reductions in fasting TGs and increases in HDL-C were also observed with alirocumab treatment.

Phase 3 studies that evaluated Q4W regimen – efficacy results

Two studies EFC13786 and R727-CL-1308 (first-step analysis), have evaluated the 150 mg Q4W and 300 mg Q4W, respectively, as initiation dose regimen with a possible up-titration to 150 mg Q2W. For both studies, LDL-C reduction was observed at Week 4 was maintained over time up to Week 24. As with Q2W dosing, changes in Non-HDL-C, Apo B, and TC showed good correlation with LDL-C.

The R727-CL-1308 (CHOICE I) study included patients with and without concomitant statin. In both of these populations, there were statistically significant effects in favor of alirocumab 300 mg Q4W with possible up-titration to 150 mg Q2W for both co-primary efficacy endpoints (percent change in LDL-C from baseline to Week 24 and to averaged Weeks 21 – 24). For LDL-C reduction, the least square (LS) mean treatment difference for alirocumab versus placebo at Week 24 was -52.4% and -58.7% for the no concomitant statin population and concomitant statin population, respectively. The results obtained at Week 12 were consistent with those at Week 24 for both populations, whereby the Week 12 effect assessed the sole contribution of the 300 mg Q4W dose regimen. Approximately 15% of patients treated with Q4W dosing who received at least 1 injection after Week 12 were up-titrated to Q2W dosing.

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

assessed the sole contribution of the 150 mg Q4W dose regimen. Approximately 50% of patients treated with Q4W dosing who received at least 1 injection after Week 12 were up-titrated to Q2W dosing.

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. [redacted].

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 event (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, 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 and pruritus were identified as adverse drug reactions (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.

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

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

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

Rationale for this study

The objective of the present study is to assess the efficacy and safety of alirocumab in insulin treated patients with Type 1 or Type 2 diabetes who currently have an LDL-C ≥70 mg/dL (1.81 mmol/L) and who, at baseline, have required, in addition to lifestyle modification, statin treatment with or without other LMT in order to achieve their LDL-C treatment goal, or who are statin intolerant. There is interest in the impact of lipid lowering therapy on measures of glycemic control as evidence has accumulated and suggests that the use of statin therapy is associated with an increased risk of diabetes. This is particularly true for people with risk factors for diabetes. Despite an increased relative risk of diabetes with statin therapy, the absolute risk is quite small. On average, it has been estimated that treatment of 255 people over a period of 4 years will result in 1 additional case of diabetes.

When balancing the benefit of therapy, treating the same number of people would prevent 5.4 vascular events (36). While this risk impacts patients with previously undiagnosed diabetes, it suggests that lipid lowering treatment could modulate glycemia. In fact, evidence suggests that it may be transmembrane cholesterol transport that imparts the added risk as a reduced prevalence of diabetes has been found in patients with familial hypercholesterolemia as compared to patients without the disease (37). As a result, understanding the impact of alirocumab on glycemic control in patients with diabetes is of interest.

In the Phase 3 program, involving a total of 5293 study participants, limited information is available in patients with diabetes who are treated with insulin and in those patients with Type 1 diabetes. Focusing the target population on patients with Type 1 or Type 2 diabetes treated with insulin will provide additional information on this potential treatment group, both from an efficacy and safety point of view (concomitant use of insulin and a monoclonal antibody). In addition, this study will provide useful information on the use of alirocumab in patients already familiar with self-injection.

It should be noted that all patients, except those with statin intolerance, will be on the maximum dose/regimen of statin that is tolerated by the patient, based on the Investigator's judgment, with or without other LMT. Those patients who are on statins and/or other LMTs at randomization should continue the treatments unchanged throughout the study.

Alirocumab will be evaluated at a dose of 75 mg Q2W with an increase of dose to 150 mg Q2W if LDL-C values at Week 8 are not <70 mg/dL.

It is possible that some patients in the 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 (35, 38, 39, 40). [redacted] The sample size of 500 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 an injectable placebo of alirocumab and is appropriate for the objectives of this study since it will provide the most robust assessment of efficacy and safety

of alirocumab. The use of placebo is ethically acceptable as all patients should be receiving standard of care treatment including maximum dose/regimen of statins that is tolerated by the patient, based on the Investigator's judgment, with or without other lipid modifying agents.

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 lowering effect and was generally well tolerated in a population of hypercholesterolemic patients with non-familial hypercholesterolemia (non-FH) or with heterozygous familial hypercholesterolemia (heFH), including patients with a history of intolerance to statin. The efficacy on LDL-C was associated with consistent results in total cholesterol (TC), apolipoprotein B (Apo B), non-high density lipoprotein cholesterol (non-HDL-C) and Apo B/Apo A-1 ratio. Reductions in Lp(a) and TG 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 treated with insulin, given the high CV risk of this population. Since no study in the ODYSSEY program (ie, the alirocumab clinical trial program) has specifically focused on patients with diabetes and that it included a limited number of patients on insulin these data should provide important information concerning the efficacy and safety of alirocumab when used concomitantly with insulin in this high risk group.

5 STUDY OBJECTIVES

5.1 PRIMARY

The primary objectives are:

- To demonstrate the superiority of alirocumab in comparison with placebo in the reduction of calculated low-density lipoprotein cholesterol (LDL-C) after 24 weeks of treatment in patients with diabetes treated with insulin and with hypercholesterolemia at high cardiovascular risk not adequately controlled on maximally tolerated LDL-C lowering therapy
- To evaluate the safety and tolerability of alirocumab in patients with diabetes treated with insulin

5.2 SECONDARY

The secondary objective is:

- To demonstrate that alirocumab is superior in comparison to placebo in its effects on other lipid parameters at Weeks 12 and 24 (ie, measured LDL-C, non-high-density lipoprotein cholesterol [non-HDL-C], apolipoprotein B [Apo B], total cholesterol [TC], lipoprotein a [Lp(a)], high-density lipoprotein cholesterol [HDL-C], triglyceride [TG] levels, triglyceride rich lipoproteins [TGRL], apolipoprotein A-1 [Apo A-1], apolipoprotein C-III [Apo C-III], LDL particle number and size)

6 STUDY DESIGN

6.1 DESCRIPTION OF THE PROTOCOL

This is a Phase 3b randomized, double-blind, placebo-controlled study to assess the efficacy and safety of alirocumab administered by subcutaneous (SC) injection in insulin treated patients with Type 1 or Type 2 diabetes and with hypercholesterolemia at high CV risk not adequately controlled on maximally tolerated LDL-C lowering therapy. The study will be multinational and multicenter. The study consists of a screening period of up to 3 weeks, a double-blind treatment period 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 with or without other lipid modifying therapies (LMT). Statin dose and dose regimen as well as dose and dose regimen of other lipid modifying treatment(s) (if applicable) should be stable throughout the entire study duration including for 4 weeks prior to the screening period, during the screening period, and from screening to randomization. Patients should be on a stable diet for glucose and lipid management throughout the entire study duration from screening to the Week 24 visit. Patients should be receiving treatment for diabetes in accordance with local/regional standards of care.

Patients will be stratified by diabetes type (ie, Type 1 diabetes versus Type 2 diabetes). Recruitment of patients with Type 2 diabetes will complete when approximately 400 patients have been randomized. Recruitment of patients with Type 1 diabetes will continue until approximately 100 patients have been randomized or the end of the targeted recruitment period (summer 2016), whichever comes first.

Alirocumab will be administered subcutaneously 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 LDL-C at the Week 8 visit is ≥70 mg/dL (1.81 mmol/L). Patients who have an LDL-C <70 mg/dL (1.81 mmol/L) at the Week 8 visit will continue with alirocumab 75 mg Q2W until the end of the 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.

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.

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 double-blind treatment period
- a safety observation period (off-treatment) of 8 weeks after the end of the double-blind treatment period

Note, the Investigator will need to document in the CRF any AEs that have occurred within 70 days of the last dose of IMP that (s)he is aware of. A phone visit will take place at Week 32 in order to ensure documentation of any AEs occurring during this period. 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.

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 1 or Type 2 diabetes treated with insulin with LDL ≥70 mg/dL (1.81 mmol/L), not adequately controlled by a stable, maximum dose/regimen of statin that is tolerated by the patient (see note below) for at least 4 weeks prior to the screening visit (Week -3) with or 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 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, or 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. Patients ≥18 years of age or legal age of majority at screening visit, whichever is greater.

I 03. Patients diagnosed with Type 1 or Type 2 diabetes at least one year prior to the screening visit (Week -3).

Note: Patients diagnosed with Type 1 diabetes need to meet all of the following criteria:

- diagnosis prior to the age of 30 years
- treated with a multiple daily injection regimen/basal-prandial insulin regimen or insulin pump regimen within 6 months after diagnosis
- C-peptide <0.2 pmol/mL at the screening visit

I 04. Glycosylated hemoglobin (HbA1c) <10% (Week -3)

Note: Patients with an elevated HbA1c (up to 10%) are eligible provided that there is no plan to target a lower HbA1c during the study, based on the judgment of the Investigator.

I 05. Patients with documented history of CVD (including CHD and/or CHD risk equivalents) and/or at least one additional CV risk factor.

Notes:

History of CHD includes at least one of the following:

- acute myocardial infarction (MI),
- silent MI,
- unstable angina,
- coronary revascularization procedure (eg, percutaneuous 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)

AND/OR

CHD risk equivalents include at least one of the following:

- Documented peripheral arterial disease (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 radio imaging must have been performed to rule out hemorrhage and non-ischemic neurological disease.

AND/OR

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 chronic kidney disease (CKD) as defined by 15 ≤eGFR <60 mL/min/1.73 m^2 for 3 months or more, including the screening visit)

I 06. 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 3 subsections:

7.2.1 Exclusion criteria related to study methodology

E 01. Plans to initiate new LMT during the course of the study or to modify the dose of the current LMT.

E 02. Not on a stable dose of LMT (including statin or other LMT) 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 03. Use of nutraceutical products or over-the-counter therapies that may affect lipids which have not been at a stable dose for at least 4 weeks prior to the screening visit (Week -3) or between screening and randomization visits.

E 04. Use of red yeast rice products within 4 weeks of the screening visit (Week -3) or between screening and randomization visits.

E 05. Use of systemic corticosteroids, unless used as replacement therapy for pituitary/adrenal disease with a stable regimen for at least 6 weeks prior to randomization.

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

E 06. Use of continuous hormone replacement therapy unless the regimen has been stable in the past 6 weeks prior to the Screening visit (Week -3) and no plans to change the regimen during the study.

E 07. 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, stroke, transient ischemic attack (TIA), endovascular procedure or surgical intervention for peripheral vascular disease.

E 08. Planned to undergo scheduled PCI, CABG, carotid or peripheral revascularization during the study.

E 09. History of New York Heart Association (NYHA) Class III or IV heart failure within the past 12 months (Appendix A).

E 10. Systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg at screening or randomization visit.

E 11. Patient who has received plasmapharesis treatment either within 2 months prior to the screening visit (Week -3), between screening and randomization, or who has plans to receive it.

E 12. Known history of hemorrhagic stroke.

E 13. Known history of loss of function of PCSK9 (ie, genetic mutation or sequence variation) or known history of homozygous familial hypercholesterolemia.

E 14. 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 15. Known history of positive HIV test.

E 16. Patient who has taken any active investigational drugs within 1 month or 5 half-lives, whichever is longer.

E 17. Patients not previously instructed on a cholesterol lowering diet prior to the screening visit (Week -3).

E 18. Patient who withdraws consent during the screening (starting from signed ICF).

E 19. Unstable weight defined as a variation of >5 kg within 2 months prior to the screening visit, as judged by the Investigator.

E 20. BMI >45 kg/m^2 or plans to undergo bariatric surgery, weight loss program, or to initiate weight loss drugs during the course of the study.

E 21. Recent initiation of weight loss drugs (ie, within 3 months prior to the screening visit or between screening and randomization) or recent bariatric surgery (within the last 6 months) and in an active weight loss phase, as judged by the Investigator.

E 22. Patients not treated with insulin for at least 6 months prior to the screening visit or 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 [Type 2 diabetes], 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 23. Not on a stable insulin dose for at least 3 months prior to screening (ie, more than a 30% variation in total daily insulin dose as judged by the Investigator), or likelihood of requiring intensification of insulin/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 24. Other antihyperglycemic medications taken by the patient have not been stable for at least 3 months before the screening visit.

E 25. History of recent decompensation of diabetes within 2 months prior to the screening visit (ie, diabetic ketoacidosis or hyperosmolar hyperglycemic state [HHS]).

E 26. Currently receiving or plans to receive renal replacement therapy during the study (eg, hemodialysis, renal transplant, etc).

E 27. 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 ±10% of the normal range of the laboratory at the screening visit.

E 28. Laboratory findings during the screening period (not including randomization labs, except for pregnancy test):

A) Serum TG >400 mg/dL (4.52 mmol/L) (1 repeat lab is allowed)

B) Positive serum or urine pregnancy test in women of childbearing potential

C) Positive test for Hepatitis B surface antigen or Hepatitis C antibody

D) eGFR <15 mL/min/1.73 m^2 according to 4-variable modification in diet of renal disease (MDRD) equation

E) ALT or AST >3 x ULN (1 repeat lab is allowed)

F) Creatine Phosphokinase (CPK) >3 x ULN (1 repeat lab is allowed)

E 29. 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, etc)
- 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 protocol
- 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 Sub-Investigator would preclude safe completion of the study or constrain endpoint assessments such as major systemic diseases, patients with short life expectancy

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

E 30. All 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 alirocumab

E 31. Hypersensitivity to alirocumab or to any of the ingredients of alirocumab

E 32. Pregnant or breastfeeding woman

E 33. Woman of childbearing potential not protected by highly-effective method(s) of birth control (as defined in the ICF and/or in a local protocol addendum in case of specific local requirement) 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 IMP. 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 amenorrheic for at least 12 months.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

Sterile alirocumab drug product will be supplied at a concentration of 75 mg/mL and 150 mg/mL in an aqueous buffer, pH 6.0, containing sucrose, histidine, and polysorbate 20, 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, as well as for those in the placebo treatment arm.

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

For those patients randomized to alirocumab, the initial dose is 75 mg administered subcutaneously 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 LDL-C value is ≥70 mg/dL (1.81 mmol/L).

Those patients randomized to placebo will be administered their injection subcutaneously Q2W throughout the duration of the 24-week treatment period.

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
  - 2 placebo injections as 1 mL each in a prefilled pen for patients receiving placebo

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 placebo, 75 mg and 150 mg, with one injection of 1 mL for each of these doses

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

8.1.1 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 IMP will consist of 1mL subcutaneous 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 IMP injection, then the patient should be advised to use an alternate location for administration of the IMP.

The IMP 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 the IMP 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 subcutaneous IMP 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 the IMP in a refrigerator. Prior to administration, the IMP should be set outside in a safe location at room temperature for about 30 to 40 minutes. Thereafter, the IMP should be administered as soon as possible.

8.1.2 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 the first IMP injection.

At the randomization visit, the first IMP 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.

IMP subcutaneous 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 the IMP 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.

IMP should be administered subcutaneously 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 IMP 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 IMP administration.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCTS

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

- Statins,
- Cholesterol absorption inhibitors (ezetimibe),
- Bile acid-binding sequestrants (such as cholestyramine, colestipol, colesevelam),
- Nicotinic acid,
- Fibrates (such as Fenofibrate),
- Omega-3 fatty acids (≥1000 mg daily),
- Insulins.

Please see Section 8.8 for further information. All fibrates are allowed at entry if the patient has tolerated the medication and remained on a stable dose. Background LMT and insulin will not be provided by the Sponsor. Patients will obtain these medications in compliance with local regulations.

8.3 BLINDING PROCEDURES

Alirocumab and placebo for alirocumab will be provided in identically matched prefilled pens and 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/IWRS that will be available 24 hours-a-day, 7 days-a-week.

In accordance with the double-blind design, study patients, Investigators and study site personnel will remain blinded to study treatment and will not have access to the randomization (treatment codes) except under circumstances described in the following subsections.

8.3.1 Methods of blinding

8.3.1.1 Adverse event

The treatment code will 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 CIB) and reasonably associated with the use of the IMP according to either the judgment of the Investigator and /or the Sponsor.

Refer to Section 10.5 for suspected unexpected ADR unblinding by the Sponsor and Section 8.3.2 (Randomization code breaking during the study) for unblinding an AE under exceptional circumstances when knowledge of the Investigational Medicinal Product is essential for treating the patient.

8.3.1.2 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 group of their patients based on LDL-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 double-blind treatment period (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.

8.3.1.3 Anti-alirocumab antibodies

Patient anti-alirocumab antibody results will not be communicated to the sites while the study is ongoing.

The sponsor's operational team will not have access to anti-alirocumab antibody results associated with a patient identification number until after the final database lock has occurred.

The lab technicians involved in the determination of patient anti-alirocumab antibody titers are excluded from the operations team and a process will be set up to prevent any potential unblinding.

8.3.2 Randomization code breaking during the study

In case of an AE, the code should only be broken in circumstances when knowledge of the IMP is required for treating the patient. If possible, contact should be initiated with the Monitoring Team/Study Physician before breaking the code. All calls will be documented by the Monitoring

Team as appropriate to include date and time of the call, name of the person contacted within the Monitoring Team, patient ID, documentation of the request, and decision for unblinding or not.

Code breaking can be performed at any time by using the proper module of the interactive voice response system (IVRS)/interactive web response system (IWRS), depending on which system is used for the site, and/or by calling any other phone number provided by the Sponsor for that purpose. However, it is preferable to contact the Study Physician to discuss the case before unblinding the case. If the blind is broken, the Investigator should document the date, time of day, and reason for code breaking, and report this information on the appropriate page of the e-CRF.

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

The code-breaking material will be also kept at the entity responsible for the "24 hour alert system"; but this system should be used in very exceptional cases only (ie, unavailability of IVR/IWR system or inability to contact Investigator and/or site staff). However, the preferred option is to unblind using IVRS. The Investigators will be informed by the clinical monitoring team about the availability of the local code-breaking material. A patient card, including the relevant "24 hour alert system" telephone number will be provided to every patient who will participate in the study. Unblinding may also be performed by the Sponsor for some SAEs in order to conform to regulatory reporting requirements (ie, for some SAEs that are both related and unexpected).

If the code is broken, the patient must permanently discontinue IMP administration.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

The randomized list of treatment kit numbers will be generated centrally by Sanofi. The IMP (alirocumab 75 or 150 mg kits, or placebo kit) will be packaged in accordance with this list.

The Trial Supply Operations Manager will provide the randomized list of treatment kit numbers and the Study Biostatistician will provide the randomization scheme to the 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 placebo or alirocumab during the double-blind treatment period. The randomization ratio alirocumab:placebo will be 2:1. For each randomized patient, 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 diabetes type (ie, Type 1 versus Type 2).

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 LDL-C level following the up-titration rules (see 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.

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

For the double-blind treatment period, each double-blind treatment kit, either alirocumab or placebo for alirocumab, will be prepared to contain 6 prefilled pens in a child resistant package.

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

In addition to the double-blind 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 at screening visit (Week-3, Visit 1). 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 CRF, including if the designated person who administers IMP 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.

8.6 STORAGE CONDITIONS AND SHELF LIFE

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

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

The IMP 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.

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

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 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.
- The Investigator or designee will enter the treatment kit packaging number(s) and the kit numbers in the e-CRF.
- IMP administration data will be recorded by the patients onto a Patient diary
- Used pens (sharps container) and the treatment kit dispensed at the previous dispensation visit are brought back by the patient at IMP kit re-supply visits only
- The Investigator or designee counts the number of remaining unused prefilled pens in the returned packs and fills in the Treatment Log Form at IMP kit re-supply visits;

- The monitor will check the data consistency between e-CRF pages and treatment log forms using the patient diary and returned, unused prefilled pen of a corresponding kit.

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 pens will be brought back to the site by the patient for the purpose of destruction.

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 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.

Nutraceutical products or over-the-counter therapies that may affect lipids are allowed (see Section 8.8.3 for exceptions) only if they have been used at a stable dose for at least 4 weeks prior to screening visit, during the screening period and during the 24 weeks of the double-blind treatment period. Examples of such nutraceutical products or over-the-counter therapies include omega-3 fatty acids at doses <1000 mg, plant stanols such as found in Benecol, flax seed oil, and psyllium.

8.8.1 Management of background lipid-modifying therapy

For background LMT, including statins, 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 with or 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, in order to make decisions on the patient's background LMT (Section 9).

From the screening visit (Week -3) until the Week 24 visit, the background LMT should not be changed. No dose adjustment, discontinuation or initiation of other statins or other LMT 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 background LMT as per his/her medical judgment.

While all fibrates are allowed at entry if the patient has tolerated the medication and remained on a stable dose, should the patient require the introduction of a fibrate during the course of the study (ie, as rescue treatment in response to a TG alert) only fenofibrate will be allowed to be added.

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 IMP. 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."

8.8.3 Prohibited concomitant medications

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

- Red yeast rice products
- Other PCSK9 inhibitors

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, with minimum changes. There shall be no significant changes in nutritional composition of the diet or in the quantity/pattern of food consumed.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

Lipid parameters

Blood sampling to determine lipid parameters (ie, TC, LDL-C, HDL-C, TG, non-HDL-C, Apo B, Apo A-1, ratio Apo B/Apo A-1, Apo C III, LDL particle size and 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.

TC, HDL-C, TG, 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 1.2. 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). 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 TC. Ratio Apo B/Apo A-1 will be calculated. Triglyceride rich lipopoprotein will be calculated by total cholesterol minus HDL cholesterol minus LDL cholesterol. 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 LDL-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.

9.1 PRIMARY ENDPOINTS

9.1.1 Primary efficacy endpoint

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

100x (calculated LDL-C value at Week 24 - calculated LDL-C value at baseline)/calculated LDL-C value at baseline.

The baseline calculated LDL-C value will be the last LDL-C level obtained before the first double-blind IMP injection. The calculated LDL-C at Week 24 will be the LDL-C level obtained within the Week 24 analysis window.

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

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

9.1.2 Primary 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 double-blind IMP injection.
- Treatment Emergent Adverse Event (TEAE) period is defined as the time from the first dose of double-blind IMP injection to the last dose of IMP injection + 70 days (10 weeks) as residual effect of treatment is expected until 10 weeks after the stop of double-blind IMP.
- 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.

9.1.2.1 Adverse events

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, as applicable.

Definitions for AEs, SAEs, and AESI, as well as obligation for reporting are further defined in Section 10.4.

Adverse events of special interest

Adverse events of special interest may be modified during a study by protocol amendment, which will enable the Company to collect additional information to better assess any potential and identified risks during the development.

For this study, the following AEs are AESI:

- Increase in alanine aminotransferase (ALT)
- Allergic events
- Local injection site reactions that are allergic in nature
- Pregnancy
- Symptomatic overdose with IMP
- Neurologic events
- Neurocognitive events

Additional information can be found in Section 10.4.1.3 and Appendix B.

9.1.2.2 Laboratory safety variables

The clinical laboratory data consist of blood analyses (including hematology, clinical chemistry, etc) and urine analyses. Clinical laboratory values will be analyzed after conversion into standard international units.

9.1.2.3 Vital signs

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

9.2 SECONDARY ENDPOINTS

9.2.1 Key secondary efficacy endpoints

- Percent change in calculated LDL-C from baseline to Week 24, using all LDL-C values during the efficacy treatment period (on-treatment estimand)
- Percent change in measured LDL-C from baseline to Week 24 (ITT estimand)
- Percent change in calculated LDL-C from baseline to Week 12 (ITT estimand)
- Percent change in measured LDL-C from baseline to Weeks 12 (ITT estimand)
- Percent change in non-HDL-C from baseline to Week 24 (ITT estimand)
- Percent change in Apo B from baseline to Week 24 (ITT estimand)
- Percent change in total cholesterol from baseline to Week 24 (ITT estimand)

- The proportion of patients reaching LDL-C <70 mg/dL at Week 24 (on-treatment estimand)
- The proportion of patients reaching LDL-C <50 mg/dL at Week 24 (on-treatment estimand)
- The proportion of patients reaching non-HDL-C <100 mg/dL at Week 24 (on-treatment estimand)
- The proportion of patients reaching non-HDL-C <80 mg/dL at Week 24 (on-treatment estimand)
- The percent change in Lp(a) from baseline to Week 24 (ITT estimand)
- The percent change in HDL-C from baseline to Week 24 (ITT estimand)
- The percent change in TG from baseline to Week 24 (ITT estimand)
- The percent change in LDL-C particle number from baseline to Week 24 (ITT estimand)
- The percent change in LDL-C particle size from baseline to Week 24 (ITT estimand)

9.2.2 Diabetes-related endpoints

- Absolute change in HbA1c from baseline to Weeks 12 and 24 (ITT and on-treatment estimands)
- Absolute change in FPG from baseline to Weeks 12 and 24 (ITT and on-treatment estimands)
- Absolute change in total daily insulin dose from baseline to Weeks 12 and 24 (ITT and on-treatment estimands)
- Absolute change in number of glucose-lowering treatments from baseline to Weeks 12 and 24 (ITT and on treatment estimands)

9.2.3 Other efficacy endpoints

- Percent change in calculated LDL-C from baseline to Week 12 (on-treatment estimand)
- Percent change in measured LDL-C from baseline to Weeks 12 and 24 (on-treatment estimand)
- Percent change non-HDL, Apo B, total cholesterol, Lp(a), HDL-C, and TG from baseline to Weeks 12 (ITT and on-treatment estimands) and Week 24 (on-treatment estimand)
- Proportion of patients reaching calculated LDL-C <50 and also <70 mg/dL at Weeks 12 (ITT and on-treatment estimands) and 24 (ITT estimand)
- Proportion of patients with 50% or greater reduction from baseline in calculated LDL-C at Weeks 12 and 24 (ITT estimand)
- Proportion of patients reaching non-HDL-C <80 mg/dL and also <100 mg/dL at Weeks 12 (ITT and on-treatment estimands) and Week 24 (ITT estimand)

- Proportion of patients reaching Apo B <80 mg/dL at Weeks 12 and 24 (ITT and on-treatment estimands)
- Percent change in LDL-C particle number and size from baseline to Week 12 (ITT and on-treatment estimands) and Week 24 (on-treatment estimand)
- Percent change in TGRL, Apo A-1, and Apo C-III from baseline to Weeks 12 and 24 (ITT and on treatment estimands)
- Absolute change in ratio Apo B/Apo A-1 and TC/HDL-C from baseline to Weeks 12 and 24 (ITT and on-treatment estimands)
- Proportion of patients reaching calculated LDL-C <70 and <50 mg/dL at Weeks 12 and 24 according to baseline A1c of <8% or ≥8% (ITT and on-treatment estimands)
- Proportion of patients reaching calculated LDL-C <70 mg/dL and <50 mg/dL at Weeks 12 and 24 according to baseline A1c of <median A1c or ≥median A1c (ITT and on-treatment estimands)

9.2.4 [redacted]

[redacted]

9.3 FUTURE USE OF SAMPLES

Not applicable.

9.4 APPROPRIATENESS OF MEASUREMENTS

The primary endpoint of the change in LDL-C from baseline is a valid surrogate 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, TC, LDL-C, HDL-C, TG, non-HDL-C, Apo A, Apo B, Apo C-III, Lp(a), LDL particle size and number) 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 injection 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 Visits 3 and 6; 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: Weeks 0, 12, and 24
- Other lipid assessments (Apo B, Apo A-1, Apo C-III, LDL particle size and number, Lp[a]): Weeks 0, 12, and 24
- Liver panel: all visits except Visits 3 and 6; 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
- Creatine Phosphokinase (CPK): all visits except Visits 3 and 6; 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 child bearing 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
- C-peptide: screening only
- PCSK9 levels will be performed only at Week 0.
- Anti-alirocumab antibodies (Week 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 are met.

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in Appendix C 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]

Insulin log

Patient should be instructed to complete the insulin log in order to record his/her daily insulin dose (for basal insulin and for prandial insulin, as applicable) for at least 7 days prior to each visit, and to bring this information to the next study visit. The patient may record the daily insulin dose for more than 7 days prior to the study visits, however only the information collected for the last 7 days prior to each visit will be entered into the CRF.

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 or 21 days 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
- Perform physical examination
- Get body weight and height measurements.
- Take vital signs including heart rate and blood pressure
- 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 Urinalysis/spot urine albumin: creatinine
- Obtain fasting blood samples for:
  - Lipids: TC, calculated LDL-C, HDL-C, TG, 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, LDH, and γGT
  - HbA1c
  - Liver panel (ALT, AST, 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)
- C-peptide

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. 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 LDL-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).
- Dispense the Insulin log and instruct the patient on how to complete it.

10.1.2 Double-blind treatment period (study site visits)

10.1.2.1 Randomization visit (Week 0/Day 1)

- Assess Inclusion/Exclusion Criteria
- Collect AEs
- Record concomitant medication
- Get body weight measurement
- Confirm no changes to patient diet
- Perform physical examination

- Take vital signs including heart rate and blood pressure
- If the patient is confirmed eligible, the Investigator will start the next study procedures:
  - IVRS/IWRS contact for randomization and allocation of a 7-digit treatment kit number according to the randomization list. Investigators should never allocate a treatment kit number to a patient without contacting IVRS/IWRS.
- Urine pregnancy test (women of childbearing potential only).
- Obtain fasting blood sample for:
  - Lipids: TC, LDL-C (calculated via Friedewald and measured via beta quantification), HDL-C, TG, non-HDL-C, Apo B, Apo A-1, Apo C-III, ratio Apo B/Apo A-1, LDL particle size and 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 γGT
  - Liver panel (ALT, AST, ALP, and total bilirubin)
  - CPK
- Review the Insulin log dispensed at Screening
- Dispense a new Insulin log

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.

- Provide double-blind IMP kit
  - The first 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 IMP administration. The patient should be observed for at least 30 minutes after the injection.
- 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 within48 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
- Collect information on IMP administration (Patient diary)
- Collect information on AEs/product complaints (if any)
- Review the Insulin log
- Confirm no changes to patient diet
- Reminders to be communicated to the patient:
  - IMP administration should be Q2W
  - 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 and Insulin log 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
- Get body weight measurement
- Confirm no changes to patient diet
- Take vital signs including heart rate and blood pressure
- Perform physical examination (Week 12 only)
- IVRS/IWRS contact (Week 12 only)
- Data collection on IMP administration and IMP compliance check by review of Patient diary
- Provide (Week 12 only):
  - Double-blind IMP kit
  - Instruction for use
- Provide patient diary
- [redacted]

- Review and collect Insulin log
- Dispense a new Insulin log
- Obtain fasting blood sample for:
  - TC, LDL-C, HDL-C, TG, non-HDL-C,
  - measured LDL-C (beta quantification): week 12 only
  - Apo B, Apo A-1, ratio Apo B/Apo A-1, Apo C-III, LDL particle size and number and Lp(a): week 12 only
- 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 γGT (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)

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)

10.1.2.4 Week 24 / end of treatment visit

- Collect AEs/product complaints
- Record concomitant medication
- Get body weight measurement
- Confirm no changes to patient diet
- Take vital signs including heart rate and blood pressure

- Perform physical examination
- IVRS/IWRS contact
- Data collection on IMP administration and IMP compliance check by review of Patient diary and treatment kit
- [redacted]
- Review and collect Insulin log
- Urinalysis and spot albumin: creatinine
- Urine pregnancy test (women of childbearing potential only).
- Obtain fasting blood sample for lipids:
  - TC, LDL-C, HDL-C, TG, non-HDL-C, Apo B, Apo A-1, ratio Apo B/Apo A-1, Apo C-III, LDL particle size and number 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 γGT
  - Hepatitis C Antibody Test
  - HbA1c
  - Liver panel (ALT, AST, ALP, and total bilirubin)
  - CPK
  - Anti-alirocumab antibodies
- Reminder to report any AEs up to 70 days after the last dose of IMP

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

- Record concomitant medication, noting also whether the patient has started a commercially available PCSK9 inhibitor
- 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 child bearing potential.

- Previous and concomitant medications (including insulin use [eg, type of insulin, frequency, and dose], 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 (heart rate, blood pressure), height, body weight.
- Faxed lab reports (dated and signed by the Principal Investigator or Sub-Investigator documenting timeliness of review).
- IVRS/IWRS confirmation fax.
- [redacted]
- Patient diary
- Insulin log
- 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 that are not administered to the patient as decided by the Investigator.

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.

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.
- SAE (or non-serious but severe in intensity) of hypersensitivity reaction considered related to IMP.
- At patient request.
- If, in the Investigator's opinion, continuation with the administration of the IMP would be detrimental to the patient's well-being.
- Intercurrent condition that requires discontinuation of the IMP (eg, laboratory abnormalities, please refer to decision tree in Appendix C).
- At the specific request of the Sponsor.
- Any code breaking requested by the Investigator.
- Patient receives double-blind 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.

10.3.4 Handling of patients after permanent treatment discontinuation

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. At the time of treatment discontinuation, the patient should have, as soon as possible, an unscheduled visit with assessments normally planned at EOT 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 EOT 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 definitive discontinuation of study treatment 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.

10.3.5 Procedure and consequence for patient withdrawal from study

The patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason.

If possible, the patients are assessed using the procedure normally planned for the EOT visit.

For patients who fail to return to the site, 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 statistical analysis plan 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 rerandomized (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 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

An 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) that needs to be monitored, documented, and managed in a pre-specified manner described in the protocol (Appendix B).

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 ≥ULN) (Appendix C).

- Allergic events.
  - 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.
- 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.
  - 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 IMP:
  - 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, if any, entered on separate AE/SAE forms.
- Of note, asymptomatic overdose should be reported as a standard AE.

- 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 AE.
- Neurocognitive events
  - All neurocognitive events will be considered as AESI

10.4.1.4 Local injection site reactions

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. If the patient experiences a local injection site reaction with no signs or symptoms except for erythema/redness, and/or swelling, and the diameter of the erythema/ redness, or swelling measure <2.5 cm, no AE for local injection site reaction needs to be reported as this is not typically considered a clinically important finding. However, if the patient has a reaction of swelling with a diameter <2.5 cm that interferes with activity, then it should be considered as a clinically relevant finding and should be reported as an AE with a corresponding grade of moderate or severe, in accordance with Appendix E.

10.4.1.5 Device deficiency

A device deficiency is any inadequacy related to the identity, quality, durability, reliability, safety or performance of the medical device including malfunctions, use errors, and inadequate labeling.

Product Complaints:

- A product complaint is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, efficacy or performance of a product after it is released for distribution. Patients will be instructed to contact their site for any questions or difficulties.
- All product complaints must be reported on a product complaint form when there is a reason to suspect a problem with the device.
- In case of a product complaint associated with the occurrence of an AE, the AE must be documented on an AE page in the CRF.

- In the case of a product complaint associated with the occurrence of a SAE, the SAE must be reported as in Section 10.4.3 in accordance with the SAE reporting procedures
- Please note that all product complaints require reporting within 24 hours (please refer to Appendix B).

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 ICF 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, a 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 for certain events, such as SAEs/AESI, 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, if possible.
- Laboratory or vital sign 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 (Appendix C)

10.4.3 Instructions for reporting serious adverse events

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

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send a notification to the 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 the IMP 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 10.4.4, 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 B for 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 C. Reporting instructions are provided in Appendix B.

- 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 B and Appendix C, 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 a myocardial infarction

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 C.

10.5 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner:

- All SAEs that are both unexpected and at least reasonably related to the IMP (SUSAR), to the regulatory authorities, IECs/IRBs as appropriate and to the Investigators.
- All SAEs that are expected and at least reasonably related to the IMPs 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)

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. Information on classifying the reaction are given in Section 10.4.1.4 and on reporting these reactions is given in Appendix B.

10.6.2 Allergic adverse events

Specific e-CRF screens are to be filled in to assess allergic reactions or allergic-like reactions that may occur during the clinical studies conducted with alirocumab.

Sometimes transient injection site reactions, irritant in nature, may occur, requiring no intervention and being of dubious significance. These reactions would not be considered to be allergic reactions.

Adverse events that may constitute an allergic reaction (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.

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 E and 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.

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 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 the IMP (characterized by but not limited to hypotension, bronchoconstriction, urticaria, edema, angioedema, nausea, vomiting). Emergency equipment and medication for the treatment of these potential adverse effects (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]

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, with a double-blind treatment kit number allocated and recorded in the IVRS/IWRS database, regardless of whether the treatment kit was used or not. Patients treated without being randomized or treated with a double-blind 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.

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

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

- The baseline calculated LDL-C value is available
- A least one calculated LDL-C value is available within one of the analysis windows up to Week 24.

11.3.1.2 Modified intent-to-treat population

The modified ITT (mITT) population (otherwise referred to as the on-treatment population) is defined as all randomized patients who took at least one dose or part of a dose of the double-blind IMP and have an evaluable primary efficacy endpoint during the efficacy treatment period.

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

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

- The baseline calculated LDL-C value is available
- At least one calculated LDL-C value is available during the efficacy treatment period and within one of the analysis windows up to Week 24.

The efficacy treatment period is defined as the time period from the first double-blind IMP injection up to 21 days after the last double-blind IMP injection.

11.3.2 Safety population

The safety population considered for safety analyses will be the randomized population who did actually receive at least one dose or part of a dose of the double-blind IMP. Patients will be analyzed according to the treatment actually received (placebo or alirocumab).

The safety analysis will focus on the Treatment Emergent Adverse Events (TEAE) period defined as the time from the first double-blind dose to the last double-blind dose of IMP + 70 days (10 weeks).

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-double-blind IMP injection.

[redacted]

11.4 STATISTICAL METHODS

Separate analyses will be performed for Type 1 diabetes patients on one hand and Type 2 diabetes patients on the other hand. However, some endpoints may also be analyzed on the pooled data (Type 1 and Type 2 diabetes patients together). These analyses will be defined later in the statistical analysis plan.

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

The total exposure will be assessed by:

- Duration of IMP exposure in weeks is defined as: (last dose of double-blind IMP injection date – first dose of double-blind IMP injection date + 14 days)/7, regardless of unplanned intermittent discontinuations.
- The total number of injections by patient.

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

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:

- 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).

This parameter will be summarized descriptively (N, Mean, SD, Median, Min and Max).

11.4.2 Analyses of efficacy endpoints

11.4.2.1 Analysis of primary efficacy endpoint(s)

The percent change in calculated LDL-C from baseline to Week 24 as defined in Section 9.1.1 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 (placebo versus alirocumab), time point (Week 8, Week 12, Week 20 and Week 24), treatment-by-time point interaction, as well as the continuous fixed covariates of baseline LDL-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 95% confidence intervals (CIs). To compare the alirocumab group to the placebo group, an appropriate contrast statement will be used to test the differences of these estimates, at the 2-sided 0.05 level. Separate analyses will be performed for Type 1 diabetes patients on one hand (alpha risk = 0.05) and Type 2 diabetes patients on the other hand (alpha risk = 0.05).

Let μ0 and μ1 be the population means of the percent change from baseline in calculated LDL-C at Week 24 under placebo and alirocumab, respectively. The null hypothesis that will be tested is:

$$H0 : \mu 0 = \mu 1$$
$$versus$$
$$H1 : \mu 0 \neq \mu 1$$

Robustness of this statistical method will be assessed via sensitivity analyses detailed in the SAP, including different methodologies for missing data (multiple imputation and potentially pattern

mixture modeling). In addition, sensitivity analysis will be conducted using measured LDL-C to evaluate the robustness of the results regardless of the way to assess LDL-C. Correlation of calculated LDL-C with measured LDL-C will be explored graphically as deemed necessary.

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 9.2.3), descriptive summaries and analyses will be performed in the ITT population or mITT population depending on the estimand used.

For descriptive summaries, percent change from baseline in calculated LDL C, C, HDL-C, TG, and non-HDL-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), TGRL, LDL-C particle size, and LDL-C particle number. For TG 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 calculated LDL-C), continuous measurements expected to have a non-normal distribution (eg, TG), and binary measurements (eg, proportion of patients reaching LDL-C <70 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 TG 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 nonnormal distribution (ie, TG 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, 95% CI and p-value.

Binary endpoints

Binary secondary efficacy endpoints defined in Section 9.2 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 95% 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).

11.4.2.3 Multiplicity considerations

In order to handle multiple key secondary efficacy endpoints, the overall type-I error will be controlled by the use of a sequential inferential approach. Statistical significance of the primary parameter at the 0.05 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 0.05 level.

No further adjustments will be made for other efficacy endpoints for which p-values will be provided for descriptive purpose only.

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 double-blind IMP.

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.
- PCSA 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.
- Treatment period: the treatment period used for quantitative analysis is defined as the time from first dose of double-blind IMP injection to the last dose of double-blind IMP injection + 21 days

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
- 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, alkaline phosphatase and total bilirubin, are used to assess possible drug induced liver toxicity. The proportion of patients with PCSA values at any postbaseline 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 preferred terms 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 system organ class (SOC) (sorted by internationally agreed order), high-level group term (HLGT), high level term (HLT) and preferred term (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 from the first dose of double-blind IMP injection to the first occurrence of the event will be calculated (only the first event will be counted). Patients without any event will be censored at the end of the TEAE period. Incidence rates at 6 months of exposure 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, HLGT, HLT and PT showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, 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 SE will be plotted over time (at same time points) in each treatment group.

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

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

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

Hepatitis C Test

The number and percentage of patients with an observed seroconversion for Hepatitis C Test will be provided by treatment group. 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 and mITT population and will be descriptive only. Summary statistics, including the mean, median, Q1, Q3, SE, minimum, and maximum of the 4 endpoints (HbA1c, FPG, total daily insulin dose, 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 [redacted]

[redacted]

Handling missing data

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

[redacted]

11.5 INTERIM ANALYSIS

If needed for the purpose of scientific communication, both the efficacy and safety analyses will be performed at the Week 24 cut-off date and an update of the safety analysis at the end of the study, a two-step analysis as described below. 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 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.

The first-step analysis will 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.

Selected individuals who are not involved in the conduct of the study after the first step analysis will perform the second step analysis; individual patient identification will not be released to anyone who is directly involved in the conduct of the study. The second step analysis process, the measures used to protect the blind and the integrity of the study, as well as a communication plan and confidentially agreement will be described in a separate document if two analyses are to be conducted.

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

The ICF 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, ICF, Investigator’s Brochure, Investigator’s curriculum vitae [CV], etc) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

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

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

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

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATORS

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 Subinvestigators and/or Study Coordinators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All Subinvestigators and Study Coordinators shall be appointed and listed in a timely manner. The Subinvestigators 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, IMP allocation, patient compliance with the IMP regimen, IMP accountability, concomitant therapy use and quality of data.

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, the monitoring team must check the CRF entries against the source documents, except for the pre-identified source data directly recorded in the CRF. The ICF will include a statement by which the patient allows the Sponsor’s duly authorized personnel, the

Ethics Committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the CRFs (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]

14.4 PROPERTY RIGHTS

[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 are 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]

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 ICF. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised ICF prior to implementation of the change and patient signature should be re-collected if necessary.

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