AMENDED CLINICAL TRIAL PROTOCOL 01

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COMPOUND: alirocumab (SAR236553/REGN727)

A Randomized, Double-Blind, Parallel Group Study to Evaluate the Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Ezetimibe in Asia in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled With Their Statin Therapy

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STUDY NAME: ODYSSEY EAST

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CLINICAL TRIAL SUMMARY

COMPOUND: Alirocumab (SAR236553/REGN727) STUDY No: EFC13889	
TITLE	A Randomized, Double-Blind, Parallel Group Study to Evaluate the Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Ezetimibe in Asia in High Cardiovascular Risk Patients With Hypercholesterolemia Not Adequately Controlled With Their Statin Therapy
INVESTIGATOR/TRIAL LOCATION	China, India and other Asia countries; Multi-center
PHASE OF DEVELOPMENT	Phase 3
STUDY OBJECTIVE(S)	**Primary objective** • To demonstrate the reduction of low-density lipoprotein cholesterol (LDL-C) by alirocumab as add-on therapy to stable maximally tolerated daily statin therapy in comparison with ezetimibe 10 mg daily after 24 weeks of treatment in Asia in patients with hypercholesterolemia at high cardiovascular (CV) risk. **Key Secondary objective(s)** • To evaluate the effect of alirocumab 75 mg in comparison with ezetimibe 10 mg on LDL-C after 12 weeks of treatment • To evaluate the effect of alirocumab on other lipid parameters: eg, Apolipoprotein (Apo) B, non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), lipoprotein a (Lp[a]), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and Apo A-1 • To evaluate the safety and tolerability of alirocumab • To evaluate the development of anti-alirocumab antibodies • To evaluate the pharmacokinetics (PK) of alirocumab
STUDY DESIGN	This is a randomized, double-blind, double-dummy, unbalanced (2:1, alirocumab: ezetimibe), parallel-group, multi-center study. Randomization will be stratified according to prior history of myocardial infarction (MI) or ischemic stroke [Yes/No], high-intensity statin treatment (Yes defined as atorvastatin 40 to 80 mg or rosuvastatin 20 to 40 mg, No for simvastatin whatever the dose daily, atorvastatin below 40 mg daily or rosuvastatin below 20 mg daily), and Country. After randomization, patients will receive double-blind, double-dummy study treatment (either alirocumab or ezetimibe) over a period of 24 weeks on top of stable maximally tolerated daily statin therapy. A dose up-titration of alirocumab from 75 mg to 150 mg may occur at Week 12 for patients randomized to alirocumab (see below). The study consists of: • A screening period of up to 3 weeks, including an intermediate visit during which the patient or another designated person (such as spouse, relative, etc) will be trained to self-inject/inject with a placebo for alirocumab. • A double-blind, double-dummy treatment period of 24 weeks with either A or B below:

	A) Alirocumab 75 mg subcutaneous (SC) every 2 weeks (Q2W) + Placebo for ezetimibe by mouth (PO) daily. At Week 12, patients will, in a blinded manner, either: - Continue alirocumab 75mg Q2W + placebo for ezetimibe PO daily, if the Week 8 LDL-C is <70 mg/dL (1.81 mmol/L). OR - Dose up-titrate to alirocumab 150 mg Q2W + placebo for ezetimibe PO daily, if the Week 8 LDL-C is ≥70 mg/dL (1.81 mmol/L). Lipid values obtained at Week 8 for the purpose of up-titration will not be communicated to investigators to maintain the blind. The continuation of the 75 mg dose or dose up-titration to the 150 mg dose will occur automatically through Interactive Voice Response System (IVRS) or Interactive Web Response System (IWRS) without site or patient awareness. OR B) Placebo for alirocumab subcutaneous Q2W + ezetimibe 10 mg PO daily • A follow-up period of 8 weeks after the end of double-blind treatment period (DBTP) The lipid results obtained from specimens collected after randomization will be masked to maintain blinding. No attempts should be made by the investigator or patient to routinely have the patient's lipid values independently evaluated after randomization until the follow up visit. Patients should be on a stable diet (National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) Therapeutic Lifestyle Changes (TLC) diet or equivalent) throughout the entire study duration from screening to the follow-up visit. Daily dose of statin should be stable throughout the whole study duration from screening to the follow-up visit. Fibrates, other than fenofibrate, are not allowed during the study. During the double-blind period, modification to the statin therapy or addition of other lipid modifying therapy (LMT) is allowed only under the following circumstances: • Exceptional circumstances (such as muscle symptoms) per the Investigator's judgment • Patient meets the pre-specified TG alert (TG ≥500 mg/dL [5.65 mmol/L]). Lab alerts will be sent.
STUDY POPULATION **Main selection criteria**	**Main Inclusion Criteria** I01. Patients with hypercholesterolemia and established coronary heart disease (CHD) or CHD risk equivalents who are not adequately controlled with a maximally tolerated daily dose of statin* at a stable dose for at least 4 weeks prior to the screening visit (Week -3). *Definition of maximally tolerated dose (any of the following are acceptable): - Atorvastatin 40 mg to 80 mg daily - Rosuvastatin 20 mg to 40mg daily - Simvastatin 40 mg daily

	- Patients not able to be on any of the above statin doses should be treated with the dose of daily atorvastatin, rosuvastatin or simvastatin which is considered appropriate for the patient as per the investigator's judgment or concerns. Some examples of acceptable reasons for a patient taking a lower statin dose include, but are not limited to: adverse effects on higher doses, advanced age, low body mass index (BMI), local prescribing information, concomitant medications and comorbid conditions such as impaired glucose tolerance/impaired fasting glucose. The reason(s) will need to be documented in the case report form. **Main Exclusion Criteria** E01. Patients without established CHD or CHD risk equivalents E02. LDL-C <70 mg/dL (<1.81 mmol/L) at the screening visit (Week -3) in patients with history of documented CV disease E03. LDL-C <100 mg/dL (<2.59 mmol/L) at the screening visit (Week -3) in patients without history of documented CV disease NOTE – Cardiovascular disease (CVD) is defined as CHD, ischemic stroke or peripheral arterial disease (PAD) as described in Section 7.1 E04. Change in statin dose or dose regimen from screening to randomization E05. Currently taking a statin other than atorvastatin, rosuvastatin or simvastatin E06. Atorvastatin, rosuvastatin or simvastatin is not taken daily or not taken at a registered dose E07. Daily doses above atorvastatin 80 mg, rosuvastatin 40 mg or simvastatin 40 mg E08. Use of cholesterol absorption inhibitor (ie, ezetimibe), omega-3 fatty acid (at doses ≥1000 mg daily), nicotinic acid, fibrates, bile acid-binding sequestrant, or red yeast rice products in the past 4 weeks prior to screening visit (Week -3) E09. Fasting serum TG >400 mg/dL (>4.52 mmol/L) at the screening period
Total expected number of patients **Expected number of sites**	Approximately 600 randomized patients (400:200, alirocumab:ezetimibe). At least 110 patients in total from pre-selected sites will have PK analysis during the study, in order to have 60 patients on alirocumab treatment (at least 30 Chinese and 24 Indian patients). Approximately 69 sites.
STUDY TREATMENT(s)	
Investigational medicinal product(s) **Formulation**	**Alirocumab** Sterile alirocumab drug product supplied at a concentration of 75 mg/mL and/or 150 mg/mL in histidine, pH 6.0, polysorbate 20, and sucrose.
Route(s) of administration	Subcutaneous (SC) injection in the abdomen
Dose regimen	• 75 mg Q2W OR

	• 75 mg Q2W up to Week 12 followed by 150 mg Q2W from Week 12 onwards At Week 12, in a blinded manner managed by IVRS/IWRS process, the patient will either continue alirocumab 75 mg Q2W if the Week 8 LDL-C is <70 mg/dL (1.81 mmol/L) or up-titrate to alirocumab 150 mg Q2W if Week 8 LDL-C is ≥70 mg/dL (1.81 mmol/L).
Placebo **Formulation**	Placebo for alirocumab • Sterile solution consisting of histidine, pH 6.0, polysorbate 20, and sucrose
Route(s) of administration	SC in the abdomen
Dose regimen	N/A
Investigational medicinal product(s) **Formulation**	Ezetimibe 10 mg ezetimibe 10 mg tablets -over encapsulated
Route(s) of administration	PO
Dose regimen	10 mg daily
Placebo **Formulation**	Placebo for ezetimibe capsules to match ezetimibe
Route(s) of administration	PO
Dose regimen	N/A
ENDPOINT(S)	**Primary endpoint** • The percent change in calculated 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) **Secondary endpoint(s)** • The percent change in calculated LDL-C from baseline to Week 24 in the modified ITT (mITT) population, using all LDL-C values during the efficacy treatment period (on-treatment estimand) • The percent change in calculated LDL-C from baseline to Week 12 (ITT and on-treatment estimands) • The percent change in Apo B from baseline to Week 24 (ITT and on-treatment estimands) • The percent change in non-HDL-C from baseline to Week 24 (ITT and on-treatment estimands) • The percent change in TC from baseline to Week 24 (ITT estimand) • The percent change in Apo B, non-HDL-C, TC from baseline to Week 12 (ITT estimand) • The proportion of patients reaching calculated LDL-C <70 mg/dL (1.81 mmol/L) at Week 24 (ITT and on-treatment estimands) • The percent change in Lp(a), HDL-C, fasting TG and Apo A-1 from baseline to Week 24 (ITT estimand) • The percent change in Lp(a), HDL-C, fasting TG and Apo A-1 from baseline to Week 12 (ITT estimand)

	Other Secondary Efficacy Endpoints • The proportion of patients with calculated LDL-C <100 mg/dL (2.59 mmol/L) at Week 12 and Week 24 (ITT estimand) • The proportion of patients reaching calculated LDL-C <70 mg/dL (1.81 mmol/L) at Week 12 (ITT estimand) • The absolute change in calculated LDL-C (mg/dL and mmol/L) from baseline to Week 12 and Week 24 (ITT estimand) • The absolute change in ratio Apo B/Apo A-1 from baseline to Week 12 and Week 24 (ITT estimand) • The proportion of patients with Apo B <80 mg/dL (0.8 g/L) at Week 12 and Week 24 (ITT estimand) • The proportion of patients with non-HDL-C <100 mg/dL (2.59 mmol/L) at Week 12 and Week 24 (ITT estimand) • The proportion of patients with non-HDL-C <130 mg/dL (3.37 mmol/L) at Week 12 and Week 24 (ITT estimand) • The proportion of patients with calculated LDL-C <70 mg/dL (1.81 mmol/L) and/or ≥50% reduction from baseline in calculated LDL-C (if calculated LDL-C ≥70 mg/dL [1.81 mmol/L]) at Week 12 and Week 24 (ITT estimand) • The proportion of patients with ≥50% reduction in calculated LDL-C at Week 12 and Week 24 (ITT estimand) • The absolute change in ratio TC/HDL-C from baseline to Week 12 and Week 24 (ITT estimand) • The percent change in TC from baseline to Week 12 and 24 (on-treatment estimand) • The percent change in Apo B from baseline to Week 12 (on-treatment estimand) • The percent change in non-HDL-C from baseline to Week 12 (on-treatment estimand) • The percent change in Lp(a) from baseline to Week 12 and 24 (on-treatment estimand) • The proportion of patients reaching calculated LDL-C <100 mg/dL (2.59 mmol/L) at Week 24 (on-treatment estimand) **Safety Endpoints** • Safety parameters (adverse events [AEs]) (including adjudicated CV events), laboratory data, vital signs assessed throughout the study. **Other Endpoints** • Anti-alirocumab antibodies assessed throughout the study. • Serum alirocumab concentration assessed throughout the study. • The absolute change in glycated Hemoglobin A1c (HbA1c) from baseline to Week 12 and 24.

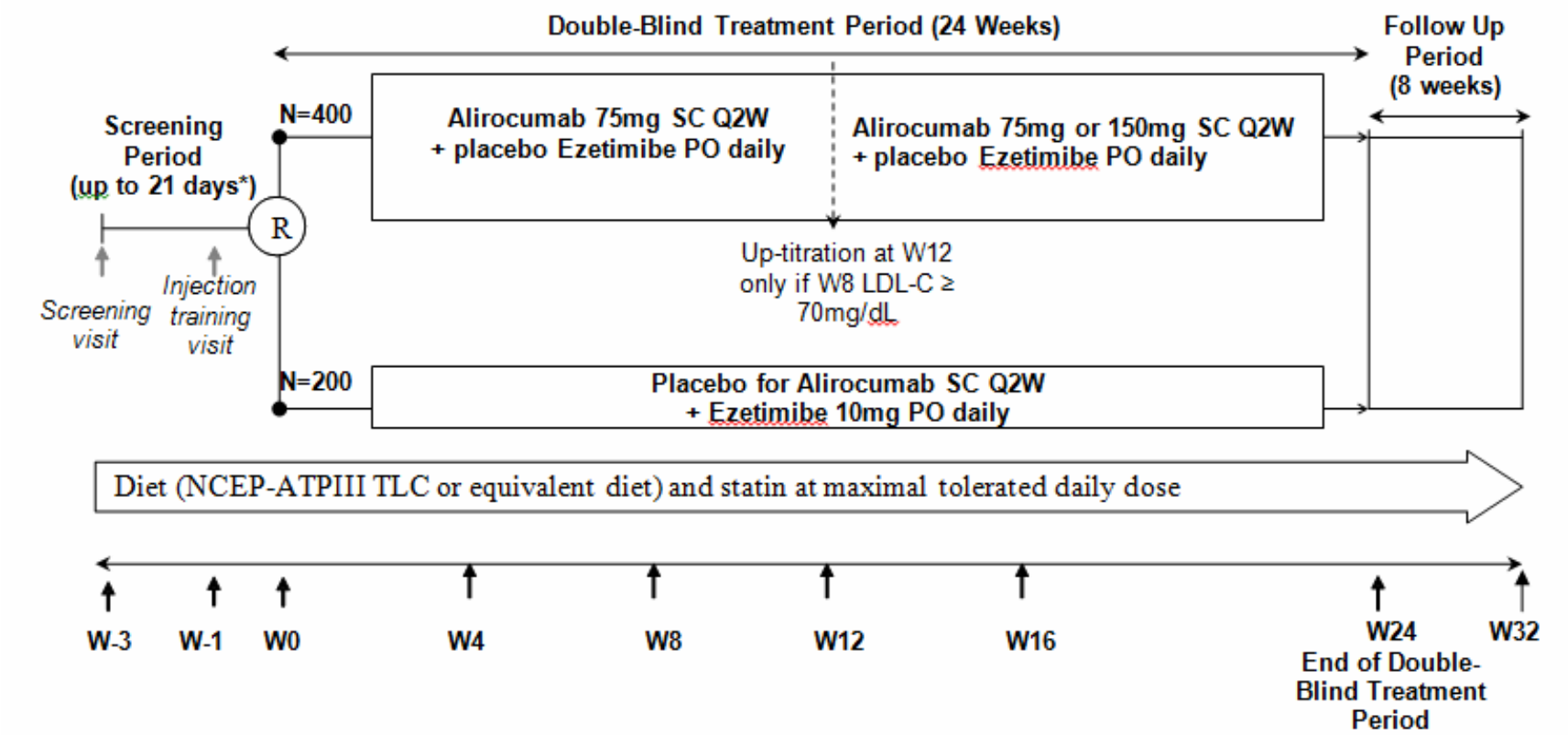
ASSESSMENT SCHEDULE	**Patient assessments in the screening period** • On-site visits: Week -3 (screening visit), Week -1 (injection training visit). **Patient assessments in the double-blind treatment period** • On-site visits: Day 1/Week 0 (randomization visit), Week 4, Week 8, Week 12, Week 16, Week 24 (end of treatment visit) **Patient assessments in the follow-up period** • On-site visit: Week 32 (8 weeks after the end of treatment visit)
STATISTICAL CONSIDERATIONS	**Sample Size Determination** A total sample size of 96 patients (64 in alirocumab and 32 in ezetimibe arms) will have 95% power to detect a difference in mean percent change in LDL-C of 20% with a 0.05 two-sided significance level and assuming a common standard deviation (SD) of 25% and all these patients having an evaluable primary endpoint. Nevertheless, to meet registration requirement and provide safety documentation in participating countries the final total sample size will be 600 with a randomization ratio 2:1 (alirocumab: 400, ezetimibe: 200). **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 the randomized population who had an evaluable primary endpoint. The primary endpoint will be considered evaluable 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 within one of analysis window up to Week 24. The mITT population is defined as all randomized patients who took at least one dose or part of dose of the double-blind investigational medicinal product (IMP) (injection or capsule) and had an evaluable primary efficacy endpoint during the efficacy treatment period. The primary efficacy endpoint will be considered evaluable 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 or capsule, whichever comes first) up to 21 days after the last double-blinded IMP injection or the day of last capsule intake + 3 days, whichever comes first 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 (injection or capsule). The

	safety population will be analyzed according to the treatment actually received. **Primary Analysis** The percent change in calculated LDL-C from baseline to Week 24 will be analyzed in the ITT population using mixed-effect model with repeated measures (MMRM) approach to handle missing data. All post-baseline data available within Week 4 to Week 24 analysis window will be used (on-treatment and off-treatment through Week 24). The model will include the fixed categorical effects of treatment group (alirocumab versus ezetimibe), time point (Week 4, Week 8, Week 12, Week 16, Week 24),randomization strata, treatment-by-time point interaction and strata-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 ezetimibe using appropriate contrasts, and the 95% confidence interval (CI) of the difference will be provided. **Analysis of key secondary efficacy endpoints** A hierarchical procedure 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, key secondary endpoints will be tested sequentially, using the order defined in section “Key secondary efficacy endpoints”. Continuous secondary endpoints anticipated to have a normal distribution (ie, lipids other than Lp[a] and TG), will be analyzed using the same MMRM model as for the primary endpoint with the continuous fixed covariates of corresponding baseline value and baseline value-by-time point interaction. Continuous secondary endpoints anticipated to have a non-normal distribution (ie, Lp[a] and TG) 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. **Safety Analysis** Safety analysis (AE [including adjudicated CV events], laboratory, vital signs will be descriptive), based on the safety population. The safety analysis will focus on Treatment Emergent Adverse Events (TEAE) period, defined as the time from the first double-blind IMP dose to the last dose of double-blind IMP injection + 70 days (10 weeks).
DURATION OF STUDY PERIOD (per patient)	Approximately 35 weeks (screening: 3 weeks, DBTP: 24 weeks, and follow-up period: 8 weeks).

STUDY COMMITTEES	**Steering Committee**: ☐ Yes ☒ No **Data Monitoring Committee:** ☒ Yes ☐ No The independent Data Monitoring Committee (DMC) is implemented in order to monitor patient safety by conducting formal reviews of accumulated safety data. The DMC will provide the Sponsor with appropriate recommendations on the conduct of the clinical trial to ensure the protection and the safety of the enrolled patients in the study. **Adjudication Committee:** ☒ Yes ☐ No The Cardiovascular Events Adjudication Committee (CEC) will be responsible for defining, validating and classifying, in a blinded fashion, pre-specified cardiovascular events and all death. Classification of events will be as follows: CHD death, non-fatal MI, fatal and non-fatal ischemic stroke, unstable angina requiring hospitalization, congestive heart failure requiring hospitalization, and ischemia-driven coronary revascularisation procedure. In addition, the classification of the cause of all deaths will occur. All events for adjudication will be defined in the adjudication Charter.

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



* Every effort should be made to ensure that the screening window is as short as possible and ideally within two weeks.

1.2 STUDY FLOW CHART

	Screening period		Double-blind Treatment Period						Follow-up period
Day (D) / Week (W) / Month (M)	W-3 (D-21 to -8)	W-1 (D-7)	W0 (D1)	W4 (D29)	W8 (D57)	W12 (D85)	W16 (D113)	W24 (D169) End of Treatment	W32 (D225)
Visit Number	1	2	3	4	5	6	7	8	9
Visit Window (Days)		±7	+3	±7	±7	±3	±7	±3	±7
Design:									
Informed consent	X								
Patient demography	X								
Inclusion/Exclusion Criteria	X	X	X[d]						
Medical/family//surgical history, alcohol habits, smoking habits	X								
Prior medication history	X								
Physical examination			X[d]					X	X[a]
Body weight	X		X[d]			X		X	X
Measured height	X								
Randomization			X						
Patient diary dispensation / review / Collection[e]			X	X	X	X	X	X	
IVRS/IWRS contact	X	X	X			X		X	X
Treatment:									
Injection training		X[b]	X[c]						
Review diet			X[d]			X		X	

	Screening period		Double-blind Treatment Period						Follow-up period
Day (D) / Week (W) / Month (M)	W-3 (D-21 to -8)	W-1 (D-7)	W0 (D1)	W4 (D29)	W8 (D57)	W12 (D85)	W16 (D113)	W24 (D169) End of Treatment	W32 (D225)
Visit Number	1	2	3	4	5	6	7	8	9
Visit Window (Days)		±7	+3	±7	±7	±3	±7	±3	±7
Double-blind IMP kit dispensation[e]			X			X			
The time of the first injection of the IMP			X						
Compliance check of IMP (review patient diary and treatment kit) and data collection on IMP administration				X	X	X	X	X	
Concomitant medication	X	X	X[d]	X	X	X	X	X	X
Vital signs:									
Heart rate (HR), blood pressure (BP)	X	X	X[d]	X	X	X	X	X	X
Safety:									
AEs / SAEs recording	X	X	X	X	X	X	X	X	X
12-lead electrocardiogram (ECG)	X							X	
Laboratory Testing - Efficacy									
TC,calculated LDL-C, HDL-C, TG, non-HDL-C[f]	X		X[d]	X	X	X	X	X	
Apo B, Apo A-1, Apo B/Apo A-1 ratio and Lp(a)			X[d]			X		X	
Laboratory Testing - Safety									
Hematology and chemistry[g]	X		X[d]			X		X	X[a]
Creatine phosphokinase (CPK)	X		X[d]			X		X	X[a]
Liver panel[h]	X		X[d]	X	X	X	X	X	X[a]

	Screening period		Double-blind Treatment Period						Follow-up period
Day (D) / Week (W) / Month (M)	W-3 (D-21 to -8)	W-1 (D-7)	W0 (D1)	W4 (D29)	W8 (D57)	W12 (D85)	W16 (D113)	W24 (D169) End of Treatment	W32 (D225)
Visit Number	1	2	3	4	5	6	7	8	9
Visit Window (Days)		±7	+3	±7	±7	±3	±7	±3	±7
Hepatitis B surface antigen	X								
Hepatitis C antibody	X							X[i]	
Serum pregnancy test[j]	X								
Urine pregnancy test[j]			X[d]			X		X	X
Urinalysis	X		X[d]			X		X	X[a]
Laboratory Testing - Other									
HbA_{1c}	X					X		X	X[a]
Thyroid-stimulating hormone (TSH)	X								
Anti-alirocumab antibodies[k]			X	X		X		X	X[l]
Library samples[m]			X[d]	X		X		X	
PK samples[k, n]			X	X		X	X	X	
[redacted]									
[redacted]			X						
[redacted]			X						

a To be obtained at the follow up visit only in case of clinically relevant abnormal values for these parameters(or clinically relevant abnormal finding for physical examination) at the end of double-blind treatment visit.

b Injection training at screening period visit Week -1 is performed with placebo. Investigators will have the option of providing a second placebo for alirocumab for patients who require additional self-injection training prior to randomization, e.g. the patient or investigator may elect to have the patient inject at home or at the study site.

c Injection training at randomization visit Week 0/Day 1 is performed at the site by the patient or a trained designated person with double-blind study treatment kit allocated by IVRS/IWRS. Further training with a double-blind treatment can be done between Week 0 and 4 and at additional scheduled or unscheduled visits, as per patient or investigator's judgment.

d To be performed before randomization.

e Along with kit dispensation, the treatment administration package should be given as well as the IMP diary and injection instruction manual, as needed.

f LDL-C will also be measured (via the beta-quantification method) at Week 0 and Week 24

g Hematology includes: complete blood cell count (CBC) including red blood cell distribution width (RDW) and reticulocyte count, hematocrit, hemoglobin (Hb), red blood cell count, white blood cell count with differential count and platelets. Chemistry includes: glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, uric acid, lactate dehydrogenase (LDH), total protein, albumin, and gamma-glutamyl transferase (γGT).

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

i Positive HCV antibody results for the W24 assessment will be followed up with confirmatory test.

j Women of Child Bearing Potential (WOCBP) only.

k PK and anti-alirocumab antibodies collections are to be done prior to the IMP injection.

l Patients who have a titer at or above 240 for anti-alirocumab antibody at follow up visit will have additional antibody sample(s), at 6 to 12 months after the last dose and thereafter, about every 3 to 6 months until titer returns below 240.

m Library samples should be collected, as permitted by local regulatory policies. They may be stored for up to 10 years or as permitted by local regulatory policies, whichever is shorter, for exploratory research of PCSK9 levels, PCSK9 function, effect(s) of PCSK9 inhibition with a monoclonal antibody, lipoprotein sub-fraction, inflammation, and cardiovascular risk markers (eg, lipoprotein–associated phospholipase A2).

n An additional random PK sample to be collected 5 days (± 2) after dosing, on or after week 22.

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3 LIST OF ABBREVIATIONS

ADA:	anti-drug antibody
AEs:	adverse events
AESI:	adverse event of special Interest
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
Apo:	apolipoprotein
AST:	aspartate aminotransferase
BMI:	body mass index
BP:	blood pressure
CABG:	coronary artery bypass graft surgery
CBC:	complete blood cell count
CEC:	Cardiovascular Events Adjudication Committee
CHD:	coronary heart disease
CI:	confidence intervals
CIB:	clinical investigator's brochure
CKD:	chronic kidney disease
CPK:	Creatine phosphokinase
CV:	cardiovascular
CVD:	cardiovascular disease
DBTP:	double-blind treatment period
DMC:	Data Monitoring Committee
DNA:	deoxyribonucleic acid
DRF:	discrepancy resolution form
ECG:	electrocardiogram
e-CRF:	electronic case record form
FH:	familial hypercholesterolemia
GCP:	good clinical practice
Hb:	hemoglobin
HbA1c:	glycated hemoglobin A1c
HDL-C:	high density lipoprotein cholesterol
HLGT:	high level group term
HLT:	high level term
HMG CoA:	3-hydroxy-3-methyl-glutaryl-CoA reductase
HR:	heart rate
ICF:	informed consent form
ICH:	International Conference on Harmonization
IEC:	Independent Ethics Committee
IMP:	investigational medicinal product
IRB:	Institutional Review Board
ITT:	intent-to-treat
IV:	intravenous

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
LMT:	lipid modifying therapy
LOCF:	last Observation Carried Forward
Lp(a):	lipoprotein a
LTT:	lowest level term
MedDRA:	medical dictionary for regulatory activities
MI:	myocardial infarction
MMRM:	mixed effect model with repeated measures
mRNA:	messenger ribonucleic acid
NCEP ATP III:	national cholesterol education program adult treatment panel III
NIMP:	non investigational medicinal products
non-HDL-C:	non-high-density lipoprotein cholesterol
NYHA:	New York Heart Association
PAD:	peripheral arterial disease
PCI:	percutaneous coronary intervention
PCSK9:	proprotein convertase subtilisin kexin type 9
PK:	pharmacokinetics
PO:	by mouth = per os
PT:	preferred term
Q2W:	every 2 weeks
Q4W:	every 4 weeks
RDW:	red blood cell distribution width
SAEs:	serious adverse events
SAP:	Statistical Analysis Plan
SC:	subcutaneous
SD:	standard deviation
SE:	standard errors
SNP:	single nucleotide polymorphisms
SOC:	system organ class
SUSAR:	suspected unexpected serious adverse reaction
TC:	total cholesterol
TEAE:	treatment emergent adverse events
TG:	triglycerides
TLC:	therapeutic lifestyle changes
TSH:	thyroid stimulating hormone
WOCBP:	women of child bearing potential
γGT:	gamma glutamyl transferase

4 INTRODUCTION AND RATIONALE

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

Alirocumab is also referred to as SAR236553 or REGN727. However, for this study protocol (EFC13889), it will be referred to as alirocumab.

Background on patient populations:

This study will be performed in Asia and will include patients with high CV risk due to established coronary heart disease (CHD) or CHD risk equivalents and having hypercholesterolemia.

Hypercholesterolemia, particularly an increase in low density lipoprotein cholesterol (LDL-C) levels, constitutes a major risk for the development of atherosclerosis and CHD (1), a leading cause of death and disability in the world (2). Cardiovascular mortality is projected to double globally between 1990 and 2020, with developing countries bearing about 80% of the increased disease burden (3). In general across Asia, along with the rapid urbanization and economic development during the past 20 years, there have been trends toward increases in serum total cholesterol (TC) levels and CHD mortality rates (4). As in western societies, there is a direct (continuous) relationship between plasma TC concentrations and CHD mortality, although the mean TC is lower in many Asian societies compared with western societies having higher proportions of Caucasians (4). The study published in 2012 showed serum TC and LDL-C levels were high and increasing in the Chinese population (5).

LDL-C is identified as the primary target of cholesterol lowering therapy (6) and is accepted as a valid surrogate endpoint (7, 8, 9). Numerous studies have demonstrated that reducing LDL-C levels mainly via 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG CoA) inhibition, reduces the risk of CHD, with a strong direct relationship between LDL-C levels and CHD events; for each 1 mmol/L (~40 mg/dL) reduction in LDL-C, cardiovascular disease (CVD) mortality and morbidity is lowered by 22% (10). Greater reductions in LDL-C produce greater reduction in 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 very high cardiovascular risk (10, 11, 12, 13).

The Third Report of the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) in 2001(14) and the Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice in 2003 (15) have recommended an LDL-C level of less than 100 mg/dL as the goal of therapy for patients at high risk for CHD. On the basis of accumulating data with statins in CHD patients, the National Cholesterol Education Program in conjunction with the American Heart Association and the American College of Cardiology subsequently introduced in 2004 a more aggressive, but optional, LDL-C goal of less than 70 mg/dL (1.81 mmol/L) for patients at very high risk for CHD, even if baseline LDL-C

levels were below 100 mg/dL (16). The Task Force for the management of dyslipidemia of the European Society of Cardiology and the European Atherosclerosis society recently recommended in all patients at very high cardiovascular risk a LDL-C goal of less than 1.81 mmol/L (70 mg/dL) and/or ≥50% LDL-C reduction when target level cannot be reached (6). There is no specific guideline for dyslipidemia treatment to be applicable in whole Asia Pacific region. Generally, national guideline is in line with global guideline as in United States/European Union.

Current LDL-C-lowering medications include statins, cholesterol absorption inhibitors (ie, ezetimibe), fibrates, niacin, and bile acid sequestrants; statins are the most commonly prescribed as they have shown a great ability to lower LDL-C and reduce CHD events. However despite these available treatments that can be also used in combination, many high risk patients fail to reach the guideline target level (17). REALITY-Asia study found LDL-C goal attainment is low in Asia, particularly in patients with CHD/diabetes (18). The CEPHEUS Pan-Asian survey published in 2012 still showed a large proportion of patients in Asia with hypercholesterolemia on lipid-lowering drugs are not at recommended LDL-C levels by updated NCEP ATP III, LDL-C goal was attained in 55.4% of high risk(<100 mg/dL), and only 34.9% of very high-risk patients (<70 mg/dL) (19). These data indicate a need for more effective treatments to help more patients in Aisa to achieve their guideline-recommended cholesterol treatment targets.

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

Proprotein convertase subtilisin kexin type 9 (PCSK9) belongs to the subtilisin family of serine proteases and is highly expressed in the liver. PCSK9 is involved in regulating the levels of the low-density lipoprotein receptor (LDL-R) protein (20, 21). 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-C removal, and therefore, higher LDL-C circulating levels. Experiments with mice have shown that increasing PCSK9 protein levels decreases levels of LDL-R protein in the liver while PCSK9 knockout mice have increased levels of LDL-R in the liver (22, 23). In humans, PCSK9 mutations have been identified: the gain-of-function mutations are rare and cause an autosomal dominant form of severe hypercholesterolemia and premature CHD, whereas loss-of-function mutations are more common and are associated with reduced plasma levels of LDL-C and protection from CHD (24, 25).

Therefore blocking PCSK9 binding to the LDL-R can potentially benefit patients with hypercholesterolemia by decreasing their plasma LDL-C levels. In addition, PCSK9 messenger ribonucleic acid (mRNA) and protein levels are increased in response to statins, potentially attenuating their cholesterol-lowering effect (26).

Summary of select clinical studies with alirocumab:

Phase 1 studies

No safety signal was raised from completed Phase 1 studies.

Results of 6 phase 1 studies showed that alirocumab administered to healthy subjects and patients by intravenous (IV) or subcutaneous (SC) administration was generally well-tolerated at all doses. No safety signal was raised from completed Phase 1 studies. Treatment Emergent Adverse Events

(TEAE) did not display a dose relationship. No pattern of AEs related to the drug was identified. In all the phase 1 studies, administration of alirocumab induced rapid, substantial, and sustained reductions from baseline in mean LDL-C, up to 60%. The magnitude and duration of the reductions were related to the dose.

Larger doses of alirocumab were associated with greater and longer-lasting reductions in LDL-C. In study R727-CL-1001, the effects of SC doses of alirocumab as an add-on to stable doses of atorvastatin or given without concomitant statin were similar in patients with familial hypercholesterolemia (FH) and in patients with non-FH.

Phase 2 studies

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

Efficacy results:

In both dose-finding studies, statistically significant decreases in percent change from baseline in LDL-C at 12 weeks were observed in all alirocumab groups compared to the placebo group. The greatest decrease was seen in the 150 mg every 2 weeks (Q2W) group, with a mean decrease from baseline of up to 72.4% (the least square mean difference versus placebo of -67.3% in DFI11565, -69.1% in DFI12361, -57.2% in R727-CL-1003; all p <0.0001) (27). Decreases observed with the doses administered Q2W were maintained from the first injection throughout the study. Large decreases in LDL-C from baseline to 12 weeks were also observed with doses administered every 4 weeks (Q4W); however, the treatment effect was not fully maintained over a 4-week period (ie, the time interval between the two injections) in all these statin-treated patients.

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

Safety results:

Alirocumab was well tolerated in all completed Phase 2 studies throughout the treatment period and for all treatment groups. Injection site reactions were reported in patients including placebo treated patients; the reporting of these events was greatest in the R727-CL-1003 study (40.3% in alirocumab-treated patients versus 12.6%, 9.3% and 3.3% in DFI11565, DFI12361 and DFI11566, respectively); however these events were generally transient. Rare cases of hypersensitivity reactions were reported. Among all serious adverse events (SAEs) reported for all alirocumab studies, only one case, leucocytoclastic vasculitis (angiitis), was reported as being related to alirocumab (DFI11565 study). The patient developed one episode of diarrhea followed on the same evening by rash in arms, legs and abdomen 9 days after the first administration of

alirocumab 300 mg Q4W. The diagnosis was confirmed by skin biopsy. The patient was discontinued from study drug but completed the study. The lesions resolved after a course of tapering steroid administration. No particular signal was noted for TEAEs related to musculoskeletal or connective tissue disorders as well as no elevations in liver enzymes. For detailed information, please refer to the IB (28).

Phase 3 studies:

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

Phase 3 studies that evaluated Q2W regimen – efficacy results:

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

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

Phase 3 studies that evaluated Q4W regimen – efficacy results:

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

The EFC13786 study included a vast majority of statin intolerant patients with many on background ezetimibe therapy. At Week 24, statistically significant LS mean treatment difference

for alirocumab (150 mg Q4W with possible up-titration to 150 mg Q2W) versus placebo of -56.4% was achieved for LDL-C reduction. The results obtained at Week 12 showed statistically significant LS mean treatment difference of -44.9%, whereby the Week 12 effect assessed the sole contribution of the 150 mg Q4W dose regimen.

Clinical safety

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

Phase 2 and Phase 3 safety results:

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

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

There was no safety signal observed with neurologic events and neurocognitive disorders, alanine aminotransferase (ALT) increase and hepatic disorders, adjudicated CV events, diabetes mellitus, and ophthalmologic disorders. The most common adverse reactions in patients treated with alirocumab were local injection site reactions (6.2% patients in the alirocumab group versus 4.2% in control groups in the global pool). Injection site reactions, influenza and pruritus were identified as adverse drug reactions. Rare and sometimes serious allergic adverse reactions (e.g., hypersensitivity, eczema nummular, urticaria, and hypersensitivity vasculitis) have been reported from clinical studies in patients receiving alirocumab.

There was no safety signal in patients who had at least 2 consecutive values of LDL-C <25 or 15 mg/dL (0.65 or 0.39 mmol/L), particularly in regard to neurological or other adverse effects that could potentially be related to low LDL-C (29). 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.

Selection of the dose:

Two main doses of alirocumab are evaluated in the ongoing ODYSSEY Phase 3 program: 75 mg and 150 mg, to be administered subcutaneously Q2W, based on data from the phase 1 and

2 programs. The selection of doses, dosing frequency and up-titration approach is also based on the expected LDL-C reduction needed to provide the best benefit in terms of CVD reduction, and potential safety considerations regarding low LDL-C values.

The current and most relevant evidence around the effects of achieved low LDL-C levels comes from examinations of large statin trials (30, 31, 32) and patients with PCSK9 loss-of-function mutations (33). The patients achieving the lower levels of LDL-C had the lower CV event rates. To date, there is no evidence that very low LDL-C levels result in significant adverse health effects based on these sources of information, though this conclusion is based on a relatively low number of patients with very low LDL-C who have been studied.

Based on the results of the two dose finding studies, the Q2W dosing regimen best maintained constant LDL-C lowering throughout the interdosing interval, with the maximum efficacy at 12 weeks provided by the 150 mg Q2W dosing. However, for many patients, the magnitude of effect observed with the 150 mg Q2W dose may not be needed to achieve the target LDL-C goal, and starting with a lower dose may be undertaken. Using a dose response model, 75 mg Q2W has been selected: all patients will be initially treated with 75 mg Q2W, and only those patients whose LDL-C levels remain equal to or higher than 70 mg/dL after 8 weeks of treatment will be dose up-titrated to 150 mg Q2W (at week 12). With this treatment scheme, most patients with primary hypercholesterolemia can be expected to achieve their target LDL-C level, with few patients reaching a level below 25 mg/dL.

Rationale for protocol design:

The objective of the present study is to demonstrate the superiority of alirocumab versus ezetimibe in Asia in patients at high cardiovascular risk and who require additional pharmacological management since their current maximally tolerated statin therapy failed to achieve the LDL-C treatment goal.

The target population in this study is patients at high cardiovascular risk. The definition of high cardiovascular risk is based on existing guidelines (6, 16). In the context of a clinical trial, this definition has been focused on objective parameters whenever possible, when guidelines definition mentioned conditions that could encompass various levels of severity, such as peripheral arterial disease (PAD). Patients with type 2 diabetes without a history of CAD or CVD are considered high risk per guidelines, but have a risk for a CV event that is deemed less than patients who have had a previous CHD event (34, 35, 36). Thus, stringent criteria, based on consultation with the steering committee in ODYSSEY trials, have also been added for diabetes. Randomization of patients with DM and 2 or more additional risk factors but without CHD, PAD, or stroke will be limited to 25% of the overall randomized population.

The control arm that has been selected for this study is ezetimibe 10 mg by mouth (PO) daily. This will allow for a study comparing the addition of alirocumab to a maximal tolerated dose of statin against a treatment option (ie, ezetimibe) which is available in routine clinical practice (37). Ezetimibe has been recommended as a possible agent that may be used in combination with statin, when LDL-C target levels have not been reached (6, 38).

The sample size of 600 patients with treatment duration for 24 weeks is intended to provide efficacy and safety experience in Asia patient populations that will ultimately derive potential benefit from the drug.

A treatment difference of 20% on LDL-C reduction with alirocumab versus ezetimibe could be expected at 24 weeks of treatment. This is based on a treatment effect of about 25% to 30% on LDL-C reduction with ezetimibe 10 mg when added to ongoing statin therapy (39, 40, 41, 42,43) and a treatment effect of about 50% on LDL-C reduction with alirocumab 75 mg Q2W expected, based on simulations from the efficacy profile observed in the phase 2 studies.

Preliminary pharmacokinetic (PK) data from Phase 2 studies DFI11565, DFI11566 and R727-CL-1003, showed that exposure to alirocumab declined during the 8-week follow-up period that followed the double-blind treatment period (DBTP), with serum total concentrations of alirocumab still detectable, but at very low levels. Therefore to ensure sufficient low, non-effective serum alirocumab concentrations, patients will continue to be followed during a follow-up period of 8 weeks (ie, 10 weeks after last dosing).

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 patients with non-FH or with heterozygous FH. The efficacy on LDL-C was associated with consistent results in TC, Apo B, non-HDL-C and Apo B/Apo A-1 ratio and a positive trend for HDL-C, TG and Lp(a). There was no evidence that alirocumab adversely affects other CV risk factors, eg, body weight, blood pressure (BP), glucose, or C-reactive protein.

Important identified or potential risks with alirocumab are local injection site reactions, immunogenicity and hypersensitivity reactions. Local injection site reactions were reported in both alirocumab and placebo treatment groups. Patients are monitored for these AEs in the Phase 3 program. A substantial number of patients reached low LDL-C levels (<25 mg/dl [0.65 mmol/L]) with no safety signal identified to date. However, further monitoring for potential AEs associated with low LDL-C levels will be implemented. Although no particular signal related to creatinine phosphokinase (CPK) elevation and associated AEs (eg, myalgia, rhabdomyolysis) was detected with the coadministration of alirocumab and statins over a maximum duration of 12 weeks, monitoring for such AEs will continue for all the Phase 3 studies. An independent Data Monitoring Committee (DMC) will meet periodically to review unblinded safety data for all Phase 3 studies, including this study.

This specific study is undertaken to demonstrate in Asia in hypercholesterolemic patients with established CHD or a CHD risk equivalent and who are not at their LDL-C goal that alirocumab 75 mg Q2W or 75 mg Q2W/150 mg Q2W as add-on therapy to statin causes a statistically significant and clinically meaningful reduction in LDL-C. This population that is not at LDL-C goal on optimized statin therapy represents a highest risk group with a well identified medical need that may be addressed by adding alirocumab to their statin therapy, in comparison to current treatment option, ie, adding ezetimibe.

5 STUDY OBJECTIVES

5.1 PRIMARY

To demonstrate the reduction of LDL-C by alirocumab as add-on therapy to stable maximally tolerated daily statin therapy in comparison with ezetimibe 10 mg daily after 24 weeks of treatment in Asia in patients with hypercholesterolemia at high CV risk.

5.2 SECONDARY

The secondary objectives are:

- To evaluate the effect of alirocumab 75 mg in comparison with ezetimibe 10 mg on LDL-C after 12 weeks of treatment
- To evaluate the effect of alirocumab on other lipid parameters: eg, Apo B, non-HDL-C, TC, Lp(a), HDL-C, TG, Apo A-1
- To evaluate the safety and tolerability of alirocumab
- To evaluate the development of anti-alirocumab antibodies
- To evaluate the PK of alirocumab

6 STUDY DESIGN

This is a randomized, double-blind, double-dummy, active-controlled, unbalanced (2:1, alirocumab:ezetimibe), parallel-group, multi-national, multi-center study to evaluate the efficacy and safety of alirocumab versus ezetimibe in high CV risk in Asia in patients with hypercholesterolemia not adequately controlled with their statin therapy. Not adequately controlled is defined as an LDL-C ≥70 mg/dL (1.81 mmol/L) at the screening visit (Week -3) in patients with a history of documented CVD OR LDL-C ≥100 mg/dL (2.59 mmol/L) at the screening visit (Week -3) in patients without a history of documented CVD. Randomization will be stratified according to prior history of myocardial infarction (MI) or ischemic stroke [Yes/No], and high-intensity statin treatment (Yes defined as atorvastatin 40 to 80 mg daily or rosuvastatin 20 to 40 mg daily, No for simvastatin whatever the dose daily, atorvastatin below 40 mg daily or rosuvastatin below 20 mg daily) and Country. After randomization, patients will receive double-blind, double-dummy study treatment (either alirocumab or ezetimibe) over a period of 24 weeks on top of stable maximally tolerated daily statin therapy. A dose up-titration of alirocumab from 75 mg to 150 mg depending on Week 8 LDL-C levels may occur at Week 12 for patients randomized to alirocumab. Patients will be followed for 8 weeks after the last visit of the DBTP.

6.1 DESCRIPTION OF THE PROTOCOL

The study consists of 3 periods: screening, double-blind treatment, and follow up.

- Screening period – up to 3 weeks in duration including an intermediate visit during which the patient (or another designated person such as spouse, relative, etc) will be trained to self-inject/inject with placebo for alirocumab. Eligibility assessments will be performed to permit the randomization of the patients into the study. Investigators will have the option for providing a second training kit of placebo for alirocumab for patients who require additional self-injection training prior to randomization visit, eg, the patient or investigator may elect to have patient inject at home or at study site.
- Double-blind treatment period – A randomized, double-blind study treatment period of 24 weeks. The first injection during the double-blind period will be done at the site on the day of randomization (Week 0 [D1] -V3) and as soon as possible after the contact with interactive voice response system (IVRS)/ interactive web response system (IWRS) for randomization into the study. The subsequent injections will be done by the patient (self-injection) or another designated person (such as spouse, relative, etc) at a patient-preferred location (eg, home, study site).

Patients randomized to alirocumab will receive a dose of 75 mg of the investigational medicinal product (IMP) from randomization (V3) up to Week 12 (V6) (ie, Weeks 0, 2, 4, 6, 8, and 10) + placebo for ezetimibe PO daily.

At the Week 12 visit (V6) these patients will, in a blinded manner, either:

- Continue alirocumab 75 mg Q2W from Week 12 onwards until the last injection at Week 22 + Placebo for ezetimibe PO daily, if the Week 8 LDL-C is <70 mg/dL (1.81 mmol/L)

OR

- Dose up-titrate to alirocumab 150 mg Q2W from Week 12 onwards until the last injection at Week 22), + Placebo for ezetimibe PO daily if the Week 8 LDL-C is ≥70 mg/dL (1.81 mmol/L).

NOTE: Lipid values obtained at Week 8 for the purpose of up-titration will not be communicated to investigators to maintain the blind. The continuation of the 75 mg dose or dose up-titration to the 150 mg dose will occur automatically through IVRS/IWRS process without site or patient awareness.

Patients randomized to ezetimibe will receive placebo for alirocumab SC Q2W until the last injection at Week 22 + ezetemibe 10 mg PO daily from randomization (V3) up to Week 24 (V8).

- Follow-up period – A period of 8 weeks after the end of the DBTP.

The laboratory measurement of lipid parameters will be performed by a central laboratory (central lab) during the study. Local laboratory testing for lipid parameters is prohibited after randomization of the patient, except for the safety of the patient as per investigator's judgment. The specific results of the central lab testing for lipid parameters from samples obtained after randomization will not be communicated to the sites. However, under some circumstances, the central lab will inform sites of TG alert (see Section 10.6.4).

Statin should be stable (including dose) throughout the whole study duration from screening to the follow-up visit barring exceptional circumstances whereby overriding concerns (including but not limited to TG alert posted by the central lab) warrant such changes, as per the investigator's judgment.

Fibrates, other than fenofibrate, are not allowed during the study.

Patients should be on a stable diet (NCEP-ATP III therapeutic lifestyle changes [TLC] diet or equivalent – see Appendix A) throughout the entire study duration from screening. The dietician or site staff with appropriate training will review the patient's diet at the screening visit and periodically throughout the study.

Patients with prespecified CV events (see Section 10.6.3) from randomization until the final follow up visit should have an adjudication package prepared and sent to the independent Cardiovascular Events Adjudication Committee (CEC).

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

At least 110 patients in total from pre-selected sites who consented for PK sampling will have PK analysis during the study, in order to have 60 paitents on alirocumab treatment (at least 30 Chinese and 24 Indian patients).

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

The study duration includes a screening period of up to 3 weeks, a 24-week DBTP for efficacy and safety assessment and an 8-week post-treatment follow-up period for all patients after the last visit of the DBTP.

Thus, the study duration per patient is about 35 weeks (up to 3 weeks screening + 24 weeks double-blind treatment + 8 weeks follow-up).

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

Patients who have a titer at or above 240 for anti-alirocumab antibody at follow up visit will have additional antibody sample(s), at 6 to 12 months after the last dose and thereafter, about every 3 to 6 months until titer returns below 240.

The end of the study per patient is the last protocol planned visit, or the resolution/stabilization of all SAEs, and AESI, or the resolution of anti-alirocumab (titer below 240), whichever comes last.

6.2.2 Determination of end of clinical trial (all patients)

The end of the study is defined as being the last patient last on site visit as scheduled by protocol.

6.3 STUDY COMMITTEES

Data Monitoring Committee:

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

Cardiovascular Events Adjudication Committee:

The CEC is composed of experts in the field of cardiovascular diseases, independent from the Sponsor and the Investigators. This committee will be responsible for defining, validating and classifying, in a blinded fashion, pre-specified cardiovascular events and all deaths. Classification of events will be as follows: CHD death, non-fatal MI, fatal and non-fatal ischemic stroke, unstable angina requiring hospitalization, congestive heart failure requiring hospitalization, and ischemia-driven coronary revascularization procedure (percutaneous coronary intervention [PCI], coronary artery bypass graft surgery [CABG]). In addition, the classification of the cause of all deaths will occur. A charter and an adjudication operational manual will specify the procedures, criteria, and classification used for adjudication of these events.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

I 01. Patients with hypercholesterolemia and established CHD or CHD risk equivalents (see below for definitions) who are not adequately controlled with a maximally tolerated daily dose of statin* at a stable dose for at least 4 weeks prior to the screening visit (Week -3)

*Definition of maximally tolerated dose (any of the following are acceptable):

- Atorvastatin 40 mg to 80 mg daily
- Rosuvastatin 20 mg to 40 mg daily
- Simvastatin 40 mg daily
- Patients not able to be on any of the above statin doses, should be treated with the dose of daily atorvastatin, rosuvastatin or simvastatin which is considered appropriate for the patient as per the investigator's judgment or concerns. Some examples of acceptable reasons for a patient taking a lower statin dose include, but are not limited to: adverse effects on higher doses, advanced age, low body mass index (BMI), local prescribing information, concomitant medications, comorbid conditions such as impaired glucose tolerance/impaired fasting glucose. The reason(s) will need to be documented in the case report form.

A) Documented history of CHD (includes one or more of the following):

- Acute MI
- Silent MI
- Unstable angina
- Coronary revascularization procedure (eg, PCI, CABG)
- Clinically significant CHD diagnosed by invasive or non-invasive testing (such as coronary angiography, stress test using treadmill, stress echocardiography or nuclear imaging)

B) CHD risk equivalents (includes one or more of the following 4 criteria):

i) Documented peripheral arterial disease (PAD) (one of the following criteria [a, b, or c] must be satisfied):

(a) Current intermittent claudication (muscle discomfort in the lower limb produced by exercise that is both reproducible and relieved by rest within 10 minutes) of presumed atherosclerotic origin TOGETHER WITH ankle-brachial index equal to or less than 0.90 in either leg at rest OR

(b) History of intermittent claudication (muscle discomfort in the lower limb produced by exercise that is both reproducible and relieved by rest within

10 minutes) TOGETHER WITH endovascular procedure or surgical intervention in one or both legs because of atherosclerotic disease OR

(c) History of critical limb ischemia TOGETHER WITH thrombolysis, endovascular procedure or surgical intervention in one or both legs because of atherosclerotic disease

ii) Documented previous ischemic stroke with a focal ischemic neurological deficit that persisted more than 24 hours, considered as being of atherothrombotic origin. CT or MRI must have been performed to rule out primary hemorrhage and non-ischemic neurological disease.

iii) Documented chronic kidney disease (CKD) as defined by 30 ≤eGFR <60 mL/min/1.73 m^2 for 3 months or more, including the screening visit

iv) Known history of diabetes mellitus AND 2 or more additional risk factors (as listed below):

(a) History of hypertension (established on antihypertensive medication)

(b) Documented history of ankle-brachial index ≤0.90

(c) Documented history of microalbuminuria or macroalbuminuria (44) OR dipstick urinalysis at screening visit (Week -3) with >2 + protein

(d) Documented history of preproliferative or proliferative retinopathy or laser treatment for retinopathy

(e) Known family history of premature CHD (CHD in father or brother before 55 years of age; CHD in mother or sister before 65 years of age)

I 02. 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. Patients without established CHD or CHD risk equivalents

E 02. LDL-C <70 mg/dL (<1.81 mmol/L) at the screening visit (Week -3) in patients with an history of documented CV disease

E 03. LDL-C <100 mg/dL (<2.59 mmol/L) at the screening visit (Week -3) in patients without history of documented CV disease

NOTE – CVD is defined as CHD, ischemic stroke or PAD as described in Section 7.1

E 04. Change in statin dose or dose regimen from screening to randomization

E 05. Currently taking a statin that is not atorvastatin, rosuvastatin or simvastatin

E 06. Atorvastatin, rosuvastatin or simvastatin is not taken daily or not taken at a registered dose

E 07. Daily dose above atorvastatin 80 mg, rosuvastatin 40 mg or simvastatin 40 mg

E 08. Use of cholesterol absorption inhibitor (ie, ezetimibe), omega-3 fatty acid (at doses ≥1000 mg daily), nicotinic acid, fibrates, bile acid-binding sequestrant, or red yeast rice products within the past 4 weeks prior to screening visit (Week -3) or between screening and randomization visits

E 09. Use of nutraceutical products or over-the-counter therapies that may affect lipids which have not been at a stable dose/amount for at least 4 weeks prior to the screening visit (Week -3) or between screening and randomization visits

E 10. Patient who has received plasmapheresis treatment within 2 months prior to the screening visit (Week -3), or has plans to receive during the study.

E 11. History of a MI, unstable angina leading to hospitalization, CABG, PCI, uncontrolled cardiac arrhythmia, carotid surgery or stenting, stroke, transient ischemic attack, carotid revascularization, endovascular procedure or surgical intervention for peripheral vascular disease within 3 months prior to the screening visit (Week -3, V1)

E 12. Planned to undergo scheduled PCI, CABG, carotid or peripheral revascularization during the study

E 13. Systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg at screening visit or randomization visit

E 14. History of New York Heart Association (NYHA) Class III or IV heart failure within the past 12 months (Appendix B)

E 15. Known history of hemorrhagic stroke

E 16. Age <18 years or legal age of majority at the screening visit (Week -3) whichever is greater

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

E 18. Newly diagnosed (within 3 months prior to randomization visit [Week 0]) or poorly controlled ($HbA1_c$ >9% at the screening visit [Week -3]) diabetes

E 19. Presence of any clinically significant uncontrolled endocrine disease known to influence serum lipids or lipoproteins.

NOTE: Patients on thyroid replacement therapy can be included if the dosage has been stable for at least 12 weeks prior to screening and between screening and randomization visits, and thyroid stimulating hormone (TSH) level is within the normal range at the screening visit.

E 20. History of bariatric surgery within 12 months prior to the screening visit (Week -3)

E 21. Unstable weight defined by a variation >5 kg within 2 months prior to the screening visit (Week -3)

E 22. Known history of homozygous or heterozygous FH

E 23. Known history of loss of function of PCSK9 (ie, genetic mutation or sequence variation)

E 24. 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 (Week 0)

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

E 25. Use of continuous estrogen or testosterone 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 26. History 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 27. Known history of a positive HIV test

E 28. Patient who has taken any investigational drugs other than the alirocumab training placebo kits within 1 month or 5 half lives, whichever is longer

E 29. Patient who has been previously treated with at least one dose of alirocumab or any other anti-PCSK9 monoclonal antibody in other clinical trials

E 30. Patient who withdraws consent during the screening period (patient who is not willing to continue or fails to return)

E 31. Conditions/situations such as:

Any clinically significant abnormality identified at the time of screening that in the judgment of the Investigator or any Subinvestigator would preclude safe completion of the study or constrain endpoints assessment such as major systemic diseases, patients with short life expectancy.

Considered by the Investigator or any Subinvestigator as inappropriate for this study for any reason, eg:

- Deemed unable to meet specific protocol requirements, such as scheduled visits

- Deemed unable to administer or tolerate long-term injections as per the patient or the investigator
- Investigator or any Subinvestigator, pharmacist, study coordinator, other study staff or relative thereof directly involved in the conduct of the protocol, etc
- Presence of any other conditions (eg, geographic, social) actual or anticipated, that the Investigator feels would restrict or limit the patient's participation for the duration of the study

E 32. Laboratory findings during the screening period (not including randomization Week 0 labs):

- Positive test for Hepatitis B surface antigen or Hepatitis C antibody (confirmed by reflexive testing)
- Positive serum beta-hCG or urine pregnancy test (including Week 0) in women of childbearing potential
- Triglycerides >400 mg/dL (>4.52 mmol/L) (1 repeat lab is allowed)
- eGFR <30 mL/min/1.73 m^2
- ALT or AST >3 x ULN (1 repeat lab is allowed)
- CPK >3 x ULN (1 repeat lab is allowed)
- TSH <LLN or >ULN (1 repeat lab is allowed)

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

E 33. All contraindications to the ezetimibe or warning/precaution of use (when appropriate) as displayed in the respective National Product Labeling

E 34. All contraindications to the background statins 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 35. Known hypersensitivity to monoclonal antibody or any component of the drug products

E 36. Pregnant or breast-feeding women

E 37. Women of childbearing potential not protected by highly-effective method(s) of birth control and/or who are unwilling or unable to be tested for pregnancy

NOTE: Women of childbearing potential must have a confirmed negative pregnancy test at screening and randomization visits. They must use an effective contraceptive method throughout the entire duration of the study treatment, and for 10 weeks after the last intake of IMP (injection or capsule, whichever come last), and agree to repeat urine pregnancy test at designated visits. The applied methods of contraception have to meet the criteria for a highly effective method of

birth control according to the ‘Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals’ (45). 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/or 150 mg/mL both as 1 mL volume in an auto-injector.

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

Ezetimibe 10 mg tablets over-encapsulated.

Match placebo for over-encapsulated ezetimibe tablets.

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 auto-injector), contingency alternatives are:

- in case of disruption of the 150 mg auto-injector only, if the use of 75 mg auto-injectors is maintained, patients will need to administer 2 injections as follows:

- 2 injections of 75 mg as 1 mL each in an auto-injector for patients receiving the 150 mg dose,
- 1 injection of 75 mg as 1 mL in an auto-injector plus 1 injection of placebo as 1 mL in an auto-injector for patients receiving the 75 mg dose,
- 2 placebo injections as 1 mL each in an auto-injector for patients receiving placebo.

OR

- in case of disruption of either 75 mg or 150 mg or both auto-injectors, 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 manual for alirocumab IMP administration (injection instruction manual) will be provided to patients containing detailed instructions on use. Also, an administration package containing gauze, alcohol swabs, Band-aids, etc will be provided to the patients.

The alirocumab IMP could be administered by self-injection or by another designated person (such as a spouse, relative, etc). The used auto-injector will be discarded in a sharps container which will be provided to patients. It is recommended that the IMP injections be rotated within an anatomical area (eg, right abdomen then left abdomen). If another concomitant drug is being

injected in the abdomen, then the patient should be advised to use a different part of the abdomen for administration of the IMP.

Patients will be asked to store the alirocumab IMP in a refrigerator (DO NOT FREEZE). 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.

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

8.1.2 Timing of administration

A training injection is planned on Week -1 (V2) with a placebo for alirocumab. A second training injection with placebo for alirocumab may be administered between Week -1 and randomization visit.

During the double-blind treatment period, alirocumab or placebo for alirocumab will be administered SC Q2W, starting at Week 0 continuing up to the last injection (Week 22) 2 weeks before the end of the DBTP. 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.

Further training with the scheduled double-blind alirocumab IMP can be done between W 0 and W 4 and at additional scheduled or unscheduled visits, as per investigator's judgment.

Double-blind IMP will start as soon as possible after the call for randomization using the treatment kit number provided by the IVRS/IWRS. The first injection after randomization 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 double-blind injection.

Alirocumab IMP injection should be administered Q2W SC 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 on patient's preference.

If by mistake or due to other circumstances an injection is delayed by more than 7 days or completely missed, then the patient should return to the original schedule of study treatment administration without administering delayed injections. On the other hand, if the delay is 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 study treatment administration.

Ezetimibe 10 mg or placebo for ezetimibe capsules will be taken orally once daily at approximately the same time of the day, with or without food. Preferably, on the injection days the IMP capsule will be administered roughly at the time of injection (either before or shortly after). The capsules must be taken until the day before the end-of-treatment visit (early or not), and not stopped at the time of the last injection.

8.2 NON-INVESTIGATIONAL MEDICINAL PRODUCT(S)

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

- Statins (atorvastatin, rosuvastatin, simvastatin)
- Fenofibrate

Please see Section 8.9 for further information.

8.3 BLINDING PROCEDURES

8.3.1 Methods of blinding

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

Ezetimibe and placebo for ezetimibe will be provided in identically matched caps and packaged identically which includes labeling to protect the blind.

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

In accordance with the double-blind design, 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 Section 8.3.2.

8.3.1.1 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 after randomization and until after the final database lock has occurred.

8.3.1.2 Anti-alirocumab antibodies

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

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

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

Patients who have a titer at or above 240 for anti-alirocumab antibody at follow-up visit will have additional antibody sample(s), at 6 to 12 months after the last dose and thereafter, about every 3 to 6 months until titer returns below 240.

In order to maintain the blind of the study, the requests for sample collection of post-study anti-alirocumab antibodies will also be made on patients with titers below 240 at the follow-up visit (sham request).

8.3.1.3 Pharmacokinetics measurements

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

8.3.1.4 Committees

The independent CEC will review and adjudicate their respective events in a blinded manner.

The DMC will receive blinded by treatment group or unblinded (if necessary) confidential reports from an independent statistician for review (Section 6.3).

8.3.2 Randomization code breaking during the study

In case of an adverse event, the code must be broken by the site only in exceptional circumstances when knowledge of the IMP is essential for treating the patient. If possible, a contact should be initiated with the Monitoring Team/Medical Monitor 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 centralized treatment allocation system and/or by calling any other phone number provided by the Sponsor for that purpose. However, it is preferable to contact the Medical Monitor 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 (or "relevant information as required by") on the appropriate page of the electronic-Case Record Form (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, AEs, SAEs), the study treatment should not be disclosed on the forms.

The code-breaking can also be performed by contacting the "24 hour alert system"; but this system should be used in very exceptional cases only (ie, unavailability of a centralized treatment allocation system or inability to contact Investigator and/or site staff). However, the preferred option is to unblind using a centralized treatment allocation system. The Investigators will be informed by the clinical monitoring team about the availability of the local code-breaking details (through an emergency centralized 24 hour telephone system for use with e-SMS). 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 that are both related and unexpected in order to conform to regulatory reporting requirements.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

Two randomized lists of treatment kit numbers will be generated centrally by Sanofi. The IMP (alirocumab 75 mg, 150 mg, or placebo for alirocumab kits and ezetimibe or placebo for ezetimibe kits) will be packaged in accordance with these 2 lists.

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 treatment kits to the patients.

Patients will be randomized to receive either alirocumab or ezetimibe during the double-blind study treatment period using a ratio 2:1, with permuted-block randomization. Randomization will be stratified according to prior history of MI or ischemic stroke [Yes/No], statin treatment (atorvastatin 40 to 80 mg daily or rosuvastatin 20 to 40 mg daily versus simvastatin whatever the dose daily, atorvastatin below 40 mg daily or rosuvastatin below 20 mg daily) and Country/region.

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).

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 patient will be considered as not randomized and withdrawn from the study.

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

8.5 DOSE UP-TITRATION

During the DBTP, patients randomized to alirocumab will receive a dose of 75 mg of the IMP from randomization (V3) up to Week 12 (V6) (ie, Weeks 0, 2, 4, 6, 8, and 10) + placebo for ezetimibe PO daily. At the Week 12 visit (V6) these patients will, in a blinded manner, either:

- Continue alirocumab 75 mg Q2W from Week 12 onwards until the last injection at Week 22 + Placebo for ezetimibe PO daily, if the Week 8 LDL-C is <70 mg/dL (1.81 mmol/L)

OR

- Dose up-titrate to alirocumab 150 mg Q2W from Week 12 onwards until the last injection at Week 22), + Placebo for ezetimibe PO daily if the Week 8 LDL-C is ≥70 mg/dL (1.81 mmol/L).

NOTE: Lipid values obtained at Week 8 for the purpose of up-titration will not be communicated to investigators to maintain the blind. The continuation of the 75 mg dose or dose up-titration to the 150 mg dose will occur automatically through IVRS/IWRS process without site or patient awareness.

Patients randomized to ezetimibe will receive placebo for alirocumab SC Q2W until the last injection at Week 22 + ezetemibe 10 mg PO daily from randomization (V3) up to Week 24 (V8).

8.6 PACKAGING AND LABELING

Packaging is in accordance with the administration schedule.

For the DBTP, each double-blind alirocumab treatment kit, either alirocumab or placebo for alirocumab, will be supplied in kits of ready to use autoinjectors (see Section 8.1). Each kit will be prepared to contain 6 auto injectors in a mimic child-resistant package for a 12 week supply of alirocumab or placebo (ie, each autoinjector provides 2 weeks of treatment). The content of the labeling is in accordance with the local regulatory specifications and requirements.

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

In addition to the alirocumab double-blind treatment kits, a training kit containing 1 placebo for alirocumab auto injector will be prepared for the purpose of instructing patients on injection administration which is to be performed prior to randomization at the injection training visit (Week -1, V2). If deemed necessary, a second injection training with placebo for alirocumab can be performed before the randomization visit using an additional training kit.

The double-blind ezetimibe kits, either ezetimibe 10 mg or placebo for ezetimibe, will be prepared to contain 3 monthly child resistance wallets of 36 capsules in each.

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

8.7 STORAGE CONDITIONS AND SHELF LIFE

Alirocumab will be shipped to the sites at 2°C to 8°C on an as-needed basis.

At sites, the alirocumab IMP kits (alirocumab or placebo for alirocumab) will be stored in a refrigerator between +2°C and +8°C (36°- 46°F) by the site. The temperature of the site refrigerator should be checked daily and recorded on a log sheet. Based on ongoing real time and accelerated stability data, as well as research stability data, alirocumab is stable until the date specified on the labels.

The ezetimibe kits (ezetimibe 10 mg or placebo for ezetimibe) will be stored between +2°C and +30°C (36°- 86°F) by the site. The temperature of the site storage room should be checked weekly at least 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.

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

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

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

8.8 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 Clinical Trial Protocol 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.

8.8.1 Treatment accountability and compliance

IMP administration data will be recorded by the patients onto a patient's diary.

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 numbers and he/she will dispense the treatment kits to the patient.
- The accountability is to be performed at alirocumab IMP kit re-supply visits only (see Section 10.1.2). The used and unused IMP kit(s) should be brought back to such visits for accountability purposes. Sharps container will be supplied to each patient for used auto injectors. The patients should return it to the site for destruction purpose at the end of study participation.
- All ezetimibe kits are returned by the patient at the designated visit.
- The Investigator or designee will complete the corresponding treatment log form from patient's diary.
- The Investigator/study coordinator will enter data in the appropriate e-CRF pages, according to data recorded in the treatment log form.
- The monitor will check the data consistency between e-CRF pages, treatment log forms using patient's diary, and returned unused auto-injectors or capsules of a corresponding kit.

8.8.2 Return and/or destruction of treatments

It is Sanofi's responsibility to ensure the destruction of all used or unused alirocumab. All used and unused treatments kits will be retrieved by the Sponsor or destroyed on site, depending on local requirements.

A detailed treatment log of the returned and destroyed IMP will be established with the Investigator or designee and countersigned by the Investigator and the Monitoring Team.

The physician will not destroy the used or unused autoinjectors unless Sanofi provides written authorization.

8.9 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient concomitantly to the study (from screening visit until follow-up visit).

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

For background statins (and any additional LMT as per Section 8.9.1), sites must follow the national product label for the safety monitoring and management of patients.

Nutraceutical products or over-the-counter therapies that may affect lipids are allowed only if they have been used at a stable dose for at least 4 weeks prior to screening visit, during the screening period and maintained during the 24 weeks of the DBPT. 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.

8.9.1 Management of background lipid modifying therapy / Rescue therapy

Patients must have been on stable maximally tolerated daily registered doses of statins for at least 4 weeks before screening visit.

During the study, the patients should stay on these stable maximally tolerated registered daily doses of statins. Lipid profile values from samples obtained after randomization will be blinded. Nevertheless, sites will be made aware of TG alert, in order to make decisions on the patient's background LMT.

From the screening visit (Week -3) until Week 24 of the DBPT, the background LMT should not be changed. No dose adjustment, discontinuation or initiation of other statins should take place during this time, barring exceptional circumstances whereby overriding concerns (including but not limited to TG alert posted by the central lab) warrant such changes, as per the investigator's judgment.

For a TG alert (see Section 10.6.4) 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.

In summary, background statin therapy should not be modified from screening to the follow up visit. However, up to Week 24, if a confirmed TG alert is reached or if there is an overwhelming clinical concern (at the discretion of the investigator) then modification of the background LMT is allowed.

8.9.2 Contraception

Women of childbearing potential must take an effective contraceptive method throughout the study treatment and for 10 weeks after the last intake of IMP (injection or capsule, whichever comes last) (eg, Follow-up visit).

8.9.3 Prohibited concomitant medications

Forbidden concomitant medications from the initial screening visit until the randomization visit include the following:

- Statins other than atorvastatin, rosuvastatin and simvastatin
- Fibrates
- Cholesterol absorption inhibitor (ie, ezetimibe)
- Omega-3 fatty acid (at doses ≥1000 mg daily)
- Nicotinic acid
- Bile acid-binding sequestrant (such as cholestyramine, colestipol, colesevelam)
- Red yeast rice products

Forbidden concomitant medications after the randomization visit until the follow up period include the following:

- Statins other than atorvastatin, rosuvastatin and simvastatin
- Fibrates (except fenofibrate if patient meets the prespecified TG alert [TG ≥500 mg/dL (5.65 mmol/L)])
- Cholesterol absorption inhibitor (ie, ezetimibe)
- Omega-3 fatty acid (at doses ≥1000 mg daily)
- Bile acid-binding sequestrant (such as cholestyramine, colestipol, colesevelam)
- Red yeast rice products

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 EFFICACY ENDPOINTS

9.1.1 Primary efficacy endpoint

The primary efficacy endpoint is the percent change in calculated 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). Primary endpoint is defined as:
100 x (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 defined as the earliest between the first double-blind injection and the first capsule intake.

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) 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 Statistical Analysis Plan (SAP).

9.1.2 Secondary efficacy endpoints

9.1.2.1 Key secondary efficacy endpoints

- The percent change in calculated LDL-C from baseline to Week 24 in the mITT population, using all LDL-C values during the efficacy treatment period as defined in Section 11.3.1.2 (on-treatment estimand).
- The percent change in calculated LDL-C from baseline to Week 12 (ITT estimand).
- The percent change in calculated LDL-C from baseline to Week 12 (on-treatment estimand).
- The percent change in Apo B from baseline to Week 24 (ITT estimand).
- The percent change in Apo B from baseline to Week 24 (on-treatment estimand).
- The percent change in non-HDL-C from baseline to Week 24 (ITT estimand).
- The percent change in non-HDL-C from baseline to Week 24 (on-treatment estimand).
- The percent change in TC from baseline to Week 24 (ITT estimand).
- The percent change in Apo B from baseline to Week 12 (ITT estimand).

- The percent change in non-HDL-C from baseline to Week 12 (ITT estimand).
- The percent change in TC from baseline to Week 12 (ITT estimand).
- The proportion of patients reaching calculated LDL-C <70 mg/dL (1.81 mmol/L) at Week 24 (ITT estimand).
- The proportion of patients reaching calculated LDL-C <70 mg/dL (1.81 mmol/L) 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 fasting TG from baseline to Week 24 (ITT estimand).
- The percent change in Apo A-1 from baseline to Week 24 (ITT estimand).
- The percent change in Lp(a) from baseline to Week 12 (ITT estimand).
- The percent change in HDL-C from baseline to Week 12 (ITT estimand).
- The percent change in fasting TG from baseline to Week 12 (ITT estimand).
- The percent change in Apo A-1 from baseline to Week 12 (ITT estimand).

9.1.2.2 Other secondary efficacy endpoints

- The proportion of patients with calculated LDL-C <100 mg/dL (2.59 mmol/L) at Week 12 and Week 24 (ITT estimand)
- The proportion of patients reaching calculated LDL-C <70 mg/dL (1.81 mmol/L) at Week 12 (ITT estimand).
- The absolute change in calculated LDL-C (mg/dL and mmol/L) from baseline to Week 12 and Week 24 (ITT estimand).
- The absolute change in ratio Apo B/Apo A-1 from baseline to Week 12 and Week 24 (ITT estimand).
- The proportion of patients with Apo B <80 mg/dL (0.8 g/L) at Week 12 and Week 24 (ITT estimand).
- The proportion of patients with non-HDL-C <100 mg/dL (2.59 mmol/L) at Week 12 and Week 24 (ITT estimand).
- The proportion of patients with non-HDL-C <130 mg/dL (3.37 mmol/L) at Week 12 and Week 24 (ITT estimand).
- The proportion of patients with calculated LDL-C <70 mg/dL (1.81 mmol/L) and/or ≥50% reduction in calculated LDL-C (if calculated LDL-C ≥70 mg/dL [1.81 mmol/L]) at Week 12 and Week 24 (ITT estimand).
- The proportion of patients with ≥50% reduction in calculated LDL-C at Week 12 and Week 24 (ITT estimand).
- The absolute change in ratio TC/HDL-C from baseline to Week 12 and Week 24 (ITT estimand).

- The percent change in TC from baseline to Week 12 and 24 (on-treatment estimand)
- The percent change in Apo B from baseline to Week 12 (on-treatment estimand)
- The percent change in non-HDL-C from baseline to Week 12 (on-treatment estimand)
- The percent change in Lp(a) from baseline to Week 12 and 24 (on-treatment estimand)
- The proportion of patients reaching calculated LDL-C <100 mg/dL (2.59 mmol/L) at Week 24 (on-treatment estimand)

9.1.3 Efficacy assessment method

9.1.3.1 Lipid parameters

Total cholesterol, HDL-C, TG, Apo B, Apo A-1, and Lp(a) will be directly measured by the Central Laboratory as per the schedule in Section 1.2. LDL-C will be calculated using the Friedewald formula (17) at all visits (except Week -1 and Follow Up visit). 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. LDL-C will also be measured (via the beta quantification method) at Week 0 and Week 24.Non-HDL-C will be calculated by subtracting HDL-C from the TC. Apo B/Apo A-1 ratio will be calculated. Detailed procedures of sample preparation, storage and shipment will be described in the specific laboratory manual which will be provided to sites. Information on the processing, methodology and other relevant information will be available in the Reference Laboratory Manual.

Efficacy endpoints will not be considered as AEs, such as those involving abnormalities in lipid levels, unless meeting the criteria in Section 10.4.3.

9.2 SAFETY ENDPOINTS

Observation period

The observation of safety data will be as follows:

- PRE-TREATMENT period: The PRE-TREATMENT observation period is defined from the signed informed consent up to the first dose of double-blind IMP (injection or capsule, whichever comes first).
- TEAE period: The TEAE observation period is defined as the time from the first dose of double-blind IMP (injection or capsule, whichever comes first) to the last dose of double-blind 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: The POST-TREATMENT observation period is defined as the time starting the day after the end of the TEAE period up to the end of the study (see definition in Section 6.2.1).

9.2.1 Adverse event

All AEs diagnosed by the investigator, irrespective of the result of the adjudication for CV events, will be reported and described.

All AEs will be coded to a "lowest level term (LTT)", "preferred term (PT)", "high level term (HLT)", "high level group term (HLGT)" and associated primary "system organ class (SOC)" using the version of medical dictionary for regulatory activities (MedDRA) currently in effect at Sanofi at the time of the considered database lock.

AEs of clinical interest include the following:

- General allergic reactions (using special e-CRF pages, see Section 10.4.5.1, Section 10.4.5.2 and Section 10.6.2)
- Local injection site reactions (using special e-CRF pages) (please refer to Section 10.6.1)
- Hemolytic anemia (using special e-CRF pages, see Section 10.4.5.1)
- Neurological (including neurocognitive) AEs (using special e-CRF pages, see Section 10.4.5.1, and Section 10.4.5.2)
- Ophtalmologic AEs (using special e-CRF pages, see Section 10.4.5.1 and Section 10.4.5.2)

Adjudicated CV events include all CV AEs positively adjudicated (see Section 10.6.3). The adjudication categories are the following:

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

In addition, the classification of all deaths will occur.

Adverse event observation period

The AE observations are per the observation periods defined above.

Death observation period

The death observations are per the observation period defined above. In addition, "post-study" death includes all deaths reported after the end of the study (see definition of end of study period per patient in Section 6.2.1).

9.2.2 Safety laboratory

The clinical laboratory data consist of urinalysis, hematology (complete blood cell count [CBC] including red blood cell distribution width [RDW] and reticulocyte count, hematocrit, hemoglobin [Hb], red blood cell count, white blood cell count with differential blood count and platelet), standard chemistry (glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, uric acid, lactate dehydrogenase [LDH], total protein, albumin and gamma glutamyl transferase [γGT]). Hepatitis C antibody, liver panel (ALT, aspartate aminotransferase [AST], alkaline phosphatase [ALP], and total bilirubin), and CPK.

Some additional safety laboratory parameters may be reflexively measured, based on actual data (please refer to Section 10.4.5.1).

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

9.2.3 Vital signs measurement

Vital signs include: heart rate (HR), systolic and diastolic BP in sitting position.

9.3 OTHER ENDPOINTS

9.3.1 Anti-alirocumab antibody assessments

Anti-alirocumab antibodies include the antibody status (positive/negative) and antibody titers.

9.3.1.1 Sampling time

Serum samples for anti-alirocumab antibody determination will be drawn periodically throughout the study as per schedule noted in the study flowchart of Section 1.2. All scheduled samples will be obtained before IMP injection (pre-dose).

Patients who have a titer at or above 240 for anti-alirocumab antibody at follow-up visit will have additional antibody sample(s), at 6 to 12 months after the last dose and thereafter, about every 3 to 6 months until titer returns below 240.

In order to maintain the blind of the study, the requests for sample collection of post-study anti-alirocumab antibodies will be made on patients with titers below 240 at the follow-up visit. The sponsor will notify the sites.

9.3.1.2 Sampling procedure

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

9.3.1.3 Bioanalytical method

All anti-alirocumab antibody (anti-drug antibody [ADA]) samples will be analyzed by the Regeneron Clinical Bioanalysis group.

Anti-alirocumab antibody samples will be analyzed using a validated non-quantitative, titer-based bridging immunoassay. It involves an initial screen, a confirmation assay based on drug specificity, and a measurement of the titer of anti-alirocumab antibodies in the sample. [redacted]

Samples that are positive in the ADA assay will be assessed for neutralizing antibodies using a validated, non-quantitative, competitive ligand binding assay [redacted]

9.3.2 Glycated hemoglobin A1c

The absolute change in glycated hemoglobin A1c ($HbA1_{c)}$ (%) from baseline to Week 12 and Week 24.

9.3.3 Pharmacokinetic variables

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

At least 110 patients in total from pre-selected sites who consented for PK sampling will have PK analysis during the study, in order to have 60 paitents on alirocumab treatment (at least 30 Chinese and 24 Indian patients).

9.3.3.1 Sampling time

Serum samples for total alirocumab concentration will be collected before IMP (pre-dose), after randomization at Week 0 (randomization visit). Additional samples will be collected before IMP (pre-dose) at Week 4, Week 12, Week 16 and Week 24, as per the study flowchart (see Section 1.2).

To collect information on the absorption phase, an optional PK sample will be collected at 5 days (±2) after the Week 22 IMP injection or later.

Randomized patients who agree to have this additional PK sample will be required to provide additional consent prior to collection of the PK sample.

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

9.3.3.2 Sampling procedure

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

9.3.3.3 Bioanalytical method

All PK samples will be analyzed by the Regeneron Clinical Bioanalysis Group.

PK samples will be analyzed for the determination of total alirocumab concentrations (ie, free alirocumab and alirocumab present in PCSK9: alirocumab complexes) using a validated enzyme-linked immunosorbent assay (ELISA). [redacted]

PK samples can also be analyzed for the determination of the total and free PCSK9 levels using validated ELISA. [redacted]

9.3.4 Pharmacogenetic Samples

[redacted]

[redacted]

10 STUDY PROCEDURES

For all visits after Day 1/Week 0 (randomization visit), a timeframe of a certain number of days will be allowed. The window period for visits at Weeks 12 and 24 are ± 3 days, and for all other site visits it is ±7 days during the DBTP, and follow-up period. A window period of +3 days is allowed for the randomization visit (Day 1/Week 0) and ±7 days for the injection training visit during the screening period (Week -1).

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

Blood samplings:

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

NOTE: if 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 (see above conditions).

Laboratory tests:

The laboratory data are collected in accordance with the study schedule in Section 1.2:

- Hematology
- Chemistry
- Liver panel: in case of total bilirubin values above the normal range, differentiation into conjugated and non-conjugated bilirubin will occur automatically.
- CPK
- Hepatitis B surface antigen
- Hepatitis C antibody: positive tests will be confirmed with reflexive testing at the end of treatment only.
- Serum pregnancy test

Urine samplings:

- Urinalysis - will assess for pH, specific gravity, and for the presence of blood, protein, glucose, ketones, nitrates, leukocyte esterase, uro-bilinogen and bilirubin.
- Urine pregnancy test

NOTE:

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/SAE as applicable. Please also refer to Section 10.4.3.

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in Appendix C, Appendix D and Appendix E.

Other endpoints assessment methods

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

- Glycemic parameters (HbA1c) and serum glucose will be measured, periodically throughout the study as per the schedule in Section 1.2.

NOTE: in case of high HbA1c values at screening, the investigator is responsible for the optimization of the patient's treatment to achieve HbA1c targets as defined by local guidelines or the Standards of Medical Care in Diabetes-2012 by the American Diabetes Association (46,47).

PK samples

Serum samples for assessment of alirocumab concentration will be obtained periodically throughout the study as per schedule note in study flowchart of Section 1.2.

Library samples

Library (plasma and serum) samples should be collected, as permitted by local regulatory policies. They will be collected periodically throughout the study as per schedule noted in the study flowchart of Section 1.2. The first scheduled sample at randomization visit will be obtained before IMP injection (predose).

Library samples will be coded to maintain patient confidentiality and may be stored for up to 10 years for exploratory research that may include the study of PCSK9 levels, PCSK9 function, effect(s) of PCSK9 inhibition with a monoclonal antibody, lipoprotein sub-fractionation, and mechanisms of hyperlipidemia and CV disease (eg lipoprotein–associated phospholipase A2). If needed, samples may also be used to identify markers associated with toxicity. [redacted]

Detailed procedure of sample preparation, storage and shipment will be described in the specific laboratory manual which will be provided to sites. Library samples will be sent to a central laboratory (only for randomized patients) for long-term storage between –70°C to –85°C.

- Plasma samples: 8.5 mL blood volume to be collected as specified in the specific laboratory manual

- Serum samples: 2.5 mL blood volume to be collected as specified in the specific laboratory manual

Physical examination:

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

Blood pressure / heart rate:

Blood pressure 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 five 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.

NOTE: in case of high BP values at screening the investigator is responsible for the optimization of the patient's treatment to achieve BP targets as defined by local guidelines or the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (48).

Electrocardiogram:

The 12-lead electrocardiogram (ECG) should be performed after at least 10 minutes rest and in the supine position. The electrodes should be positioned at the same place as much as possible, for each ECG recording throughout the study. The ECG will be interpreted locally by the investigator. Any new and/or clinically significant changes in ECG parameters should be immediately rechecked for confirmation before making any decision for the concerned patient. Any clinically significant abnormality should be documented as an AE/SAE as applicable. Please also refer to Section 10.4.3. Each trace will be analyzed in comparison with the screening recorded trace. All ECG traces will be kept as source data.

Body weight and height

Body weight should be obtained with the patient wearing undergarments or very light clothing and no shoes, and with an empty bladder. The same scale should be used throughout the study.

The use of calibrated balance scales is recommended, if possible. Self-reported weights are not acceptable; patients must not read the scales themselves.

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

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 (and as short as possible, upon receipt of laboratory eligibility criteria) prior to randomization/Day 1 visit. The first screening visit (Week -3) can take place from 21 to 8 days before the randomization visit. If it is planned to have another designated person administer the injections to the patient during the study, then this person should be present at the injection training visit (Week -1).

10.1.1.1 Screening Visit (Visit1/Week -3 /Day -21 up to -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 study-related investigations
- Assess inclusion/exclusion criteria
- Obtain patient demography – age, gender, race, and ethnicity
- Obtain medical history (including menopausal status), surgical history, alcohol habits, and smoking habits
- Obtain family medical history including risk factors related to premature CHD (before 55 years of age in a male, 65 years in a female first degree relative), allergy and Type 2 diabetes
- Document prior medication history within the previous 12 weeks, especially for LMT (including statin) 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
- Get body weight and height measurements
- Take vital signs including HR and BP
- Contact IVRS/IWRS for notification of screening. Patient number will be allocated by the IVRS/IWRS. This patient number is composed of a 9-digit number containing the 3-digit country code, the 3-digit center code and the 3-digit patient chronological number (the 3-digit patient chronological number is 001 for the first patient screened in a center, 002 for the second patient screened in the same center)
- Collect AEs from this point onward:

All AEs and SAEs will be collected from the time of informed consent signature and throughout the study until the post study treatment follow up visit.

- Perform 12-lead ECG
- Urinalysis
- Obtain fasting blood sample for:

- Lipids: measure or calculation of TC, LDL-C, HDL-C, TG, non-HDL-C
- Hematology: CBC including RDW and reticulocyte count, hematocrit, Hb, red blood cell count, white blood cell count with differential blood count and platelet
- Chemistry: glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, uric acid, LDH, total protein, albumin and γGT
- HbA1c
- TSH
- Liver panel (ALT, AST, ALP, and total bilirubin)
- CPK
- Hepatitis B surface antigen and hepatitis C antibody tests
- Serum pregnancy test (women of child bearing potential [WOCBP] only).

NOTE: All patients will be qualified for randomization based on the laboratory results obtained at this visit.

- An appointment will be given for the next visit.
- If it is planned to have another designated person administer the injections to the patient during the study, then this person should also be present at the next visit (injection-training visit at Week -1)

10.1.1.2 Injection-training Visit at Screening (Visit 2/Week -1/Day -7 ± 7)

- Assess inclusion/exclusion criteria
- Collect AEs
- Record concomitant medication
- Take vital signs including HR and BP
- IVRS/IWRS contact for allocation of a batch number for training kit
- Record batch number allocated in e-CRF
- Injection training should be provided as outlined in Section 8.1
- The placebo for alirocumab should be administered by the patient or another designated person (such as spouse, relative, etc) at the study site under supervision of site staff with appropriate feedback
- If patient will undergo the second optional injection training with placebo for alirocumab, 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 batch number for a second training kit
  - Record the second batch number allocated in e-CRF
  - Dispense the second placebo training injection to the patient for self-administration

- An appointment will be given for the next visit
- Remind patient to be in fasting conditions (ie, overnight, at least 10 to12 hours fast and refrain from smoking) for next visit. Also, alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the next visit are discouraged

10.1.2 Double-Blind Double-Dummy Treatment Period (Study Site Visits)

10.1.2.1 Randomization Visit (Visit 3/Week 0/Day 1 + 3)

- Assess Inclusion/Exclusion Criteria
- Collect AEs
- Record concomitant medication
- Review patient's diet. Patient should be on a NCEP ATP III TLC diet or equivalent.
- Perform physical examination
- Get body weight measurement
- Take vital signs including HR and BP
- [redacted]
  - [redacted]
- Present ICF for the optional PK (for a subset of patients), and if patient agrees to participate then obtain written consent.
  - If patient declines participation in the PK then this has no consequences for participation in the study otherwise.
- Urinalysis
- Urine pregnancy test (WOCBP only).
- Obtain fasting blood sample for:
  - Lipids: measure and/or calculation of TC, LDL-C, HDL-C, TG, non-HDL-C, Apo B, Apo A-1, Apo B/Apo A-1 ratio and Lp(a)
  - Library samples
  - Hematology: CBC including RDW and reticulocyte count, hematocrit, Hb, red blood cell count, white blood cell count with differential blood count and platelet
  - Chemistry: glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, uric acid, LDH, total protein, albumin and γGT
  - Liver panel (ALT, AST, ALP, and total bilirubin)
  - CPK

- Anti-alirocumab antibodies (to be performed prior to the IMP injection, after randomization)
- Serum alirocumab concentration (PK), for specifically consented patients only (to be performed prior to the IMP injection, after randomization)
- [redacted]

- If the patient is confirmed eligible (and in fasting conditions), the Investigator will start the next study procedures:
  - IVRS/IWRS contact for randomization and allocation of two 7-digit treatment kit numbers according to the randomization list, for the alirocumab injections and the ezetimibe capsules. Investigators should never allocate a treatment kit number to a patient without contacting IVRS/IWRS.
- Double-blind IMP kits dispensation as per treatment kit numbers provided by IVRS/IWRS along with schedule reminder. The patient injection instruction manual and treatment administration package should be provided. The patient diary should be given and instructions on its completion should be reviewed.
- The first double-blind IMP injection and the first ezetimibe capsule administration will take place at the study site, but only after the collection of the fasting blood samples and after the assessment of all evaluations planned at that visit. 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.
- Reminders
  - An appointment will be given for the next study site visit.
  - Remind patient to be in fasting conditions (ie, overnight, at least 10 to 12 hours fast and refrain from smoking) for next study site visit. Also, alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the next study site visit are discouraged.
  - Patient to bring the diary, at the next study site visit.
  - Patient to bring used and unused kits at the next study site visit

10.1.2.2 Visit 4/ Week 4, Visit 5/ Week 8 and Visit 7/Week 16 (Day 29, 57 and 113 ± 7)

- Collect AEs
- Record concomitant medication
- Take vital signs including HR and BP
- Data collection on IMP administration and IMP compliance check by review of diary and treatment kit
- Obtain fasting blood sample for:
  - Lipids: measure or calculation of TC, LDL-C, HDL-C, TG, non-HDL-C
    NOTE – For Week 8 visit, please ensure that unscheduled fasting blood sample through the Central Lab for the lipid parameters are obtained if the lipid lab parameters

are not done as per schedule or the lipid labs were drawn but an issue is later discovered with the samples which require retesting.

- Liver panel (ALT, AST, ALP, and total bilirubin)
- Anti-alirocumab antibodies (Visit 4/Week 4 only) (to be performed prior to the IMP injection)
- Library sample (Visit 4/Week 4 only)
- Serum alirocumab concentration (Visit 4/Week 4 and Visit 7/Week 16 only), for specifically consented patients only

- Reminders
  - An appointment will be given for the next study site visit.
  - Remind patient to be in fasting conditions (ie, overnight, at least 10 to 12 hours fast and refrain from smoking) for next study site visit. Also, alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the next study site visit are discouraged.
  - Patient to bring the diary at the next study site visit.
  - Patient to bring used and unused kits at the next study site visit

10.1.2.3 Visit 6/Week 12 (Day 85 ± 3):

- Collect AEs
- Record concomitant medication
- Get body weight measurement
- Take vital signs including HR and BP
- Review patient's diet. Patient should be on a NCEP-ATPIII TLC diet or equivalent
- Urinalysis
- Urine pregnancy test (WOCBP only).
- Obtain fasting blood sample for:
  - Lipids: measure and/or calculation of TC, LDL-C, HDL-C, TG, non-HDL-C, Apo B, Apo A-1, Apo B/Apo A-1 ratio and Lp(a)
  - Library samples
  - Serum alirocumab concentration (PK), for specifically consented patients only
  - Hematology: : CBC including RDW and reticulocyte count, hematocrit, Hb, red blood cell count, white blood cell count with differential blood count and platelet
  - Chemistry: glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, uric acid, LDH, total protein, albumin and γGT
  - HbA1c
  - Liver panel (ALT, AST, ALP, and total bilirubin)

- CPK
- Anti-alirocumab antibodies (to be performed prior to the IMP injection)

- Data collection on IMP administration and IMP compliance check by review of diary and treatment kit accountability.
- IVRS/IWRS contact to get treatment kit number for two kits resupply, for the alirocumab injections and the ezetimibe capsules.
- Double-blind IMP kits dispensation as per treatment kit numbers provided by IVRS/IWRS along with schedule reminder and the treatment administration package should be provided. The patient injection instruction manual and diary may be given, as needed.
- Reminders
  - An appointment will be given for the next study site visit.
  - Remind patient to be in fasting conditions (ie, overnight, at least 10 to 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.
  - Patient to bring the diary at the next study site visit.
  - Patient to bring used and unused kits at the next study site visit

10.1.2.4 Unscheduled PK visit / 5 days (± 2) after Week 22 IMP injection or after (optional)

- Obtain fasting blood sample 5 days (±2 days) after the IMP injection for:
  - Serum alirocumab concentration (PK)

10.1.2.5 Visit 8/Week 24 (Day 169 ± 3): End of treatment visit

- Collect AEs
- Record concomitant medication
- Get body weight measurement
- Take vital signs including HR and BP
- Review patient's diet. Patient should be on a NECP-ATP III TLC diet or equivalent
- Perform 12-lead ECG
- Perform physical examination
- IVRS/IWRS contact to document the end of treatment
- Data collection on IMP administration and IMP compliance check by review of diary and treatment kit accountability.
- Urinalysis
- Urine pregnancy test (WOCBP only).

- Obtain fasting blood sample for:
  - Anti-alirocumab antibodies (to be performed prior to the IMP injection).
  - Lipids: measure and/or calculation of TC, LDL-C, HDL-C, TG, non-HDL-C, Apo B, Apo A-1, Apo B/Apo A-1 ratio and Lp(a)
  - Library samples
  - Hematology: CBC including RDW and reticulocyte count, hematocrit, Hb, red blood cell count, white blood cell count with differential blood count and platelet
  - Chemistry: glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, uric acid, LDH, total protein, albumin and γGT
  - Hepatitis C Antibody Test (with automatic confirmatory testing if positive)
  - HbA1c
  - Liver panel (ALT, AST, ALP, and total bilirubin)
  - CPK
  - Serum alirocumab concentration (PK)
- Reminders
  - 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, if needed. Also, alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the next study site visit are discouraged.
  - Sharp-container (containing all used auto-injectors) must be returned at site for destruction.

10.1.3 Follow-Up Period

10.1.3.1 Follow-Up Visit (Visit 9/ Week 32/ Day 225 ± 7)

- Collect AEs
- Record concomitant medication
- Get body weight measurement
- Take vital signs including HR and BP.
- Perform physical examination (only in case of clinically relevant abnormality at the end of treatment visit)
- IVRS/IWRS contact to document the end of study
- Urinalysis (only in case of clinically relevant abnormal value at the end of treatment visit)
- Urine pregnancy test (WOCBP only)
- Obtain fasting blood sample for:

- Anti-alirocumab antibodies (as per schedule note in study flowchart of Section 1.2)
- Only in case of clinically relevant abnormal values for these parameters at the end of treatment visit will the following be obtained at this visit:

a) Hematology: CBC including RDW and reticulocyte count, hematocrit, Hb, red blood cell count, white blood cell count with differential blood count and platelet

b) Chemistry: glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, uric acid, LDH, total protein, albumin and γGT

c) HbA1c

d) Liver panel (ALT, AST, ALP, and total bilirubin)

e) CPK

10.2 DEFINITION OF SOURCE DATA

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

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

Source documentation may be found in the following:

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

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 if the stop can be made temporarily; permanent IMP discontinuation should be a last resort. Any IMP discontinuation should be fully documented in the e-CRF and source notes. In any case, the patient should remain in the study as long as possible.

Pregnancy will lead to definitive treatment discontinuation in all cases.

10.3.1 Temporary treatment discontinuation with investigational medicinal product(s)

Temporary treatment discontinuation (also referred to as treatment interruption) may be considered by the Investigator because of suspected AEs. Reinitiating 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 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).

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

Treatment interruption is defined as one or more scheduled injections or one or more capsules 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 (also referred to as treatment discontinuation) is any treatment discontinuation associated with the definitive decision from the Investigator or the patient not to re-expose the 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 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 e-CRF.

Patients should discontinue the 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.
- Serious adverse event (or non-serious but severe in intensity) of hypersensitivity reaction considered related to IMP.
- At patient request "i.e., withdrawal of the consent for treatment"
- If, in the investigator's opinion, continuation with the administration of the IMP would be detrimental to the patient's well-being.
- Intercurrent condition that requires discontinuation of the IMP (eg, laboratory abnormalities, please refer to decision tree Appendix D.
- At the specific request of the Sponsor.
- Any code breaking requested by the Investigator.
- Patient receives double-blind treatment prior to randomization

10.3.4 Handling of patients after permanent treatment discontinuation

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 end of treatment visit (this should take place within 5 days of treatment discontinuation, if possible) and then resume the original study schedule until end of study (ie, follow up visit). In particular, in case of early treatment discontinuation before week 24, all efforts should be done to perform the week 12 and week 24 visits.

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

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

For patients randomized and not treated, all efforts should be made to perform the Week 12 and Week 24 visits in order to collect the laboratory data and at the least, the lipid parameters.

10.3.5 Procedure and consequence for patient withdrawal from study

The patients may withdraw from the study, before study completion if they decide to do so, at any time and irrespective of the reason. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-patient contact follow-up, eg, medical records check. Patients requesting withdrawal should be informed that withdrawal of consent for follow-up may jeopardize the public health value of the study. If possible, the patients should be assessed using the procedures defined above. All study withdrawals should be recorded by the Investigator in the appropriate screens of the e-CRF and in the patient's medical records (with, in this medical records, at least date of withdrawal and reason for) when considered as confirmed.

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

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

The SAP will specify how these patients lost to follow-up for their primary endpoints will be considered.

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

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

Please refer to Appendix C for AE reporting requirements.

10.4.1.1 Adverse event

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

10.4.1.2 Serious adverse event

A **Serious Adverse Event** 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 intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

NOTE: The following medically important events intend to serve as a guideline for determining which condition has to be considered as a medically important event. It 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…),
  - convulsions (seizures, epilepsy, epileptic fit, absence…)
- Development of drug dependency or drug abuse,
- ALT >3 ULN + total bilirubin >2 ULN or asymptomatic ALT increase >10 ULN,
- Suicide attempt or any event suggestive of suicidality,
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling),
- Bullous cutaneous eruptions,
- Cancers diagnosed during the study or aggravated during the study,
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study.

10.4.2 Adverse event of special interest

Adverse event of special interest are AEs (serious or non-serious) that need to be monitored, documented, and managed in a pre-specified manner described in the protocol. Please see Section 10.4.5 and Appendix C for additional information.

10.4.3 General guidelines for reporting adverse events

All AEs regardless of seriousness or relationship to IMP, spanning from the signature of the ICF, until the end of the study (post-study treatment follow up visit), are to be recorded on the corresponding screen(s) included in the e-CRF.

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

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

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

See Appendix C for a summary of AE reporting guidelines.

10.4.4 Instructions for reporting serious adverse events

In the case of occurrence of a 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 the notification to the Monitoring Team and Pharmacovigilance after approval of the Investigator within the e-CRF or after a standard delay.
- SEND (preferably by fax or e-mail) the 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 source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the e-CRF as appropriate, and further documentation as well as additional information (for Lab data, concomitant Medication, patient status ..) should be sent (by fax or e-mail) to the Monitoring Team within 24 hours of knowledge. In addition, any effort should be made to further document each Serious AE that is fatal or life threatening within the week (7 days) following initial notification.
- A back-up plan will be used (using paper flow) when the e-CRF system does not work.

10.4.5 Guidelines for reporting adverse events of special interest

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

For these AEs, the Sponsor will 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.

- ALT ≥3 ULN (if baseline ALT <ULN) Or ALT ≥2 times the baseline value (if baseline ALT ≥ULN) (Please refer to related flowchart in Appendix D.
- Allergic events
  - General allergic drug reactions and/or local injection site reactions deemed to be allergic (or have an allergic component) that require consultation with another physician for further evaluation of hypersensitivity/allergy, as per the investigator's medical judgment or as per Section 10.6.2, should be reported as an AESI with immediate notification. These reactions require completion of the specific e-CRF screen (see Section 10.6.2)
  - General allergic events, and all injection site reactions require completion of the specific e-CRF screen (see Section 10.6.2), regardless of requirements for immediate reporting.
- Hemolytic anemia (See Section 10.4.6.1 and Appendix E)
  - If there is a decrease in Hb and reflexive testing as per Appendix E suggesting hemolysis, then report this as an AESI with immediate notification. Special e-CRF screen will need to be completed.
- Pregnancy
  - Pregnancy occurring in a female patient enrolled in the clinical trial will be recorded as a pre-specified AE with immediate notification and IMP should be discontinued in all cases. It will be qualified as an SAE only if it fulfills the SAE criteria. The follow-up of the pregnancy will be mandatory until the outcome has been determined.
  - Pregnancy occurring in a female partner of a male patient enrolled in the clinical trial, if permitted by the female partner and by local regulatory policies, pregnancy will be recorded as a pre-specified AE with immediate notification. The pregnancy will be qualified as an SAE only if it fulfills the SAE criteria and should be followed-up until the outcome has been determined.
- Symptomatic Overdose with IMP
  - Alirocumab or placebo for alirocumab:

  f) 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 the intended dose within the intended therapeutic interval (ie, 2 or more injections from the double-blind treatment kit are administered in <7 calendar days); to be reported using the corresponding screens in the e-CRF using

the Term 'Symptomatic OVERDOSE (accidental [or intentional])'. The patient should be monitored and appropriate symptomatic treatment instituted.

g) The circumstances of the overdose should be clearly specified in the verbatim.

- Ezetimibe or placebo for ezetimibe:

a) An overdose (accidental or intentional) is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic capsule counts) and defined as at least twice the intended dose within the intended therapeutic interval (ie, 2 or more capsules from the double-blind treatment kit are administered within one calendar day); to be reported using the corresponding screens in the e-CRF using the Term 'Symptomatic OVERDOSE (accidental [or intentional])'. The patient should be monitored and appropriate symptomatic treatment instituted.

- Neurological (including neurocognitive) Events
  - Neurological (including neurocognitive) Events that require additional examinations/procedures and/or referral to a specialist should be reported as an AESI with immediate notification.
- Ophthalmologic Events
  - Ophthalmologic Events that require additional examinations/procedures and/or referral to a specialist should be reported as an AESI with immediate notification.

10.4.5.2 Reporting of adverse events of special interest (AESI) without immediate notification

See Appendix C.

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

- Asymptomatic overdose with IMP
  - Alirocumab or placebo for alirocumab:

    An overdose (accidental or intentional) is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic injection counts) and defined as at least twice the intended dose within the intended therapeutic interval (ie, 2 or more injections from the double-blind treatment kit are administered in <7 calendar days); to be reported using the corresponding screens in the e-CRF using the Term 'Asymptomatic OVERDOSE (accidental [or intentional])'. The patient should be monitored for any AEs and treated, as needed.
  - Ezetimibe or placebo for ezetimibe:

    An overdose (accidental or intentional) is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic capsule counts) and defined as at least twice the intended dose within the intended therapeutic interval (ie, 2 or more capsules from the double-blind treatment kit are administered within one calendar day); to be reported using the corresponding screens in the e-CRF using the

Term 'Asymptomatic OVERDOSE (accidental [or intentional])'. The patient should be monitored for any AEs and treated, as needed.

- Local injection site reactions (see Section 10.6.1)
  - Local injection site reactions that are considered as non-allergic events and that are related to the IMP 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 (See Appendix G). Special e-CRF screens will need to be completed. If such an AE were to occur, then do not report the individual components of the reaction but rather the term "local injection site reaction", the individual components being described in the specific e-CRF screen.
- Allergic events (local injection site reaction and/or general allergic reaction) not referred for consultation with another physician (see Section 10.4.5.1) should be reported as AESI without immediate notification
  - All allergic events will need to have allergy specific e-CRF screens completed (see Section 10.6.2), regardless of requirements for immediate reporting.
- Neurological (including neurocognitive) events
  - Any AEs related to neurological (including neurocognitive) abnormalities with the exception of those requiring additional examinations/procedures and/or referral to a specialist (as mentioned in Section 10.4.5.1) should be reported as AESI without immediate notification
- Ophthalmologic events
  - Any AEs related to ophthalmologic abnormalities with the exception of those requiring additional examinations/procedures and/or referral to a specialist (as mentioned in Section 10.4.5.1), should be reported as AESI without immediate notification

10.4.6 Guidelines for management of specific laboratory abnormalities

Laboratory abnormalities with pre-specified monitoring should be monitored, documented, and managed according to the related flowchart in protocol Appendix C, Appendix D and Appendix E

- Neutropenia
- Thrombocytopenia
- Increase in ALT
- Acute renal insufficiency
- Increase in CPK and suspicion of rhabdomyolysis
- Decrease in Hb (defined as ≥1.5 g/dL)

10.4.6.1 Hemoglobin decrease

Please refer to Appendix E.

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

- If the following pattern of abnormalities is noted:
  - Reticulocyte count >Central Lab's upper limit of the reference range (also referred to as ULN) AND
  - Haptoglobin <Central Lab's lower limit of the reference range (also referred to as LLN) AND
  - LDH >ULN AND
  - Indirect bilirubin >ULN (only if the total bilirubin >ULN)

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

- If the results are normal or the pattern of abnormality is something other than that described above, then the investigator should exercise his/her medical judgment in the interpretation of the results, necessity for workup of the decrease in Hb or referral to a hematologist.

If a second Hb measurement demonstrating a further decrease of ≥1 g/dL from the last available value is observed, even if the previous work-up was negative, the same investigations can be repeated and a hematology consultation can be requested at the discretion of the Investigator or at the Sponsor's request.

10.5 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner all SAEs that are both unexpected and at least reasonably related to the IMP (Suspected Unexpected Serious Adverse Reaction [SUSAR]), to the Health Authorities, Independent Ethics Committee (IEC)/Institutional Review Board (IRB) as appropriate and to the Investigators.

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

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

Any other AE not listed as an expected event in the CIB or in this protocol will be considered as 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. See Section 10.4.5.2 and Appendix C for further information.

10.6.2 Allergic adverse events

See Section 10.4.5.1 and Section 10.4.5.2.

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 uncertain significance. These reactions would not be considered to be allergic reactions.

AEs 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) should be considered to be reported on the General Allergic Reaction and/or Local Injection Site Reaction Complementary Form.

AEs that are obviously not of allergic origin (eg, local injection site reactions) should only be recorded on the Local Injection Site Reaction Complementary Form. However, injection site reactions which progress/expand/worsen/etc should be evaluated as recommended in Section 10.6.2.1 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 10.3.3 for criteria for permanent treatment discontinuation.

10.6.2.1 Allergic adverse events with cutaneous involvement

AEs with cutaneous involvement which are obviously of allergic origin, general allergic reactions or local injection site reactions (with an allergic component) 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 extra-cutaneous symptoms and signs. An unscheduled Central Laboratory assessment for

hematology, chemistry, liver panel and ADA should be obtained. 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

See Section 10.4.5.2.

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 randomization visits.

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

10.6.3 Cardiovascular events

The following suspected or confirmed cardiovascular events that occur from randomization until the follow-up visit, should have a corresponding specific eCRF pages ± adjudication package prepared (as per the site manual) and submitted to the CEC:

- MI
- Cerebrovascular events (eg, stroke, transient ischemic attack, intracranial bleeding, ischemia or bleeding of spine or retina)
- Unstable angina requiring an emergency room visit or requiring/prolonging hospitalization

- Congestive heart failure requiring an emergency room visit or requiring/prolonging hospitalization
- All coronary revascularization procedures (eg, PCI, CABG)
- All deaths (including CHD death)

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

10.6.4 Laboratory alert related to TG rescue

The lipid results on blood samples obtained after the randomization visit will not be communicated to the investigators. However, sites will be notified if any of the following occur:

- TG alert:
  - TG ≥500 mg/dL (5.65 mmol/L) (any time after randomization).

Repeat testing should be done as soon as possible for the TG alert. For a confirmed TG alert, please refer to the relevant information in Section 8.9.1 for further information.

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

A total sample size of 96 patients (64 in alirocumab and 32 in ezetimibe) will have 95% power to detect a difference in means percent change in LDL-C of 20% with a 0.05 two-sided significance level and assuming a common standard deviation (SD) of 25% and all these 96 patients having an evaluable primary endpoint.

Nevertheless, to meet registration requirement and provide safety documentation in participating countries the final total sample size will be 600 with a randomization ratio 2:1 (400 in alirocumab and 200 in ezetimibe arms).

Calculations were made using nQuery Advisor 7.0.

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 populations.

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

The safety experience of patients treated and not randomized will be reported separately, and these patients will not be in the safety population.

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

ITT population: all randomized patients who had an evaluable primary endpoint. The primary endpoint is evaluable when the following 2 conditions are met:

- Availability of at least 1 baseline calculated LDL-C value;
- Availability of at least 1 calculated LDL-C value within one of the analysis windows up to Week 24

Patients in the ITT population will be analyzed according to the treatment group allocated by randomization (ie, as-randomized treatment group).

11.3.1.2 Modified Intent–to-treat (mITT) population

The mITT population is defined as the all randomized patients who took at least 1 dose or part of a dose of study drug (injection or capsule) and have an evaluable primary efficacy endpoint during the efficacy treatment period. The primary efficacy endpoint is considered as evaluable when the following 2 conditions are met:

- Availability of a baseline calculated LDL-C value;
- Availability of at least 1 calculated LDL-C value within one of the analysis windows up to Week 24 and during the efficacy treatment period.

The efficacy treatment period is defined as the time period from the first double-blind IMP (injection or capsule, whichever comes first) up to the day of last injection + 21 days or the day of last capsule intake date +3 days, whichever comes first.

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

11.3.2 Safety population

The safety population considered for safety analyses will be the randomized patients who actually received at least 1 dose or part of a dose of the double-blind IMP (injection or capsule). Patients will be analyzed according to the treatment actually received (alirocumab or ezetimibe).

In addition:

- 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 study drug from more than 1 treatment group during the trial, the treatment group allocation for as-treated analysis will be the one in which the patient was treated with the longest duration.

11.3.3 Other analysis population

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

The PK analysis will be performed in a subset of randomized and treated patients who will have at least one evaluable blood sample for PK after first double-blind IMP injection.

[redacted]

11.4 STATISTICAL METHODS

11.4.1 Extent of study treatment exposure and compliance

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

In order to ensure the continuity of the investigational treatment for the patients without interruption (only in case a disruption occurs in the availability of device components or during production of the auto injectors), 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 injection exposure in weeks defined as: (last dose of double-blind IMP injection date – first dose of double-blind IMP injection date + 14 days)/7, regardless of unplanned intermittent discontinuations.
- Duration of IMP capsule exposure in weeks defined as: (last capsule intake date – first capsule intake date + 1 day)/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

Compliance will be assessed using the following parameters:

- The mean injection frequency of IMP double-blind injections will be defined for each patient as the average number of days between 2 injections, that is: (last dose date – first dose date)/(number of injections -1).

- The compliance for capsules will be defined as the number of capsules taken / (last capsule intake date – first capsule intake date + 1) * 100 during the capsule exposure period.

These parameters 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 from baseline in calculated LDL-C at 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 4 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 (ezetimibe versus alirocumab), time point (Week 4, Week 8, Week 12, Week 16, Week 24),), randomization strata (prior history of MI or ischemic stroke [Yes/No], statin treatment [atorvastatin 40 to 80 mg daily or rosuvastatin 20 to 40 mg daily versus simvastatin whatever the daily dose, atorvastatin below 40 mg daily or rosuvastatin below 20 mg daily], and country), treatment-by-time point interaction and strata-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 (SE) and 95% confidence intervals (CI). To compare the alirocumab group to the ezetimibe group, an appropriate contrast statement will be used to test the differences of these estimates, at the 2-sided 0.05 level.

Let $\mu 0$ and $\mu 1$ be the population means of the percent change from baseline in calculated LDL-C at Week 24 under ezetimibe and alirocumab, respectively. The 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 Analysis of secondary efficacy endpoint(s)

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 9.1.2.1) and other secondary efficacy endpoints (described in Section 9.1.2.2), 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, TC, 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. For TG, measurements on not-fasting patients will be excluded. The time profile of each parameter will be plotted by treatment group with the corresponding SE. Similar tables (with either percent change from baseline or absolute change from baseline for the ratio) and plots will be provided for other efficacy parameters: ApoB, ApoA-1, ApoB/ApoA-1 ratio, Lp(a). 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 (example: percent change in calculated LDL-C), continuous measurements expected to have a non-normal distribution (example: TG), and binary measurements (example: proportion of patients reaching LDL-C <100 mg/dL).

Continuous endpoints anticipated to have a normal distribution

Continuous secondary variables defined in Section 9.1.2 anticipated to have a normal distribution (ie, 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, randomization strata, planned time points to Week 24, strata-by-time point interaction 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 variables endpoints defined in Section 9.1.2 anticipated to have a non-normal 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 and randomization strata 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 variables defined in Section 9.1.2 will be analyzed in using logistic regression with treatment group as main effect and corresponding baseline value(s) as covariate, stratified by randomization factors. 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 the 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 one treatment arm and thus the maximum likelihood estimate may not exist), the LOCF (Last Observation Carried Forward) approach would be used for handling of missing values and a stratified 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 time 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 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 9.1.2.1). 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 secondary endpoints for which p-values will be provided for descriptive purpose.

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 double IMP (injection or capsule, whichever comes first).

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 TEAE period, taking into account all evaluations performed during the TEAE period, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the 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 or capsule, whichever comes first) to the last dose of double-blind IMP injection + 21 days.

AE definition:

- Pre-treatment AEs are AEs that developed or worsened or became serious during the PRETREATMENT period;
- Treatment-emergent AEs (TEAEs) are AEs that developed or worsened or became serious during the TEAE period;
- Post-treatment AEs are AEs that developed or worsened or became serious during the POSTTREATMENT period.

Drug induced liver injury

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 post-baseline visit by baseline status will be displayed by treatment group for each parameter. A graph of distribution of peak values of ALT versus peak values of total bilirubin will also be presented. Note that the ALT and total bilirubin values are presented on a logarithmic scale. The graph will be divided into 4 quadrants with a vertical line corresponding to 3 x ULN for ALT and a horizontal line corresponding to 2 x ULN for total bilirubin.

The incidence of liver-related AEs will be summarized by treatment group. The selection of PT will be based on standardized MedDRA query (SMQ) Hepatic disorder. Time to liver-related treatment discontinuation and time to liver death may also be provided based on hepatic disorder SMQ.

11.4.3.1 Adverse events

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

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

If any clinically significant signal is detected and need 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.

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 nonrandomized patients or randomized and not treated patients
- TEAE leading to death (death as an outcome on the AE CRF page as reported by the Investigator) by primary SOC , HLGT, HLT and PT showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT.

Adjudicated cardiovascular events:

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

11.4.3.2 Laboratory and vital signs

The summary statistics (including mean, median, Q1, Q3, SE, minimum and maximum) of all laboratory variables and all vital signs parameters (raw data and changes from baseline) will be calculated for each 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.

11.4.4 Analyses of other endpoints

All analyses for other endpoints will be performed on the Safety population. The baseline value is defined as the last available value before first double-blind IMP (injection or capsule, whichever comes first).

The number and percentage of patients with 2 consecutive results, spaced out by at least 21 days, of calculated LDL-C <25 mg/dL and calculated LDL-C <15 mg/dL, respectively, will be provided by treatment group.

The antibody status (positive/negative) and antibody titers will be summarized by treatment group and visit using descriptive statistics. If appropriate, correlations between antibody titers, safety and/or efficacy endpoints will be provided by graphical methods.

$HbA1_c$ will be summarized by time points using number of available data, mean, SD, median, minimum, and maximum for each treatment group. The time profile of each parameter will be also plotted by treatment group with the corresponding SE.

Further details will be provided in SAP.

11.4.5 Analyses of pharmacokinetic variables

Serum total alirocumab concentrations, total and free PCSK9 concentrations if applicable, will be summarized by treatment group and visit using descriptive statistics. Serum concentration time profiles will be provided by treatment group. Additional plots will be prepared, as deemed necessary. Further details will be provided in SAP.

Serum total alirocumab concentrations might be used for population PK modeling if considered necessary. Further details will be provided in Population Analysis Plan and the results of population PK modeling will be reported separately from the study report.

11.4.6 Analyses of pharmacogenomics variables

[redacted]

11.5 INTERIM ANALYSIS

No interim analysis is planned.

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 International Conference on Harmonization (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.

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

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

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

As required by local regulation, the Investigator or the Sponsor must submit this clinical trial protocol to the appropriate IRB/IEC, and is required to forward to the respective other party

a copy of the written and dated approval/favorable opinion signed by the Chairman with IRB/IEC composition.

The clinical trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, ICF, CIB, Investigator's curriculum vitae, 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 CIB will be sent to the IRB/IEC.

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

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the e-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 to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All Subinvestigators shall be appointed and listed in a timely manner. The Subinvestigators 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 e-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 e-CRF entries against the source documents, except for the pre-identified source data directly recorded in the e-CRF. The informed consent form will include a statement by which the patient allows the Sponsor’s duly authorized

personnel, the Ethics Committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the e-CRFs (eg, patient's medical file, appointment books, original laboratory records). 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 AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate e-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 e-CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

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

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

The computerized handling of the data by the Sponsor 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.

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

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to, the clinical trial protocol, personal data in relation to the patients, the e-CRF, the CIB and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this clinical trial protocol and other necessary documentation to the Ethics committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Subinvestigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Subinvestigators of the confidential nature of the clinical trial.

The Investigator and the Subinvestigators shall use the information solely for the purposes of the clinical trial, to the exclusion of any use for their own or for a third party's account.

14.4 PROPERTY RIGHTS

All information, documents and IMP provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Investigator shall not and shall cause the delegated Investigator staff/Subinvestigator not to mention any information or the Product in any application for a patent or for any other intellectual property rights.

All the results, data, documents and inventions, which arise directly or indirectly from the clinical trial in any form, shall be the immediate and exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the clinical trial.

As the case may be, the Investigator and/or the Subinvestigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

14.5 DATA PROTECTION

- The patient's personal data, which are included in the Sponsor database shall be treated in compliance with all applicable laws and regulations;
- When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- The Sponsor also collects specific data regarding Investigator as well as personal data from any person involved in the study which may be included in the Sponsor’s databases, shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations.

14.6 INSURANCE COMPENSATION

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

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

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

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

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

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

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

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

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all 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

The Investigator undertakes not to make any publication or release pertaining to the study and/or results of the study prior to the Sponsor's written consent, being understood that the Sponsor will not unreasonably withhold its approval.

As the study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, a primary presentation or publication of the study results based on global study outcomes shall be sought. However, if no multicenter publication is submitted, underway or planned within twelve (12) months of the completion of this study at all sites, the Investigator shall have the right to publish or present independently the results of this study in agreement with other Investigators and stakeholders. The Investigator shall provide the Sponsor with a copy of any such presentation or publication for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other justified measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

The Investigator shall not use the name(s) of the Sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The Sponsor has the right at any time to publish the results of the study.

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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17 APPENDICES

Appendix A. Summary of TLC Diet for High Cholesterol

Total Fat	25% - 35% total calories*
Saturated fat*	< 7% total calories
Polyunsaturated fat	up to 10% total calories
Monounsaturated fat	up to 20% total calories
Carbohydrates†	50% - 60% total calories*
Protein	~15% total calories
Cholesterol	< 200 mg/day (5.172 mmol/day)
Plant Sterols	2g
Soluble Fiber such as psyllium	10g - 25g

* NCEP ATP III allows an increase of total fat to 35 percent of total calories and a reduction in carbohydrate to 50 percent for persons with the metabolic syndrome. Any increase in fat intake should be in the form of either polyunsaturated or monounsaturated fat. Trans fatty acids are another LDL-raising fat that should be kept at a low intake.

† Carbohydrate should derive predominantly from foods rich in complex carbohydrates including grains-especially whole grains-fruits, and vegetables.

Appendix B. The Stages of Heart Failure – NYHA Classification

Physicians often assess the stage of heart failure according to the NYHA functional classification system. This system relates symptoms to everyday activities and the patient's quality of life.

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

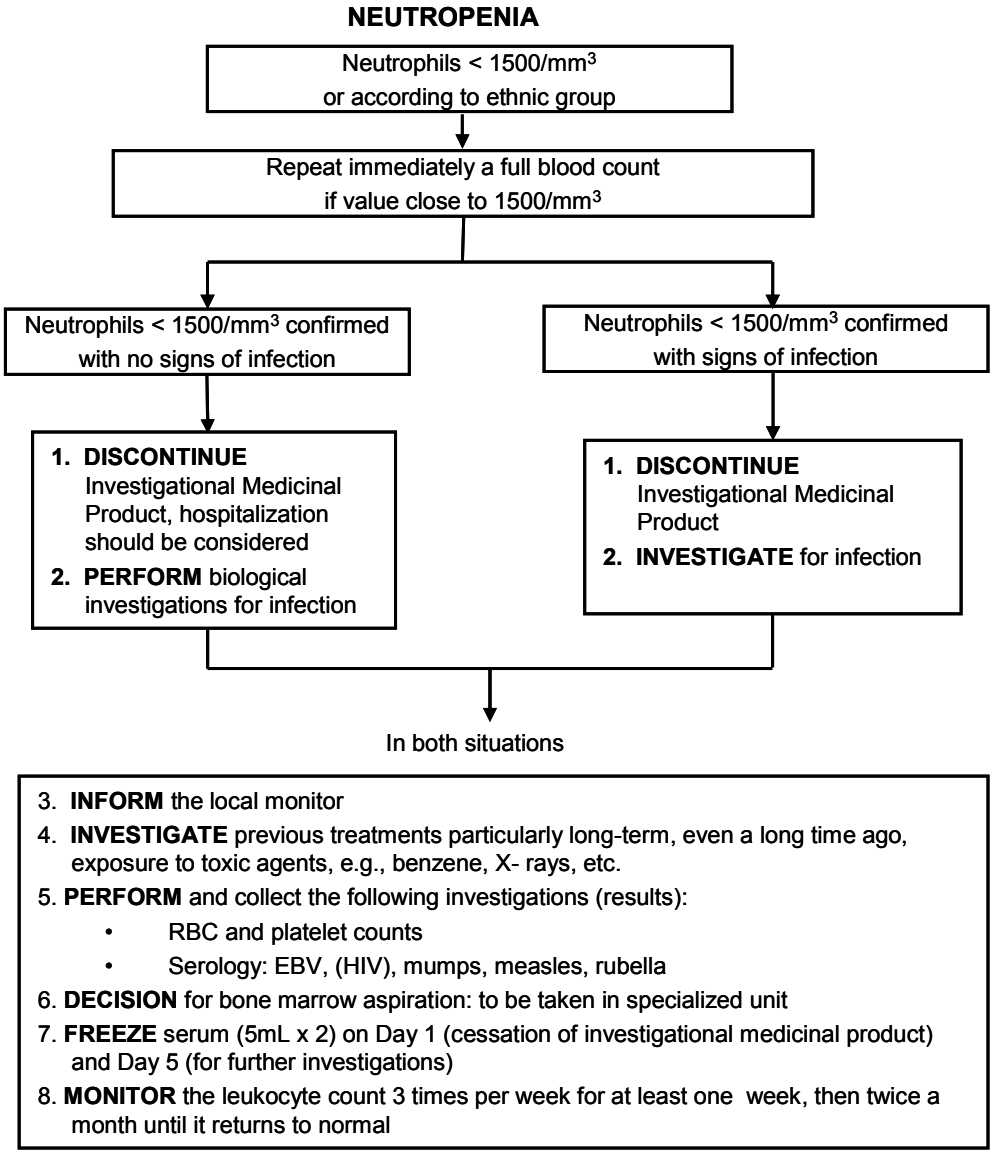
Appendix C. Summary of Adverse Event Reporting Instructions

EVENT CATEGORY	REPORTING TIMEFRAME	SPECIFIC EVENTS IN THIS CATEGORY	CASE REPORT FORM COMPLETION		
			AE form	Safety Complementary Form*	Other specific forms
Adverse Event (non-SAE, non-AESI)	Routine	Any AE that is not SAE or AESI	Yes	No	No
Serious Adverse Event (non-AESI or AESI)	Expedited (within 24 hours)	Any AE meeting seriousness criterion per Section 10.4.1.2	Yes	Yes	No, unless applicable
Adverse Event of Special Interest (AESI) WITHOUT immediate notification (non-SAE)	Routine	Asymptomatic overdose with IMP	Yes	No	No
		Local injections site reactions	Yes	No	Yes
		Allergy events (except events specified in Section 10.4.5.2)	Yes	No	Yes
		Ophthalmologic events (NOT requiring additional examinations/procedures and/or consultation with a specialist, as described in Section 10.4.5.2)	Yes	No	Yes
		Neurological (including neurocognitive) events (NOT requiring additional examinations/procedures and/or consultation with a specialist, as described in Section 10.4.5.2)	Yes	No	Yes
Adverse Event of Special Interest (AESI) WITH immediate notification (non-SAE)	Expedited (within 24 hours)	Pregnancy of female patient/subject (including male subject's partner)	Yes	Yes	Yes
		Symptomatic overdose with IMP	Yes	Yes	No
		Increase in ALT as follows: - ALT ≥3 ULN (if baseline ALT <ULN) Or - ALT ≥2 times the baseline value (if baseline ALT ≥ULN) Please refer to related flowchart (per Appendix D)	Yes	Yes	Yes
		Allergic drug reactions and/or local injections site reactions deemed to be allergic as	Yes	Yes	Yes

EVENT CATEGORY	REPORTING TIMEFRAME	SPECIFIC EVENTS IN THIS CATEGORY	CASE REPORT FORM COMPLETION		
			AE form	Safety Complementary Form*	Other specific forms
		specified in Section 10.4.5.1			
		Hemolytic anemia	Yes	Yes	Yes
		Ophthalmologic events (requiring additional examinations/procedures and/or consultation with a specialist, as described in Section 10.4.5.1)	Yes	Yes	Yes
		Neurological (including neurocognitive) events (requiring additional examinations/procedures and/or consultation with a specialist, as described in Section 10.4.5.1)	Yes	Yes	Yes
Laboratory, vital sign, or ECG abnormality (non-SAE, non-AESI) that is: - Symptomatic - Requiring corrective treatment or consultation - Leading to IMP discontinuation or dose regimen modification	Routine	Neutropenia (per Appendix D)	Yes	No	No
		Thrombocytopenia (per Appendix D)	Yes	No	No
		Acute renal insufficiency (per Appendix D)	Yes	No	No
		Increase in CPK and suspicion of rhabdomyolysis (per Appendix D)	Yes	No	No
Cardiovascular events and death from any cause	Expedited (within 24 hours)	MI, cerebrovascular events (eg, stroke, transient ischemic attack, intracranial bleeding, ischemia or bleeding of spine or retina), unstable angina requiring hospitalization, congestive heart failure requiring hospitalization, coronary revascularization (PCI, CABG), and an event with outcome of fatal (including CHD death)	Yes	Yes	Yes

*Completion of a Safety Complementary Form is required for any AE meeting a seriousness criterion, even if this is not required according to the table for a particular type of AE

Appendix D. General Guidance for the follow-up of laboratory abnormalities by Sanofi



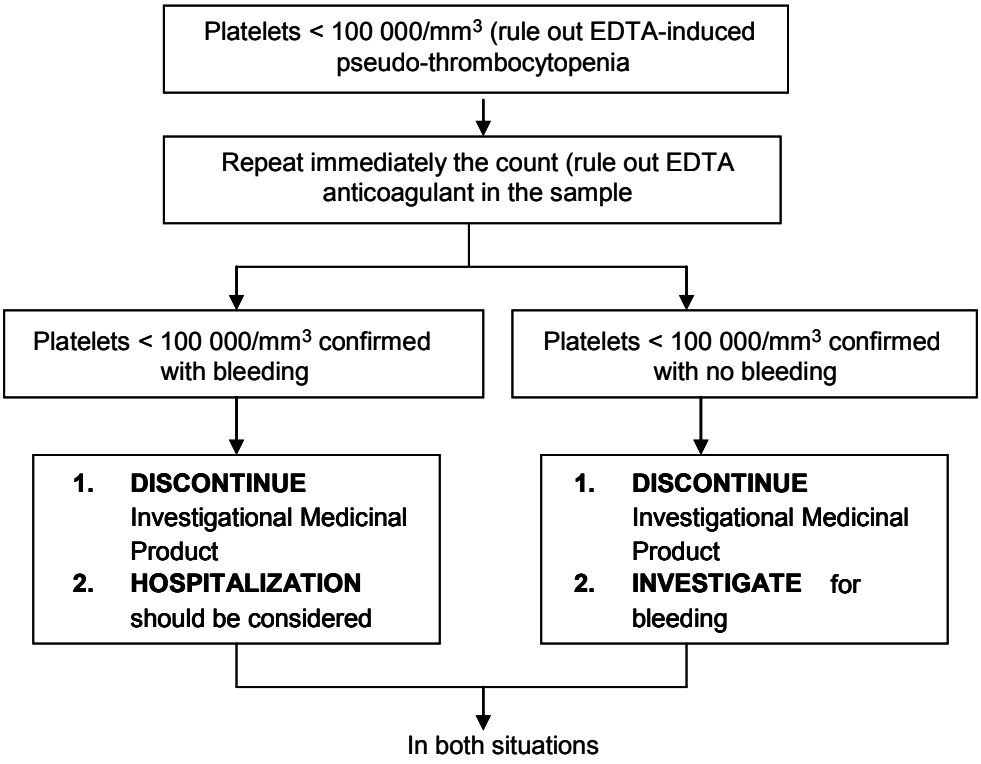
Note

- The procedures described in the above flowchart are to be discussed with the patient only in case the event occurs. If applicable (according to local regulations) , an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.
- For individuals of African descent, the relevant value of concern is <1000/mm3

Neutropenia are to be recorded as AE only if they are :

- 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 [in that case, the event (SAE) should be notified within ***24 hours*** to the MT], and/or
- Defined as an Adverse Event of Special Interest (AESI) with immediate notification

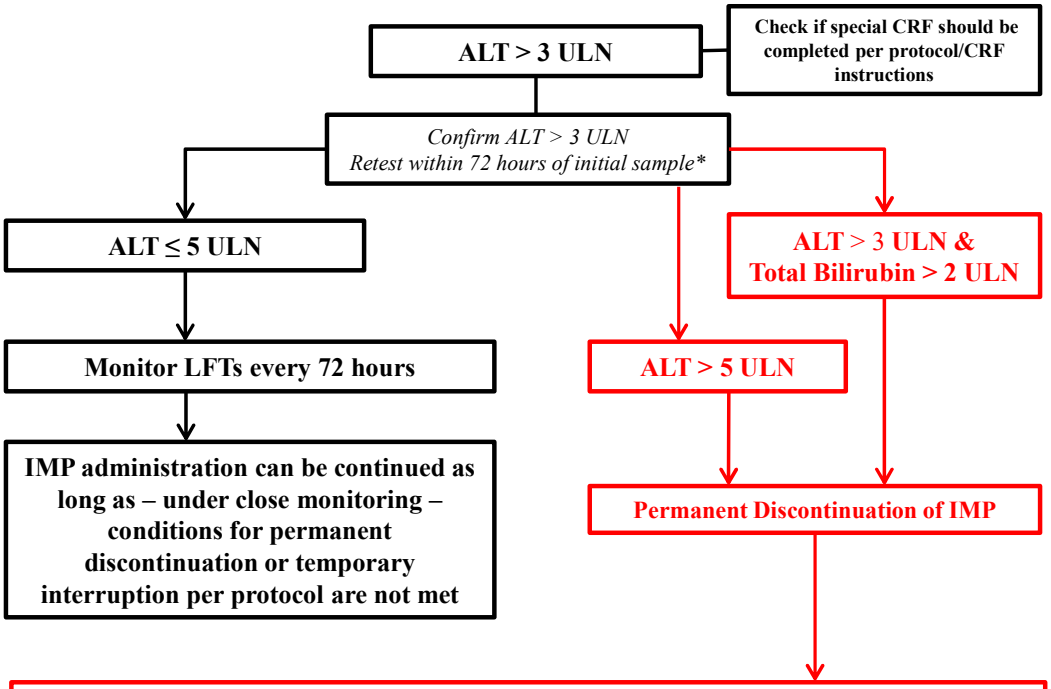
THROMBOCYTOPENIA



3. **INFORM** the local monitor
4. **QUESTION** about last intake of quinine (drinks), alcoholism, heparin administration
5. **PERFORM** or collect the following investigations
   - Complete blood count, schizocytes, creatinine
   - Bleeding time and coagulation test (fibrinogen, PT, aPTT), Fibrin Degradation Product
   - Viral serology: EBV, HIV, mumps, measles, rubella
6. **FREEZE** serum (5mL x 2) on Day 1 (end of treatment) and Day 5 to test for drug-induced antiplatelet antibodies
7. **DECISION** for bone marrow aspiration: to be taken in specialized unit
   - On Day 8 if the Platelets remain < 50 000/mm3
   - On Day 1 in the case of associated anemia and/or leukopenia
8. **MONITOR** the platelet count every day for at least one week and then regularly until it returns to normal

NOTE:
the procedures described in the above flowchart are to be discussed with the patient only in case the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs

Thrombocytopenia are to be recorded as AE only if they are:
- 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 [in that case, the event (SAE should be notified within *24 hours* to the MT], and/or
- Defined as an Adverse Event of Special Interest (AESI) with immediate notification



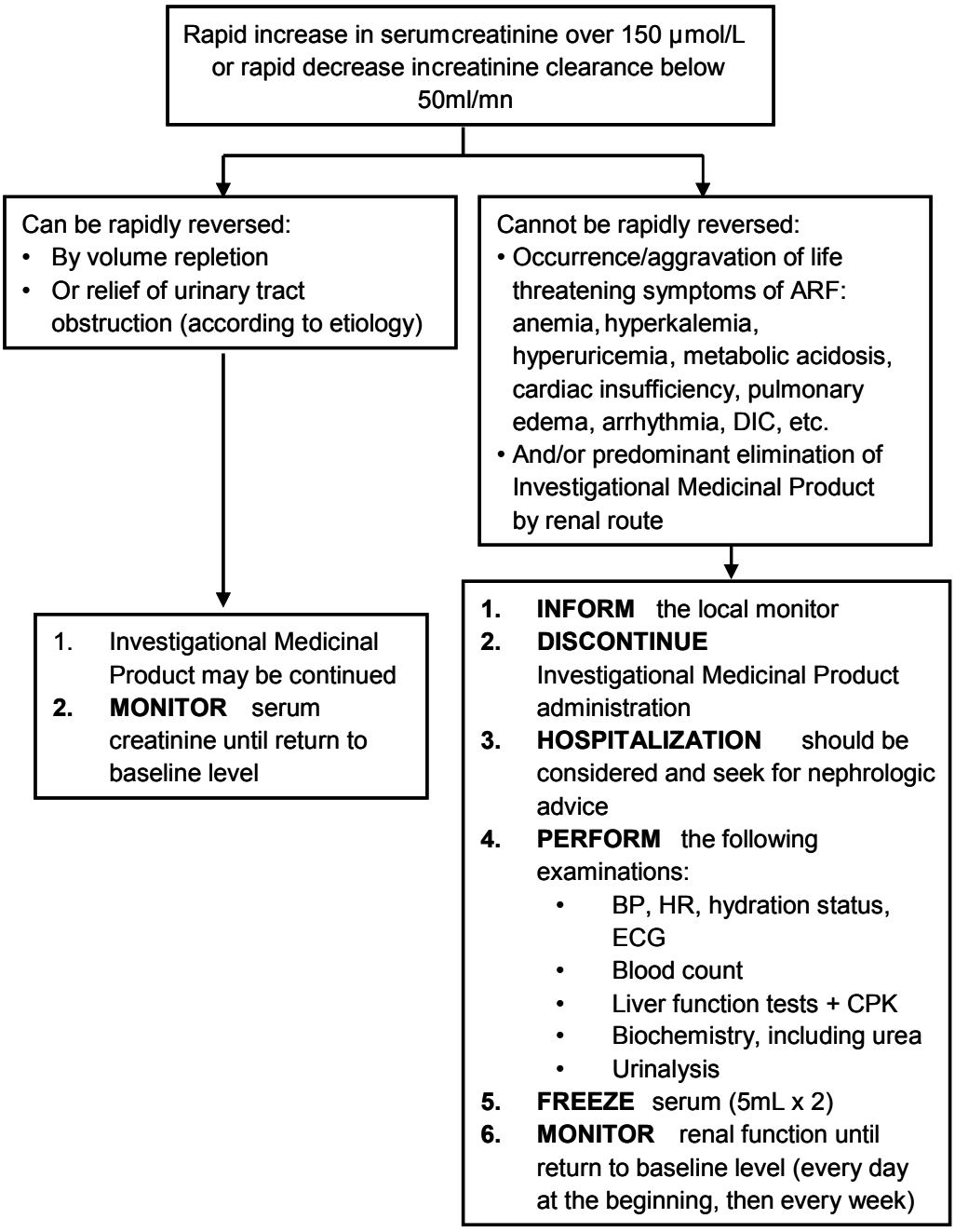
In ANY CASE, FOLLOW the instructions listed in the box below:

1. **INFORM** the Site Monitor who will forward the information to the Study Manager
2. **COMPLETE** the CRF for «ALT Increase» for any permanent discontinuations due to liver injury (See protocol/CRF instructions)
3. **INVESTIGATE** specifically for malaise with or without loss of consciousness, dizziness, and/or hypotension and/or episode of arrhythmia in the previous 72 hours; rule out muscular injury
4. **PERFORM** the following tests:
   - LFTs: AST, ALT, alkaline phosphatase, total and conjugated bilirubin and prothrombin time / INR
   - CPK, serum creatinine, complete blood count
   - Anti-HAV IgM, anti-HBc IgM, (HBV-DNA if clinically indicated), anti-HCV and HCV RNA, anti-CMV IgM and anti-HEV IgM antibodies
   - Depending on the clinical context, check for recent infection with EBV, herpes viruses, and toxoplasma
   - Hepatobiliary ultrasonography (or other imaging investigations if needed)
5. **CONSIDER** Auto-antibodies: antinuclear, anti-DNA, anti-smooth muscle, anti-LKM
6. **CONSIDER** consulting with hepatologist
7. **CONSIDER** patient hospitalization if INR>2 (or PT<50%) and/or central nervous system disburbances suggesting hepatic encephalopathy
8. **MONITOR LFTs after discontinuation of IMP:**
   - As *closely as possible* (or **every 48 hours)** until stabilization, then every 2 weeks until return to normal/baseline or clinical resolution.
9. **FREEZE** serum sample (5ml x 2)
10. **In case of SUSPICION of GILBERT Syndrome,** a DNA diagnostic test should be done

Note:
Normalization is defined as < ULN or baseline value if baseline value is >ULN.
As soon as seriousness criterion is met or the event leads to permanent treatment discontinuation, the monitoring team should be notified within 24 hours.
* If unable to retest in 72 hours, use original lab results to decide on further monitoring/ discontinuation .

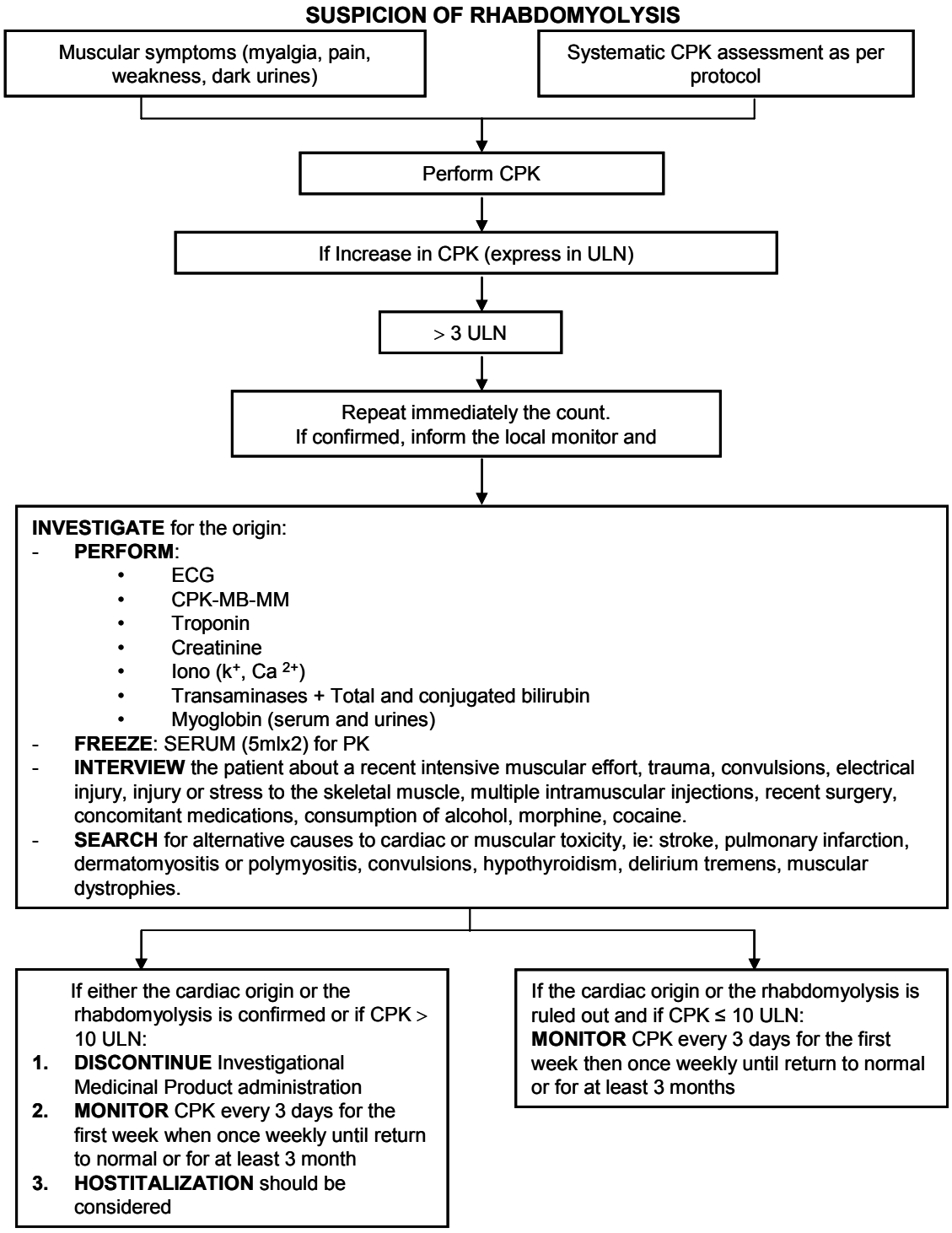
Note: ALT ≥ 3 ULN (if baseline ALT < ULN) or ALT ≥ 2 times the baseline value (if baseline ALT ≥ ULN) should be notified within 24 hours to the monitoring team (see Section 10.4.2, Section 10.4.5, and Section 11.4.6). In addition, if ALT < 3 ULN meets a seriousness criterion, the event should be notified within 24 hours to the monitoring team.

ACUTE RENAL FAILURE



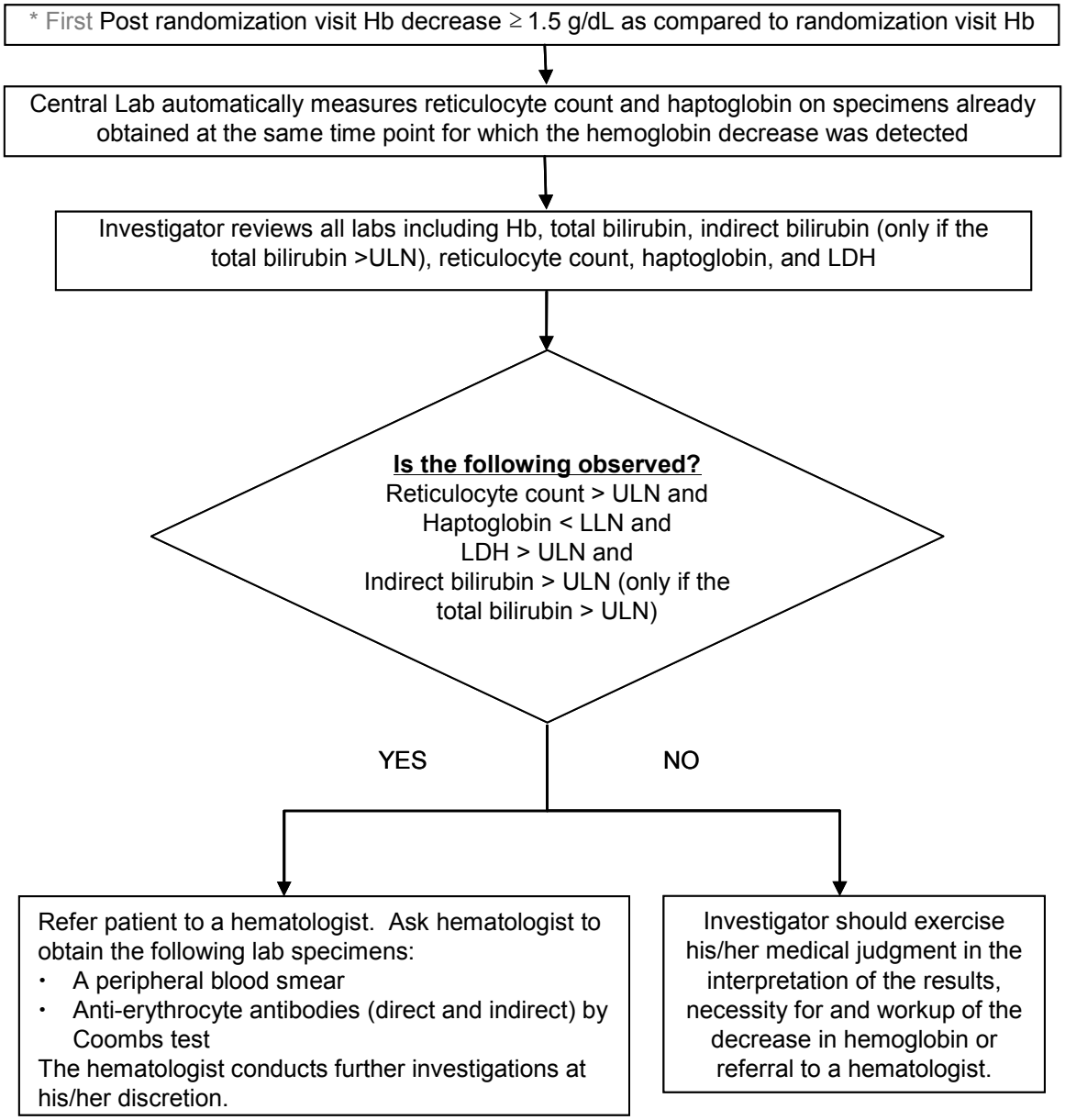
Acute renal failure is to be recorded as AE only if it is :

- 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 [in that case, the event (SAE) should be notified within ***24 hours*** to the MT], and/or
- Defined as an Adverse Event of Special Interest (AESI) with immediate notification



Suspicion of rhabdomyolysis is to be recorded as AE only if it is:
- 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 [in that case, the event (SAE) should be notified within ***24 hours*** to the MT], and/or
- Defined as an Adverse Event of Special Interest (AESI) with immediate notification

Appendix E. Guidelines for hemoglobin (Hb) decrease >=1.5 g/dL



Suspicion of hemolytic anemia is recorded as AE 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

* If a second hemoglobin measurement demonstrating a further decrease of ≥1 g/dL from the last available value is observed, even if the previous work-up was negative, the same investigations can be repeated and a hematology consultation can be requested at the discretion of the Investigator or at the Sponsor's request.

Appendix F. DNA storage samples

2. SHIPMENT CONTACT NAMES AND ADDRESSES

For Optional DNA Banking Samples:

Use for Asia-Pacific, including Thailand, Malaysia, and Australia:
Covance CLS Singapore
1 International Business Park
#05-12A/B The Synergy
Singapore 609917
Tel:
Fax:

Use for China only:
Covance CLS Shanghai
1st Floor, No. 6 Building
151 Li Bing Rd
Zhangjiang Hi-Tech Park
Shanghai 201203
China
Tel:
Fax:

Appendix G. Assessment of Local Injection Site Reactions

Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Very Severe (Grade 4)
Pain	Does not interfere with activity	Interferes with activity or repeated use of non-narcotic pain reliever	Prevents daily activity or repeated use of narcotic pain reliever	Emergency Room (ER) visit or hospitalization
Tenderness	Mild pain to touch	Pain with movement	Significant pain at rest	ER visit or hospitalization
Erythema / Redness *	2.5 – 5 cm	5.1 – 10 cm	>10 cm	Necrosis or exfoliative dermatitis
Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis
Itching	Does not interfere with activity	Interferes with activity or repeated use of topical or systemic treatment	Prevents daily activity or leads to other significant dermatologic conditions (such as infection, scarring, etc.)	Emergency Room (ER) visit or hospitalization
Other (Please specify)***	No modification of daily activities and/or does not require symptomatic treatment.	Hinders normal daily activities and/or requires symptomatic treatment.	Prevents daily activities and requires symptomatic treatment.	Emergency Room (ER) visit or hospitalization

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable
** Swelling should be evaluated and graded using the functional scale as well as the actual measurement
*** Please specify the other signs or symptoms (for example, hematoma, discoloration, re-activation, etc.)

ADAPTED from the toxicity grading scale table from the FDA Draft Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials April 2005

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	Clinical Approval	18-Dec-2015 07:35 GMT+01
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