SANOFI

NCT Number:NCT02984982

AMENDED CLINICAL TRIAL PROTOCOL NO. 3

COMPOUND: Alirocumab

TITLE : A randomized, open-label, blinded intravascular ultrasound analysis, parallel group, multicenter study to evaluate the effect of Praluent® (alirocumab) on coronary atheroma volume in Japanese patients hospitalized for acute coronary syndrome with hypercholesterolemia not adequately controlled with statin

STUDY NUMBER: ALIROL08069

STUDY NAME: ODYSSEY J-IVUS

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(electronic 1.0)

NAMES AND ADDRESSES OF

STEERING COMMITTEE	Name: Address: Tel: Fax: E-mail:	Described in attachment
MONITORING TEAM'S REPRESENTATIVE	Name: Address: Tel: Fax: E-mail:	Described in attachment
SPONSOR	Company: Address:	Described in attachment
OTHER EMERGENCY TELEPHONE NUMBERS		Described in attachment

CLINICAL TRIAL SUMMARY

COMPOUND: PRALUENT® (Alirocumab)	**STUDY No.: ALIROL08069** **STUDY NAME: ODYSSEY J-IVUS**
TITLE	A randomized, open-label, blinded intravascular ultrasound analysis, parallel group, multicenter study to evaluate the effect of Praluent® (alirocumab) on coronary atheroma volume in Japanese patients hospitalized for acute coronary syndrome with hypercholesterolemia not adequately controlled with statin
INVESTIGATOR/TRIAL LOCATION	JAPAN – Multicenter study
PHASE OF DEVELOPMENT	Phase 4
STUDY OBJECTIVE(S)	**Primary objective:** To compare the effect of Praluent® with standard of care (SoC) on coronary atheroma progression (percent change in normalized total atheroma volume [TAV]) after 9 months of treatment in patients who had acute coronary syndrome (ACS) within 4 weeks prior to randomization, with hypercholesterolemia treated with any statin **Secondary objective(s):** • To compare the effect of Praluent® with SoC on secondary endpoints including absolute change in percent atheroma volume (PAV) and normalized TAV after 9 months of treatment • To evaluate the effect of Praluent® on low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides, non-high-density lipoprotein cholesterol (non-HDL-C) and Lipoprotein(a)(Lp(a)) after 9 months treatment • To evaluate the safety of Praluent® including the occurrence of cardiovascular (CV) events (coronary heart disease [CHD] death, non-fatal myocardial infarction [MI], fatal and non-fatal ischemic stroke, unstable angina requiring hospitalization) throughout the study
STUDY DESIGN	Open-label, 1:1 randomized, blinded intravascular ultrasound (IVUS) analysis, 2-arm, parallel-group, multicenter study Randomization will be stratified by on statin therapy or not on statin therapy at the time of ACS onset. After randomization, patients will receive open-label study treatment of Praluent® 75 mg every 2 weeks (Q2W) on top of stable daily statin therapy for 36 weeks, or SoC. For patients randomized to alirocumab arm, a dose up-titration to Praluent® 150 mg Q2W may be conducted at Week 14 based on LDL-C level at Week 12 (see below). For patients randomized to SoC arm, LDL-C target level <100 mg/dL is achieved with stable dose statin therapy (within the range of statin doses approved by the Health Authority) ± other lipid modifying therapies (LMTs) except for anti-PCSK9 monoclonal antibody. Concomitant non-statin LMTs will be considered if LDL-C target level <100 mg/dL cannot be achieved with statin monotherapy. LDL-C is managed to achieve target level <100 mg/dL using the

above mentioned or other method.

The study consists of:

- A 36-week open label treatment period (study period)

- During the study period, patients randomized to alirocumab or SoC arm will receive treatment in an un-blinded manner as follows.

1. Alirocumab arm;

- Praluent® (alirocumab) 75 mg Q2W subcutaneously on top of statin therapy (atorvastatin ≥10 mg/day or rosuvastatin ≥5 mg/day) within the range of statin doses approved by the Health Authority.

- Statin (atorvastatin ≥10 mg/day or rosuvastatin ≥5 mg/day within the range of statin doses approved by the Health Authority) and non-statin LMTs will be continued at the same doses after ACS diagnosis unless modifications are necessary. The target LDL-C level is <100 mg/dL.

- At Week 14, patients randomized to alirocumab arm will, in an un-blinded manner, either:
    - Continue receiving Praluent® (alirocumab) 75 mg Q2W if the Week 12 LDL-C measured by the central laboratory is <100 mg/dL OR
    - Receive dose up-titrated to Praluent® (alirocumab) 150 mg Q2W at Week 14, if the Week 12 LDL-C measured by the central laboratory is ≥100 mg/dL.

    Continuation of Praluent® 75 mg Q2W or dose up-titration to Praluent® 150 mg Q2W will occur at each study site based on the rules as above.

- Self-injection of Praluent® (alirocumab) at home
    - Patients can choose self-injection at home any time, if they wish self-injection at home and the Investigator or sub-Investigator considers it feasible.
    - Patients are allowed to perform self-injection at home if they successfully perform the correct self-injection of Praluent® (alirocumab) under the direct supervision of site medical staff at the site once, and the Investigator or sub-Investigator considers that they can perform self-injection at home correctly.
    - Regardless of the timing when the self-injection is started, patients must visit the study site at least every 4 weeks, and at Week 0, Week 4, Week 12, Week 14, Week 24 and Week 36.
    - Patients can discontinue self-injection at home any time. The Investigator or sub-Investigator must have patients discontinue self-injection at home if the Investigator or sub-Investigator judges that the patients are not able to perform self-injection at home correctly. Patients who discontinue self-injection at home can have injections performed by medical staff at the study site.

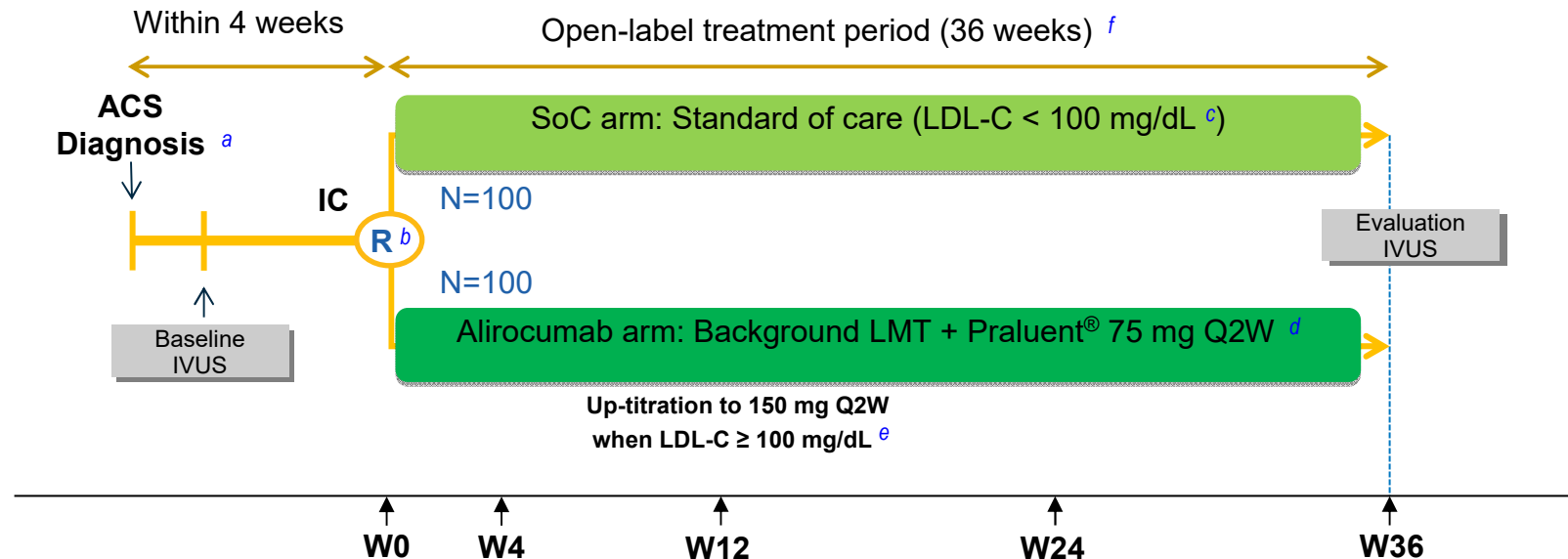|	
	2. Standard of Care arm;
	• During the study period, patients randomized to the SoC arm will, in an un-blinded manner, receive either:
	- Stable dose statin therapy of either atorvastatin ≥10 mg/day or rosuvastatin ≥5 mg/day (within the range of statin doses approved by the Health Authority) to achieve the LDL-C target level <100 mg/dL.
	- Concomitant non-statin LMTs if LDL-C target level <100 mg/dL cannot be achieved with statin monotherapy. Adjustment of LMTs is to be performed based on, but not limited to, the above rule.

STUDY POPULATION
 	
Main selection criteria
	Main inclusion criteria:
	
	I 01. Patients hospitalized for ACS (ST-elevation myocardial infarction [STEMI], non ST-elevation myocardial infarction [NSTEMI], unstable angina).
	
	I 02. LDL-C ≥100 mg/dL at ACS diagnosis (either by Friedewald method or direct method measured at each study site),:
	
	   a) Patients who have already been on any statin therapy at ACS onset. If the statin is not atorvastatin or rosuvastatin, statin will be changed to either atorvastatin ≥10 mg/day or rosuvastatin ≥5 mg/day immediately after the ACS diagnosis based on Investigators' medical judgment.
	
	   b) If patients have not been on any statin therapy at ACS onset, either atorvastatin 10 mg/day or rosuvastatin 5 mg/day is started immediately after the ACS diagnosis, and LDL-C is not adequately controlled with statin at 2 to 4 weeks after the ACS diagnosis (in principle, LDL-C target level ≥100 mg/dL, but this may not apply if the responsible physician considers the LDL-C level inadequate on statin. Patients who have LDL-C <70 mg/dL cannot be enrolled).
	
	I 03. Patients who has stenosis of at least 50% on coronary angiography within 1 week after the ACS onset, and has analyzable coronary IVUS image. The evaluated segment of IVUS is a segment where a physician considers the IVUS imaging is possible (regardless of culprit vessels or not culprit vessels) other than the culprit lesions.
	
	I 04. Patients aged ≥20 years old at ACS diagnosis.
	
	I 05. Patients who meet any of the following conditions:
	
	   - Negative hepatitis B virus surface antigen, negative hepatitis B virus total core antibody, and negative hepatitis C virus antibody.
	
	   - Negative hepatitis B virus surface antigen, positive hepatitis B virus total core antibody, negative hepatitis B virus DNA, and negative hepatitis C virus antibody.
	
	I 06. Written informed consent.

	Main exclusion criteria:
	E 01. Patients who have been previously treated with at least one dose of any anti-PCSK9 monoclonal antibody.
	E 02. Uncontrolled hypertension (multiple reading with systolic blood pressure [SBP] > 180 mmHg or diastolic blood pressure [DBP] >110 mmHg) between ACS diagnosis and randomization visit.
	E 03. Known history of hemorrhagic stroke.
	E 04. Currently under treatment with anticancer drug.
	E 05. Patients on LDL apheresis.
	E 06. Conditions/situations such as:
	• Any clinically significant abnormality identified that in the judgment of the Investigator or any sub-Investigator would preclude safe completion of the study or constrain endpoints assessment such as major systemic diseases, patients with short life expectancy.
	• Considered by the Investigator or any sub-Investigator as inappropriate for this study for any reason, e.g.:
	- Those deemed unable to meet specific protocol requirements, such as scheduled visits.
	- Investigator or any sub-Investigator, pharmacist, study coordinator, other study staff or relative thereof directly involved in the conduct of the protocol, etc.
	- Presence of any other condition (e.g., geographic, social, etc.) actual or anticipated, that the Investigator or sub-Investigator feels would restrict or limit the patient's participation for the duration of the study.
	E 07. Laboratory findings measured before the randomization visit within 4 weeks after the ACS diagnosis.
	• Positive serum or urine pregnancy test in women of childbearing potential.
Total expected number of patients	200
STUDY TREATMENT(s)	SoC (stable dose statin therapy ± other LMTs targeting LDL-C <100 mg/dL) and combination therapy (stable dose statin therapy + Praluent® 75 mg Q2W subcutaneously with up-titration to 150 mg Q2W at Week 14 if LDL-C <100 mg/dL is not achieved.)
Investigational medicinal product(s)	Praluent® (Alirocumab)
Formulation:	Alirocumab, an active ingredient of Praluent®, is a fully human monoclonal antibody that binds PCSK9. Praluent® will be supplied in a 1 mL autoinjector as an injectable drug with pH 6.0, containing histidine, polisorbate 20, and sucrose, with alirocumab concentration of 75 mg/mL or 150 mg/mL.
Route(s) of administration:	Subcutaneous administration to the abdomen, thighs, or outer area of the upper arms
Dose regimen:	Dose regimen approved in Japan: 75 mg Q2W with up-titration to 150 mg Q2W if LDL-C <100 mg/dL is not achieved.

Noninvestigational medicinal product(s)	- Atorvastatin - Rosuvastatin - Cholesterol absorption inhibitor (ezetimibe) - Fibrates (fenofibrate, bezafibrate) - Anti-platelets (aspirin, clopidogrel, etc.) - Warfarin, and other oral anticoagulants approved in Japan
Route(s) of administration:	Oral
Dose regimen:	Dose regimen approved in Japan
ENDPOINT(S)	**Primary efficacy endpoint:** - Percent change in normalized TAV from baseline to Week 36 **Key secondary efficacy endpoint:** - Absolute change in PAV from baseline to Week 36 **Other secondary efficacy endpoint(s):** - Absolute change in normalized TAV from baseline to Week 36 - Absolute and percent change in external elastic membrane (EEM) volume from baseline to Week 36 - Absolute and percent change in lumen volume from baseline to Week 36 - Absolute and percent change in calculated LDL-C from baseline to Week12, and Week 36 - Absolute and percent change in Apo B from baseline to Week 36 - Absolute and percent change in non-HDL-C from baseline to Week 36 - Absolute and percent change in total cholesterol (TC) from baseline to Week 36 - Absolute and percent change in Lp(a) from baseline to Week 36 - Absolute and percent change in HDL-C from baseline to Week 36 - Absolute and percent change in fasting triglycerides (TGs) from baseline to Week 36 - Absolute and percent change in apolipoprotein A-1 (Apo A-1) from baseline to Week 36 **Safety endpoints:** - Safety parameters (adverse events including CV events*, laboratory data and vital signs) assessed throughout the study

	*CV events: CHD death, non-fatal MI, fatal and non-fatal ischemic and/or haemorrhagic stroke, unstable angina requiring hospitalization, congestive heart failure requiring hospitalization, ischemia-driven coronary revascularization.
ASSESSMENT SCHEDULE	**Patient's assessments in the treatment period:** On-site visits: Week 0 (randomization visit), Week 4, Week 12, Week 24, Week 36
STATISTICAL CONSIDERATIONS	**Sample size determination:** The study is expected to enroll approximately 200 patients. Based on the results of ZEUS(1) and PRECISE-IVUS(2) studies, it is assumed that difference in percent change in normalized TAV from baseline between alirocumab arm and SoC arm is 8%, and the common standard deviation of percent change in normalized TAV is 15%. Under the assumption, a sample size of 150 patients (75 in the alirocumab arm and 75 in the SoC arm) will have 90% power to detect the treatment difference with two-sided significance level of 5%. Assuming that proportion of non-evaluable primary endpoint is 25%, it is considered that 200 patients (100 in the alirocumab arm and 100 in the SoC arm) will be needed. **Analysis population:** Randomized population includes all patients who have been allocated to a randomized treatment and recorded in the registration center database, regardless of whether a study drug was used or not. The primary efficacy analysis population will be the modified intent-to-treat (mITT) population, defined as the randomized population who takes at least one dose or part of dose of study drug and has an available value of normalized TAV before randomization and after 24 weeks of treatment. Patients in the mITT population will be analyzed according to the treatment arm allocated by randomization. The safety population consists of patients of randomized population who actually received at least one dose or partial dose of study treatment. The safety population will be analyzed according to the treatment actually received. **Primary analysis:** The percent change in normalized TAV will be analyzed using an analysis of covariance (ANCOVA) model with treatment arm and randomization strata as fixed effects, and the baseline normalized TAV as covariate. **Analysis of Key secondary efficacy endpoints:** Analysis of key secondary efficacy endpoint will be performed on the mITT population considering corresponding baseline value as covariate, in the same manner as for the primary endpoint. **Multiplicity adjustment:** A hierarchical procedure will be used to control the type I error and to handle multiple endpoints. If the primary endpoint analysis is significant at the two-sided 5% alpha level, the key secondary

	efficacy endpoint will be tested at the two-sided 5% level.
	The other secondary efficacy endpoints not included in key secondary endpoint will be analyzed for exploratory purpose only.
	Safety analysis:
	Safety analysis will be descriptive, based on the safety population. Safety analysis will focus on the Treatment Emergent Adverse Events (TEAE) period defined as the time from the day of randomization to the last administration + 21 days (3 weeks), or end of study, whichever comes first.
	The treatment arm allocation for as-treated analysis will defined as follows:
	• Alirocumab arm if proportion of IMP injection is ≥ 50%.
	• SoC arm if proportion of IMP injection is <50%.
	where proportion of IMP injection (%) is defined as:
	100x (Number of IMP injection)/[(Date of end of treatment - Date of randomization)/14 + 1].
DURATION OF STUDY PERIOD (per patient)	9 months

(electronic 1.0)

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN

Abbreviations: ACS, acute coronary syndrome; IC, informed consent; IVUS, intravascular ultrasound; LDL-C, low-density lipoprotein cholesterol; LMT, lipid modifying therapy; Q2W, every 2 weeks; R, randomization; SoC, standard of care.

a   If patients have not been on any statin therapy at ACS onset, either atorvastatin 10 mg/day or rosuvastatin 5 mg/day is started immediately after the ACS diagnosis.

b   At randomization, patients should have already received stable statin therapy with either atorvastatin ≥10 mg/day or rosuvastatin ≥5 mg/day for at least 2 weeks.

c   Stable dose statin monotherapy (atorvastatin ≥10 mg/day or rosuvastatin ≥5 mg/day within the range of statin doses approved by the Health Authority) will be administered to achieve the LDL-C target level <100 mg/dL. Concomitant non-statin LMTs will be considered if patients have already been on them on top of statin monotherapy at the time of ACS diagnosis or if LDL-C target level <100 mg/dL cannot be achieved by the statin monotherapy. Adjusting of LMT will occur based on above rule, but not limited.

d   Praluent® 75 mg Q2W on top of stable dose of atorvastatin ≥10 mg/day or rosuvastatin ≥5 mg/day ± other LMTs, in accordance with doses approved by the Health Authority. Concomitant non-statin LMTs will be considered if patients have already been on them on top of statin monotherapy at the time of ACS diagnosis. Background statin and/or non-statin LMT regimens should not be changed as a principle during the entire study period.

e   In the alirocumab arm, if LDL-C level at Week 12 measured by the central laboratory does not reach <100 mg/dL, Praluent® dose up-titration to 150 mg Q2W will be carried out at Week 14.

f   Patients who perform self-injection of Praluent® at home must visit the study site at least every 4 weeks, and at Week 0, Week 4, Week 12, Week 14, Week 24 and Week 36.

1.2 STUDY FLOW CHART

	Treatment																		EOT
Week (W)	W0	W2	W4	W6	W8	W10	W12	W14	W16	W18	W20	W22	W24	W26	W28	W30	W32	W34	W36
Day (D)	D1	D15	D29	D43	D57	D71	D85	D99	D113	D127	D141	D155	D169	D183	D197	D211	D225	D239	D253
Visit Number	1[a]		2				3						4						5
Visit Window (D)			±7				±7						±7						±14
Design																			
Informed consent	X[b]																		
On-site visit	X		X				X						X						X
Inclusion criteria/ Exclusion criteria	X																		
Patient demography	X																		
Medical / family / surgical history, alcohol habits, smoking habits	X[c]																		
Prior medication history	X																		
Physical examination	X																		
Body weight	X						X						X						X
Height	X																		
Randomization	X																		
Registration center contact	X																		X
Treatment																			
Praluent® administration[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	(X)[d]
Praluent® administration window (D)		±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	
Phone-call interview[e]					X			X		X				X		X			
Compliance check (IMP/NIMP)[e]	X		X		X		X		X		X		X		X		X		X
Vital signs																			
Heart rate	X		X				X						X						X
Blood pressure (sitting position)	X		X				X						X						X
Efficacy																			
IVUS imaging	X[f]																		X[g]
Transfer IVUS imaging data to central reading laboratory	X																		X

	Treatment																		EOT
Week (W)	W0	W2	W4	W6	W8	W10	W12	W14	W16	W18	W20	W22	W24	W26	W28	W30	W32	W34	W36
Day (D)	D1	D15	D29	D43	D57	D71	D85	D99	D113	D127	D141	D155	D169	D183	D197	D211	D225	D239	D253
Visit Number	1[a]		2				3						4						5
Visit Window (D)			±7				±7						±7						±14
Safety																			
AE/SAE recording including CV events	X		X		X		X		X		X		X		X		X		X
Laboratory testing - Efficacy																			
TC, calculated LDL-C, HDL-C, TG, non-HDL-C	X[h]		X				X						X						X
Apo B, Apo A-1, Apo B/Apo A-1 ratio, Lp(a)	X																		X
Laboratory testing - Safety[j]																			
Hematology and chemistry[j]	X		X				X						X						X
Hepatitis B virus core antibody[n]	X																		
Hepatitis C virus antibody	X																		X
Serum pregnancy test[k]	X																		
Urine pregnancy test[k]	X																		X
Laboratory testing - Others																			
HbA1c	X						X						X						X
hs-CRP	X																		X
Quality of Life Variables																			
EQ-5D patient questionnaire[l]	X		X				X						X						X

Abbreviations: AE, adverse event; Apo A-1, apolipoprotein A-1, Apo B, apolipoprotein B; CV, cardiovascular; D, day(s); EOT, end of treatment; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high sensitivity C-reactive protein; IMP, investigational medicinal product; IVUS, intravascular ultrasound; LDL-C, low-density lipoprotein cholesterol; NIMP, noninvestigational medicinal product; non-HDL-C, non-high-density lipoprotein cholesterol; SAE, serious adverse event; TC, total cholesterol; TG, triglyceride; W, week.

a   Randomization visit (Visit 1) is conducted after the assessment of candidate patients for inclusion/exclusion criteria.

b   Informed consent is obtained between ACS diagnosis and Visit 1.

c   Patient medical history includes lipid parameters (i.e., LDL-C used for patient selection) used for the study eligibility and HbA1c.

d   Praluent® is administered at Week 36 if the patient cannot complete the evaluation IVUS by Week 36. It should be noted that the final lipid values will be recorded at Week 36 (V5) as EOT.

e   Phone call interview will be carried out only for the patients assigned to the SoC arm. Review of IMP / NIMP administration status includes the compliance with diet therapy recommended by the Japan Atherosclerosis Society Guideline or equivalent.

f   Baseline IVUS study will be performed as following standard protocol in each site. Baseline IVUS imaging data will be transferred to the central reading laboratory.

g   Evaluation IVUS is carried out on V5 / Week 36 ± 14 days (between Week 34 and Week 38). The IVUS imaging data will be transferred immediately after the evaluation IVUS is obtained.

h   Lipid parameters will be measured at the study sites and will be used for the patient selection before randomization. The lipid parameters will be also recorded as part of the patient demography.

   i   Laboratory testing data for safety assessment except hepatitis B virus core antibody and hepatitis C virus antibody will be collected from each study site.

   j   Hematology laboratory testing includes red blood cell count, hematocrit, hemoglobin, white blood cell count with differential count, and platelet count. Chemistry laboratory testing includes glucose, sodium, potassium, chloride, creatinine, uric acid, lactate dehydrogenase (LDH), total protein, albumin, gamma-glutamyl transpeptidase (γGT), creatine phosphokinase (CPK), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and total bilirubin.

   k   Women of childbearing potential (WOCBP) only.

   l   EQ-5D patient questionnaire interview will be carried out for all patients on study treatment. For prematurely (permanently) discontinued patients, the last questionnaire interview will be carried out at the EOT visit defined in the protocol (see Section 10.3).

   m Patients can choose self-injection of Praluent® at home any time, if they wish self-injection at home and the Investigator/sub-Investigator considers it feasible.

        Before starting self-injection at home, the Investigator/sub-Investigator must explain to the patients using the operation procedure for administration of IMP. If necessary, patients can use the training kits.

        Patients are allowed to perform self-injection at home if they successfully perform the correct self-injection of Praluent® under the direct supervision of site medical staff at the study site once, and the Investigator/sub-Investigator considers that they can perform self-injection at home correctly. They can use tools to assist.

        Regardless of the timing when the self-injection is started, patients must visit the study site at least every 4 weeks, and at Week 0, Week 4, Week 12, Week 14, Week 24 and Week 36.

        Patients must record self-injection at home in the diary. At each visit, they must bring the diary, and the site medical staff must check their records. If self-injection at home is performed, IMPs will be provided for only number of times of self-injections at home until the next visit. Patients must return used and unused IMPs to the site medical staff at the next visit.

        Patients can discontinue self-injection at home any time. The Investigator/sub-Investigator must have patients discontinue self-injection at home, if the Investigator/sub-Investigator judges that the patients are not able to perform self-injection at home correctly. Patients who discontinue self-injection at home can have injections performed by medical staff at the study site.

   n   Hepatitis B virus DNA will be measured promptly if hepatitis B virus total core antibody comes back positive.

2 TABLE OF CONTENTS

(electronic 1.0)

2.1   LIST OF TABLES

2.2   LIST OF FIGURES

(electronic 1.0)

3   LIST OF ABBREVIATIONS

ACS: Acute coronary syndrome
AE: Adverse event
AESI: Adverse event of special interest
ALP: Alkaline phosphatase
ALT: Alanine aminotransferase
ANCOVA: Analysis of covariance
Apo A-1:   Apolipoprotein A-1
Apo B: Apolipoprotein B
AST: Aspartate aminotransferase
BMS: Bare metal stent
CEC: Clinical Event Committee
CHD: Coronary heart disease
CPK: Creatine phosphokinase
CRF: Case report form
CRP: C-reactive protein
CV: Cardiovascular
DBP: Diastolic blood pressure
DES: Drug eluting stent
e-CRF: Electronic Case Report Form
EEM: External elastic membrane
EOT: End of treatment
FH: Familial hypercholesterolemia
HbA1c: Hemoglobin A1c
HDL-C: High-density lipoprotein cholesterol
heFH: Heterozygous familial hypercholesterolemia
HLGT: High level group term
HLT: High level term
HRT: Hormonal replacement therapy
hs-CRP: High sensitive C-reactive protein
IEC: Independent ethics committee
IMP: Investigational medicinal product
IRB: Institutional review board
IVUS: Intravascular ultrasound
JAS: Japan Atherosclerosis Society
LDH: Lactate dehydrogenase
LDL-C: Low-density lipoprotein cholesterol
LDL-R: Low-density lipoprotein receptor
LLT: Low level term
LMT: Lipid modifying therapy
Lp(a):   Lipoprotein (a)
LS: Least square

(electronic 1.0)

MedDRA:	Medical dictionary for regulatory activities
MI:	Myocardial infarction
mITT:	Modified intent-to-treat
MMRM:	Mixed-effect model with repeated measures
NIMP:	Noninvestigational medicinal product
non-FH:	Nonfamilial hypercholesterolemia
non-HDL-C:	Non-high-density lipoprotein cholesterol
NSTEMI:	Non ST-elevation myocardial infarction
OCT:	Optical coherence tomography
PAV:	Percent atheroma volume
PCI:	Percutaneous coronary intervention
PCSA:	Potentially clinically significant abnormality
PCSK9:	Proprotein convertase subtilisin kexin type 9
PT:	Preferred term
Q2W:	Every 2 weeks
SAE:	Serious adverse event
SAP:	Statistical analysis plan
SBP:	Systolic blood pressure
SC:	Steering Committee
SE:	Standard error
SoC:	Standard of care
SOC:	System organ class
STEMI:	ST-elevation myocardial infarction
TAV:	Total atheroma volume
TC:	Total cholesterol
TEAE:	Treatment-emergent adverse event
TG:	Triglyceride
ULN:	Upper limit of normal range
WOCBP:	Women of childbearing potential
γGT:	Gamma-glutamyl transpeptidase

4 INTRODUCTION AND RATIONALE

Alirocumab is a fully human monoclonal antibody that binds proprotein convertase subtilisin kexin type 9 (PCSK9).

Alirocumab has been approved for manufacturing and sales in Japan. The approved indications, and dosage and administration are as follows:

- Drug indications: Familial hypercholesterolemia and hypercholesterolemia nevertheless it is limited to cases at high cardiovascular (CV) risk and with inadequately controlled despite of taking HMG-CoA reductase inhibitors.

- Dosage and Administration: The usual adult dosage is 75 mg of alirocumab (genetical recombination) administered subcutaneously once every 2 weeks (Q2W). In case of an insufficient response, the dosage can be increased to 150 mg.

Detailed information of alirocumab is described in the latest version of Package Insert.

Alirocumab is also referred to as SAR236553/REGN727. However, for this study, ODYSSEY J-IVUS (ALIROL08069), it will be referred to as Praluent®, since alirocumab has already been approved in Japan.

Background on patient populations:

Patients with recent acute coronary syndrome (ACS) are at very high risk for suffering recurrent coronary events. In approximately 10% of patients with ACS, CV death, recurrent myocardial infarction (MI), or stroke, occur within 1 year (3). Driven by the results of large clinical trials, early intensive statin therapy has become endorsed as a treatment recommendation (4, 5) for patients with ACS (6) to prevent the recurrent events. The use of high-dose statins has been largely demonstrated to be safe and well tolerated in Western countries (7). The strong and direct association between achieved low-density lipoprotein cholesterol (LDL-C) levels with statins, HMG-CoA reductase inhibitors, and the risk of coronary heart disease (CHD), and CHD risk reduction by lowering LDL-C level with statins has been reported. In recognition of the benefits of intensive lipid-lowering therapy, the current European guidelines and the Adult Treatment Panel (ATP) III guidelines recommend the lowering of LDL-C levels to either below 70 mg/dL or to at least achieve a 50% reduction from baseline levels in patients at high CV risk (8, 9, 10).

IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) demonstrated an incremental benefit of adding ezetimibe to standard statin therapy to reduce CV events (11). The benefit of further LDL-C reduction with alirocumab on top of statin therapy on patient CV outcomes is expected to be demonstrated in the ongoing ODYSSEY Outcomes trial (EFC11570). On the other hand epidemiological studies show lower CV event rates and higher cerebrovascular event rates in the Japanese population as compared to Western populations. In the REACH (Reduction of Atherothrombosis for Continued Health) registry, a correlation exists between being Japanese and lower CV risk at levels that are similar to that of statin use and CV

risk reduction in Western populations (12), which suggests the need to take the differences in ethnicity into consideration. Thus, there is a need to conduct an outcome or outcome surrogate marker study targeting the Japanese population to demonstrate the benefit of intensive LDL-C lowering in Japanese population.

Introduction to intravascular ultrasound (IVUS) coronary plaque measurements:

Advances in arterial wall imaging have enhanced the ability to directly visualize atherosclerotic plaque. While angiography has been widely used to quantify the extent of obstructive disease both in clinical practice and trials that evaluated anti-atherosclerotic therapies, it does not image the artery wall, the site in which plaque accumulates. Accordingly, use of wall-based imaging approaches provides the potential for more precise assessments of atherosclerotic plaque. Intravascular ultrasound (IVUS) generates high resolution images of the full thickness of the artery wall and as a result currently provides the most accurate quantitation of plaque burden (13). Serial IVUS imaging has been employed to evaluate the effect of LDL-C lowering on plaque regression (14, 15, 16). Many studies have demonstrated the effectiveness of intensive statin therapies. The Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin (SATURN) compared the effects of statin on the progression of coronary atherosclerosis of the highest doses of atorvastatin with those of rosuvastatin (17, 18). The rosuvastatin group achieved lower LDL-C levels (62.6 vs. 70.2 mg/dL) and higher high-density lipoprotein cholesterol (HDL-C) levels (50.4 vs. 48.6 mg/dL) compared with the atorvastatin group. The change in percent atheroma volume as a primary endpoint decreased in both groups consistent with plaque regression, the difference between groups not reaching statistical significance. In contrast, the secondary endpoint, change in total atheroma volume (TAV), demonstrated greater regression in the rosuvastatin treated patients. Approximately two-thirds of patients in the study demonstrated regression, reinforcing the hypothesis that aggressively lowering LDL-C to levels of 70 mg/dL and below offered significant plaque reduction. Furthermore, a meta-analysis of 6 clinical IVUS trials demonstrated a direct relationship between the burden of coronary atherosclerosis, its progression, and adverse CV events. These data support the use of atherosclerosis imaging with IVUS in the evaluation of novel anti-atherosclerotic therapies (19).

Japanese cardiologists use IVUS imaging as part of their standard coronary intervention throughout the country and many IVUS trials have been conducted (1, 18, 20, 21). This universal use of IVUS is a unique to Japanese practice, and this condition is suitable to efficiently conduct a nation-wide study using IVUS imaging. Most recently PRECISE-IVUS (Plaque Regression with Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by Intravascular Ultrasound) trial demonstrated greater plaque regression by combination therapy of ezetimibe and atorvastatin compared to atorvastatin monotherapy in patients with CHD (2).

The SATURN and the PRECISE-IVUS studies showed greater plaque regression in ACS patients when compared with non-ACS patients. Since it is suggested that patients with ACS have high initial clinical risk but their disease substrate is likely to be improved, they are considered as the patient population who can get the greatest benefit from strong lipid lowering therapy (2, 22).

Introduction to PCSK9:

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 (23, 24). Once PCSK9 is secreted into plasma, it directly binds to the LDL-R and promotes its degradation. The increased degradation of LDL-Rs leads to a reduced LDL-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 protein in the liver (25, 26). 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 developing cardiovascular disease (27, 28). One report from the Japanese population found the individual heterozygous for W428X mutation of PCSK9 had 70.4 mg/dL of plasma LDL-C, corresponding to a 44% decrease from the average LDL-C level (126.8 mg/dL) in the untreated population. This observation is consistent with the finding that the two African-American nonsense mutations were associated with a 40% reduction in plasma LDL-C levels (29). 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 (30).

Introduction to Alirocumab:

Alirocumab binds with high affinity and specificity to PCSK9, which, in turn, can no longer bind LDL-Rs. By inhibiting the binding of PCSK9 to LDL-Rs, alirocumab prevents the PCSK9-induced microsomal LDL-R degradation within the hepatocytes, thus increases the density of LDL-Rs on hepatocytes, thereby lowering LDL-C.

Results from phase 1 and 2 overseas studies have demonstrated that treatment with alirocumab has a significant LDL-C lowering effect in patients with LDL-C ≥100 mg/dL (2.59 mmol/L) who had either nonfamilial hypercholesterolemia (non-FH) (administered alone or in combination with a statin) or heterozygous familial hypercholesterolemia (heFH) (administered in combination with a statin, with or without ezetimibe). Alirocumab was generally well tolerated. LDL-C reduction was associated with consistent reduction in total cholesterol (TC), apolipoprotein B (Apo B), non-high-density lipoprotein-cholesterol (non-HDL-C) and Apo B/apolipoprotein A-1 (Apo A-1) ratio. A trend for an increase in HDL-C and for a decrease in lipoprotein (a) (Lp(a)) was also seen. Results for triglycerides (TGs) were not conclusive due to very high variability and relatively small sample sizes. A dose-finding phase 2 study (DFI12361) conducted in Japanese patients showed similar results observed in the oversea studies.

Japanese Phase 3 study (EFC13672):

In EFC13672, administration of alirocumab Q2W for 52 weeks as an add-on to stable statin therapy with or without other lipid modifying therapies (LMTs) was investigated in 41 patients with heFH and 175 patients with hypercholesterolemia who have high CV risk, who had not achieved target LDL-C level on statin therapy. An up-titration scheme was applied, with alirocumab 75 mg Q2W as the initiation dose with up-titration to 150 mg Q2W from Week 12, if LDL-C level at Week 8 is higher than the target level. Dose/dose regimens in the Japanese phase 3 study were selected based on the results obtained in the Japanese phase 2 study (DFI12361).

EFC13672 enrolled patients with heFH with LDL-C ≥100 mg/dL (2.59 mmol/L) or patients with non-FH with LDL-C ≥100 mg/dL (2.59 mmol/L) with a history of documented CHD, or patients with non-FH with LDL-C ≥120 mg/dL and categorized in primary prevention category III. These cut-off LDL-C levels were aligned with the LDL-C target level recommended in the Japan Atherosclerosis Society (JAS) guidelines (31). In the JAS guidelines, the treatment goal for the secondary prevention is set as <100 mg/dL. Since heFH is a high risk disease for the development of cardiovascular disease, it can be considered as equivalent to the secondary prevention. The treatment goal for LDL-C in heFH is set as <100 mg/dL as well. When the goal cannot be achieved in heFH cases, 50% or more reduction of LDL-C from baseline can be used as the alternative goal. For the patients who are primary prevention category III, the treatment goal for LDL-C is established as <120 mg/dL. The primary prevention category III is defined as follows:

- Non-FH patients who have any of 1) diabetes, 2) chronic kidney disease (CKD), 3) non-cardiogenic ischemic stroke, or 4) peripheral artery disease (PAD)

- A 10-year fatal CHD risk SCORE calculated using NIPPON DATA 80 ≥2%

- A 10-year fatal CHD risk SCORE calculated using NIPPON DATA 80 ≥0.5% and <2%, and have 1 or more of the following criteria

  - Hypo high-density lipoprotein cholesterolemia (<40 mg/dL)

  - Family history of premature coronary artery disease (first-degree relative and male: <55-year-old, female: <65-year-old)

  - Impaired glucose tolerance (defined as a fasting blood glucose [FBG] <126 mg/dL [7.0 mmol/L], and a 2-hour post glucose challenge value ≥140 mg/dL [7.8 mmol/L] and <200 mg/dL [11.1 mmol/L] (oral glucose tolerance test [OGTT]).

Efficacy (EFC13672):

In EFC13672, alirocumab or placebo were administered Q2W for 52 weeks to 216 patients with hypercholesterolemia (including 41 patients with heFH) who were under treatment with statin and had not achieved the target LDL-C level. The administration was initiated with 75 mg and dose was up-titrated to 150 mg at Week 12 in the patients who did not achieve the target LDL-C level at Week 8. Among 140 patients who received alirocumab at Week 12 in the alirocumab group, 2 patients received up-titration. The least square (LS) mean differences versus placebo in the percent change in LDL-C from baseline to Week 12 and Week 24 were -61.5% and -64.1% respectively, showing that the statistically significant decrease was observed at Week 24 (primary

efficacy endpoint, p<0.0001). The effect persisted up to Week 52 (LS mean present change from baseline in the alirocumab group, -62.5%).

Safety (EFC13672):

Alirocumab was well tolerated throughout the treatment period. Treatment-emergent adverse events (TEAEs) were reported in 90.9% of patients in the alirocumab group and 83.3% of patients in the placebo group. Ten patients (7.0%) in the alirocumab group and 9 patients (12.5%) in the placebo group experienced at least 1 treatment-emergent serious adverse event (SAE). There were no deaths reported. Seven patients (4.9%) in the alirocumab group and 4 patients (5.6%) in the placebo group experienced at least 1 TEAE leading to permanent investigational medicinal product (IMP) discontinuation.

Overall, 29 patients (20.3%) in the alirocumab group and 8 patients (11.1%) in the placebo group reported at least 1 TEAE that was considered by the Investigator to be related to the IMP. The most frequently reported TEAE considered to be related to the IMP was injection site reaction (18 patients [12.6%] in the alirocumab group and 3 patients [4.2%] in the placebo group). All the remaining TEAEs considered to be related to the IMP were reported in a single patient each.

Further details on alirocumab are provided in the Package Insert of Praluent®.

Rationale for protocol design in this study:

The objective of the present study is to evaluate the ability of alirocumab to progress/regress coronary atherosclerotic plaque in patients who experienced an ACS event and despite statin therapy failing to reach the goals as defined in the guidelines for these high risk patients of recurrence. As a phase 4 study, the dose regimen in this study has to be in line with the approved regimen in Japan, which is starting Praluent® at 75 mg Q2W with up-titration to 150 mg Q2W if patients do not reach their target LDL-C level.

For this randomized, open-label, blinded IVUS analysis, multicenter study, it is estimated that approximately 200 patients will be enrolled with a treatment period of 9 months and a total duration of 9 to 10 months. Despite stable statin therapy, hypercholesterolemia patients who suffer ACS events and whose LDL-C ≥100 mg/dL will be enrolled this study. Or, if patients are not on any statin therapy at ACS onset, either atorvastatin 10 mg/day or rosuvastatin 5 mg/day is started, and the patients whose LDL-C is not adequately controlled with statin (in principle, LDL-C target level ≥100 mg/dL, but this may not apply if the responsible physician considers the LDL-C level inadequate on statin. Patients who have LDL-C <70 mg/dL cannot be enrolled) at 2 to 4 weeks after the ACS diagnosis will be enrolled this study. Within 4 weeks of the index ACS diagnosis, patients will be randomized to either alirocumab arm (atorvastatin ≥10 mg/day or rosuvastatin ≥5 mg/day plus Praluent® 75 mg Q2W with/without other LMTs) or standard of care (SoC) arm (atorvastatin ≥10 mg/day or rosuvastatin ≥5 mg/day with/without other LMTs). At Week 12, if LDL-C does not reach <100 mg/dL, Praluent® will be up-titrated to 150 mg Q2W in the alirocumab arm, and dose up of atorvastatin or rosuvastatin or adding other LMTs will be considered in the SoC arm.

Treatment duration of 9 months was designed based on previous Japanese studies including ESTABLISH (18), JAPAN-ACS (20) and PRECISE-IVUS (2), each study duration was 6 months, 8-12 months and 9-12 months, respectively. This is based on Japanese standard procedure for follow-up to coronary angiography 8-10 months after the ACS onset. Also, keeping 8-10 months study duration makes it feasible to align with standard Japanese IVUS studies. If the study goes beyond this standard duration, then a very high drop-out rate is expected. Compared to the studies done in Cleveland Clinic, the study duration in Japan are shorter and yet still sufficiently proved the benefit of LDL-C reduction on disease progression. This may be because differences in target population (ACS vs. non-ACS) and target vessel (culprit vessel vs. non-culprit vessel). It is also noted that diabetes population is also well known high risk population and studies suggest more benefit of intensive LDL-C lowering in diabetes population compared to the non-diabetes population (1, 32, 33).

The proposed primary efficacy endpoint is the effect of alirocumab arm compared to SoC arm on the percent change in normalized TAV measured by IVUS. Considering the differences in IVUS study methods of Japan with the Cleveland Clinic, sample size is more appropriately calculated based on Japanese IVUS study results. Percent change in TAV has been predominantly used as a primary endpoint in Japanese IVUS studies. Based on the results in ZEUS and PRECISE-IVUS studies, it is assumed that difference in percent change in normalized TAV from baseline between alirocumab arm and SoC arm is 8%, the common standard deviation is 15% (1, 2). Considering that absolute change in percent atheroma volume (PAV) has been employed in most US IVUS studies as a primary endpoint, comparison of change in PAV between arms will be analyzed as a key secondary endpoint (34).

Based on previous Japanese IVUS studies results, IVUS parameters including primary efficacy endpoint, and percent change in TAV, will be assessed at Week 36 since this is considered sufficient to provide efficacy information of alirocumab on atherosclerosis disease progression/regression in this study (1, 2, 18, 20, 21). This treatment duration should also provide a sufficient duration of exposure to appreciate tolerability and safety profiles for alirocumab in the ACS setting. The effect of alirocumab on lipid parameters will also be assessed at Week 36 in this study.

5 STUDY OBJECTIVES

5.1 PRIMARY

To compare the effect of Praluent® with SoC on coronary atheroma progression (percent change in normalized TAV) after 9 months of treatment in patients who had ACS within 4 weeks prior to randomization, with hypercholesterolemia treated with any statin.

5.2 SECONDARY

- To compare the effect of Praluent® with SoC on secondary endpoints including absolute change in PAV and normalized TAV after 9 months of treatment.

- To evaluate the effect of Praluent® on LDL-C, Apo B, TGs, non-HDL-C and Lp(a) after 9 months treatment.

- To evaluate the safety of Praluent® including the occurrence of CV events (CHD death, non-fatal MI, fatal and non-fatal ischemic stroke, unstable angina requiring hospitalization) throughout the study.

6   STUDY DESIGN

This is a phase 4, open-label, 1:1 randomized, blinded IVUS analysis, parallel group, multicenter study to investigate the effect of alirocumab on coronary atheroma volume in Japanese patients with hypercholesterolemia, who have recently suffered from ACS and are failing to reach the recommended LDL-C levels as defined by JAS guidelines for very high CV disease risk in spite of stable statin therapy. Randomization will be stratified by 'on statin therapy' or 'not on statin' therapy at the time of ACS onset. As a phase 4 study, the dose regimen is in line with the approved regimen in Japan; starting dose is 75 mg Q2W with up-titration to 150 mg Q2W if patients do not reach their target LDL-C level.

Approximately 200 patients from approximately 40 study sites will be enrolled and randomized with a treatment period of 9 months. Patients who suffer ACS events despite stable statin therapy and whose LDL-C is ≥100 mg/dL will be enrolled. If patients are not on any statin therapy at the time of ACS onset, they will start either atorvastatin 10 mg/day or rosuvastatin 5 mg/day immediately after the ACS diagnosis, and the patients whose LDL-C is not adequately controlled with statin (in principle, LDL-C target level ≥100 mg/dL, but this may not apply if the responsible physician considers LDL-C level inadequate on statin. Patients who have LDL-C <70 mg/dL cannot be enrolled) at 2 to 4 weeks after the ACS diagnosis will be also enrolled.

6.1   DESCRIPTION OF THE STUDY

The study consists of a 36-week open-label treatment period started within 4 weeks after ACS diagnosis and appropriate percutaneous coronary intervention (PCI) with bare metal stent (BMS) or drug eluting stent (DES) placement and includes post-treatment IVUS imaging (evaluation IVUS imaging, Week 36 [end of treatment (EOT)] ± 2 weeks). The patient who did not receive PCI but has undergone coronary artery bypass graft surgery or received medical therapy only can be included if the analyzable IVUS imaging is obtained.

A 36-week open label treatment period: Patients will be randomized to either alirocumab arm or SoC arm. Randomization will be stratified by on statin therapy or not on statin therapy at the ACS onset. While the last Praluent® administration will be performed at Week 34, evaluation IVUS imaging can be carried out between Week 34 and Week 38 (Week 36 ± 2 weeks) considering potential scheduling difficulty. The Investigator/sub-Investigator is to make their best effort to schedule the evaluation IVUS imaging within this time period. If a patient cannot undergo evaluation IVUS by Week 36, the last Praluent® administration will be performed at Week 36 and the Investigator/sub-Investigator will make their best effort to carry out evaluation IVUS before Week 38 while maintaining sufficient alirocumab effect at the evaluation IVUS imaging (see Section 1.2). Patients in the SoC arm will continue the study treatment until evaluation IVUS.

- *Alirocumab arm*: Praluent® 75 mg Q2W on top of statin therapy (atorvastatin ≥10 mg/day or rosuvastatin ≥5 mg/day within the range of statin doses approved by the Health Authority) will be administered.

Note: At Week 14, patients whose LDL-C level measured at Week 12 by central laboratory remains ≥100 mg/dL in spite of 75 mg Praluent® administration, will receive Praluent® dose up-titrated to 150 mg Q2W.

Note: Patients can choose self-injection of Praluent® (alirocumab) at home any time, if they wish self-injection at home and the Investigator/sub-Investigator considers it feasible.

Before starting self-injection at home, the Investigator/sub-Investigator must explain to the patients using the operation procedure for administration of IMP. If necessary, patients can use the training kits. Patients are allowed to perform self-injection at home if they successfully perform the correct self-injection of Praluent® under direct supervision of site medical staff at the study site once, and the Investigator/sub-Investigator considers that they can perform self-injection at home correctly. They can use tools to assist.

Regardless of the timing when the self-injection is started, patients must visit the study site at least every 4 weeks, and at Week 0, Week 4, Week 12, Week 14, Week 24 and Week 36.

Patients must record self-injection at home in the diary. At each visit, they must bring the diary, and the site medical staff must check their records.

If self-injection at home is performed, IMPs will be provided for only number of times of self-injections at home until the next visit. Patients must return used and unused IMPs to the site medical staff at the next visit.

Patients can discontinue self-injection at home any time. The Investigator/sub-Investigator must have patients discontinue self-injection at home, if the Investigator/sub-Investigator judges that the patients are not able to perform self-injection at home correctly. Patients who discontinue self-injection at home can have injections performed by medical staff at the study site.

- *SoC arm*: Statin (atorvastatin ≥10 mg/day or rosuvastatin ≥ 5 mg/day) and non-statin LMTs will be continued at the same doses determined after ACS diagnosis and PCI unless modifications are considered necessary by Investigator/sub-Investigator. The target LDL-C level is set as <100 mg/dL.

Note: 1) Stable dose statin therapy (atorvastatin ≥10 mg/day or rosuvastatin ≥5 mg/day within the range of statin doses approved by the Health Authority) will be administered, and the dose will be adjusted to achieve the LDL-C target level <100 mg/dL; 2) Concomitant non-statin LMTs will be considered if LDL-C target level <100 mg/dL cannot be achieved with statin monotherapy. Adjustment of LMTs is to be performed based on, but not limited to, the above rule.

The evaluation IVUS imaging will be performed at the EOT (Week 36 ± 2 weeks). The detailed instructions of IVUS imaging procedure and the image data processing are described in the specific manual. This manual also includes detailed IVUS imaging procedures and image processing at the initial IVUS imaging performed at the time of PCI for ACS.

Note: If the study site is able to perform optical coherence tomography (OCT) at the time of the IVUS imaging, OCT will be performed as a substudy. The OCT will be performed following the OCT substudy protocol.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

The study consists of a 36-week open-label treatment period including the evaluation IVUS imaging (Week 36 ± 2 weeks) starting within 4 weeks after ACS diagnosis and appropriate PCI. The evaluation IVUS imaging is allowed to be performed between Week 34 and Week 38 depending on the Investigators/sub-Investigators' decision (36 weeks [EOT] ± 2 weeks). Therefore, the study period per patient will be up to 38 weeks.

Patients who experience ongoing SAE or 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. The end of study per patient is the last protocol planned visit or the resolution/stabilization of all SAEs or AESIs, whichever comes last.

6.2.2 Determination of end of clinical trial (all patients)

The end of study is defined as being the last patient last on-site visit as scheduled by the protocol (including visit for the evaluation IVUS imaging), or the resolution/stabilization of all SAEs and AESIs, whichever comes last.

6.3 INTERIM ANALYSIS

No interim analysis is planned.

6.4 STUDY COMMITTEES

Steering Committee:

Steering Committee (SC) provides Sponsor and Investigators scientific and strategic advices and recommendations about the study design, execution, data analysis, and publication of results.

Clinical Event Committee:

Clinical Event Committee (CEC) will be responsible for defining, validating, and classifying pre-specified CV events (non-fatal myocardial infarction, hospitalization for unstable angina, heart failure requiring hospitalization, non-fatal ischemic stroke, coronary revascularization, etc.) and other potential CV events such as ventricular arrhythmias requiring hospitalization, as well as validating the classification of the cause of all deaths in a blinded fashion. All events for adjudication will be defined in the CEC charter.

7   SELECTION OF PATIENTS

7.1   INCLUSION CRITERIA

I 01.   Patients hospitalized for ACS (ST-elevation myocardial infarction [STEMI], non ST-elevation myocardial infarction [NSTEMI], unstable angina)

Definition of ACS:

A) ST-elevation myocardial infarction (STEMI)
Patients meet all of the following items:

1. A chest symptom (chest pain, shortness of breath, etc.) suggestive of ischemia.

2. At least 1 mm of ST elevation in two or more consecutive chest leads or limb leads on ECG or a new left bundle branch block.

3. An elevation in blood test value (positive troponin T or troponin I, or creatine phosphokinase (CPK) $\geq$2 times the upper limit of normal) suggestive of myocardial necrosis.

B) Non-ST-elevation myocardial infarction (NSTEMI)
Patients meet all of the following items:

1. A chest symptom (chest pain, shortness of breath, etc.) suggestive of ischemia.

2. ST depression >0.5 mm, negative T-wave ($\geq$3 mm: dynamic T-wave inversion), or transient ST elevation $\leq$0.5 mm.

3. An elevation in blood test value (positive troponin T or troponin I, or CPK $\geq$2 times the upper limit of normal) suggestive of myocardial necrosis.

C) Unstable angina
The definition of unstable angina pectoris requires '1' and either of items '2 - 6' described below:

1. A chest symptom (chest pain, shortness of breath, etc.) suggestive of ischemia.

2. ST depression $\geq$0.5 mm or T-wave negative conversion $\geq$3 mm.

3. An elevation in troponin T.

4. Confirmation of the coronary lesion responsible for acute coronary syndrome by diagnostic imaging (coronary angiography, multiple detector computed tomography, etc.).

5. New decrease in wall motion by echocardiogram.

6. Reversible decrease in myocardial blood perfusion induced by drug, exercise, or thallium scintigraphy.

I 02.   LDL-C ≥100 mg/dL at ACS diagnosis (either by Friedewald method or direct methods measured at each study site):

  a) Patients who have already been on any statin therapy at ACS onset. If the statin is not atorvastatin or rosuvastatin, statin will be changed to either atorvastatin ≥10 mg/day or rosuvastatin ≥5 mg/day immediately after the ACS diagnosis based on Investigators' medical judgment.

  b) If patients have not been on any statin therapy at ACS onset, either atorvastatin 10 mg/day or rosuvastatin 5 mg/day is started immediately after the ACS diagnosis, and LDL-C is not adequately controlled with statin at 2 to 4 weeks after the ACS diagnosis (in principle, LDL-C target level ≥100 mg/dL, but this may not apply if the responsible physician considers the LDL-C level inadequate on statin. Patients who have LDL-C <70 mg/dL cannot be enrolled).

I 03.   Patients who has stenosis of at least >50% on coronary angiography within 1 week after the ACS onset, and has analyzable coronary IVUS image. The evaluated segment of IVUS is a segment where a physician considers the IVUS imaging is possible (regardless of culprit vessels or not culprit vessels) other than the culprit lesions.

I 04.   Patients aged ≥20 years old at ACS diagnosis.

I 05.   Patients who meet any of the following conditions.

  - Negative hepatitis B virus surface antigen, negative total hepatitis B virus core antibody, and negative hepatitis C virus antibody.

  - Negative hepatitis B virus surface antigen, positive total hepatitis B virus core antibody, negative hepatitis B virus DNA and negative hepatitis C virus antibody.

I 06.   Written informed consent.

7.2   EXCLUSION CRITERIA

Patients who will have met all the above inclusion criteria listed in Section 7.1 will be screened for the following exclusion criteria which are described in the following 3 subsections:

7.2.1 Exclusion criteria related to study methodology

E 01.   Patients who have been previously treated with at least one dose of any anti-PCSK9 monoclonal antibody.

E 02.   Uncontrolled hypertension (multiple reading with systolic blood pressure [SBP] >180 mmHg or diastolic blood pressure [DBP] >110 mmHg) between the ACS diagnosis and randomization visit.

E 03.   Known history of hemorrhagic stroke.

E 04.   Currently under treatment with anticancer drug.

E 05.   Patients on LDL apheresis.

E 06.   Conditions/situations such as:

- Any clinically significant abnormality identified that in the judgement of the Investigator or any sub-Investigator would preclude safe completion of the study or constrain endpoint assessment such as major systemic diseases, patients with short life expectancy.

- Considered by the Investigator or any sub-Investigator as inappropriate for this study for any reason, e.g.:

  - Those deemed unable to meet specific protocol requirements, such as scheduled visits.

  - Investigator or any sub-Investigator, pharmacist, study coordinator, other study staff or relative thereof directly involved in the conduct of the protocol, etc.

  - Presence of any other condition (e.g., geographic, social, etc.) actual or anticipated, that the Investigator or sub-Investigator feels would restrict or limit the patient's participation for the duration of the study

E 07.   Laboratory findings measured before the randomization visit within 4 weeks after the ACS diagnosis.

- Positive serum or urine pregnancy test in women of childbearing potential.

7.2.2   Exclusion criteria related to background therapies

E 08.   Any contraindications or warning/precaution of use to statin or other LMTs as displayed in the respective Package Insert for these treatments.

7.2.3   Exclusion criteria related to the current knowledge of Praluent®

E 09.   Any contraindications to Praluent® as displayed in the respective Package Insert for these treatments.

E 10.   Known hypersensitivity to monoclonal antibody or any component of the drug product used in the current study.

E 11.   Pregnant or breast-feeding women.

E 12.   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 serum pregnancy test before randomization visit measured at each study site and urine pregnancy test during the pre-treatment period. They must use an effective contraceptive method throughout the entire duration of the study treatment and for 10 weeks following the last injection of study treatment and agree to repeat urine pregnancy test at designated visits. The applied methods of contraception have to meet the criteria for a highly effective method of birth control according to the 'Note for guidance on non-clinical safety studies for the conduct of human clinical

trials for pharmaceuticals (CPMP/ICH/286/95'). Postmenopausal women must be amenorrheic for at least 12 months.

7.2.4 Additional exclusion criteria before randomization

E 13. Patient who has withdrawn consent before enrollment/randomization (starting from signed informed consent form).

8   STUDY TREATMENTS

8.1   INVESTIGATIONAL MEDICINAL PRODUCT(S): SUBCUTANEOUS INJECTION

Formulation

- Alirocumab, an active ingredient of Praluent®, is a fully human monoclonal antibody that binds PCSK9.

- Praluent® will be supplied in a 1 mL autoinjector as an injectable drug with pH 6.0, containing histidine, polisorbate 20 and sucrose with alirocumab concentration of 75 mg/mL or 150 mg/mL.

- The IMP will be supplied by the Sponsor to study sites during the study period. Administration of IMP will be performed at the study sites or by self-injection at home.

Route of administration

- Subcutaneous administration to the abdomen, thighs, or outer area of the upper arms.

Dose regimen

- 75 mg Q2W with up-titration to 150 mg Q2W if LDL-C <100 mg/dL is not achieved.

8.2   NONINVESTIGATIONAL MEDICINAL PRODUCT(S): ORAL ADMINISTRATION

- Atorvastatin

- Rosuvastatin

- Cholesterol absorption inhibitor (ezetimibe)

- Fibrates (fenofibrate, bezafibrate)

- Anti-platelets (aspirin, clopidogrel, etc.)

- Warfarin, and other oral anticoagulants approved in Japan (edoxaban, rivaroxaban, apixaban, etc.)

The noninvestigational medicinal products (NIMPs) will be prescribed by the Investigators as the standard treatment. Other medications/medical products not described above can be prescribed as needed.

8.3   BLINDING PROCEDURES

8.3.1   Methods of blinding

This study is an open-label design and the IMP administration during the study period will be under un-blinded manner. Despite the un-blinded IMP administration, assessment for the primary and key secondary efficacy endpoints will be conducted in the central reading laboratory based on objectively collected imaging data blinded to study treatment arms.

The study team or delegate must not summarize the primary efficacy endpoint by treatment arm, but may review the descriptive statistics of the primary efficacy endpoint by pooling the data from both arms.

8.4   METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

Sponsor will provide the randomization scheme to the registration center. Then, the registration center will generate the patient randomization list.

The IMP (i.e., Praluent®) is provided in open-label boxes.

Patient identification (patient number) is composed of 9-digit number containing the 3-digit country code, the 3-digit study site code, and the 3-digit patient chronological number.

Before randomizing a patient, the Investigator/sub-Investigator or designee will have to contact the registration center. A randomized patient is defined as a patient who has been allocated to a randomized treatment and recorded in the registration center database, regardless of whether a study drug is used or not. A patient cannot be randomized more than once in the study. If the IMP is used without contacting the registration center, patient will be considered as not randomized and withdrawn from the study.

At the randomization visit, patients will be randomized to either alirocumab arm or SoC arm at a ratio of 1:1 with permuted-block randomization using the registration center. Randomization will be stratified by 'statin therapy' or 'not on statin therapy' at the ACS onset.

8.5   PACKAGING AND LABELING

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

Each treatment kit containing Praluent® autoinjector will be prepared. Written details of packing and labeling of Praluent® will be provided as a pharmacy manual.

NIMPs will be provided at each study site through Investigator's prescription.

8.6   STORAGE CONDITIONS AND SHELF LIFE

The hospital pharmacists, or heads of the study sites, are responsible for storing the IMP (Praluent®) in a secure and safe place in accordance with local regulations, labeling specifications, policies, and procedures.

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

8.7   RESPONSIBILITIES

The hospital pharmacist, or head of the study site, will be responsible for ensuring that the IMP used in the clinical trial is securely maintained in accordance with the pharmacy manual provided by the Sponsor.

All IMP/NIMP will be dispensed in accordance with the Investigator/sub-Investigator's prescription and the hospital pharmacist will ensure that an accurate record of IMP/NIMP 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 study site (Investigator, hospital pharmacist, etc.) will be responsible for promptly addressing any request made by the Sponsor, in order to recall the IMP and eliminate potential hazards.

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

8.7.1   Treatment accountability and compliance

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

- The Investigator/sub-Investigator or designee will issue treatment number kits to patients and record their issued treatment numbers.
- The Investigator/sub-Investigator, the hospital pharmacist or designee will complete the corresponding treatment log form.
- The Investigator/sub-Investigator or study coordinator will enter data in the appropriate electronic Case Report Form (e-CRF) pages, according to data recorded in the treatment log form.
- The monitor will check the data consistency between e-CRF pages, treatment log forms, and returned unused autoinjectors of corresponding kits.

8.7.2 Return and/or destruction of treatments

- A detailed treatment log of the retrieved/destroyed IMP will be established with the hospital pharmacist and countersigned by the hospital pharmacist and the monitoring team.

- The Investigator will not destroy the unused IMP unless the Sponsor provides written authorization.

- The used IMP will be destroyed on study site according to the standard practices of the site.

- For NIMPs, which will not be provided by the Sponsor, tracking and reconciliation has to be achieved by the Investigator (or hospital pharmacist if appropriate) according to the system provide by the Sponsor.

8.8   CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient concomitantly with IMP/NIMP during the study period.

Concomitant medications should be kept to minimum during the study. However, if these are considered beneficial to the patient's welfare and unlikely to interfere with the IMP/NIMP, they may be given at the discretion of the Investigator, at stable dose (if possible). Daily administration doses of the concomitant medications will be recorded in the e-CRF and source data.

For background LMTs, including statin, Investigators must follow the Package Insert and manage with safety monitoring.

Nutraceutical products including specified health food or over-the-counter therapies that may affect lipids are allowed only if they have been used at a stable dose before the study, but in general should be avoided unless these products are required for medical reasons. Example of such nutraceutical products or over-the-counter therapies include omega-3 fatty acids at doses <1000 mg/day, plant stanols such as found in Benecol (US and Europe), flaxseed oil, psyllium, and/or herbal medicines.

Note: Use of other anti-PCSK9 monoclonal inhibitors is prohibited during the study.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 EFFICACY ENDPOINT

9.1.1 Primary efficacy endpoint

The primary efficacy endpoint is the percent change in normalized TAV from baseline to Week 36, which is defined as: 100 x (normalized TAV value at Week 36 - normalized TAV value at baseline) / normalized TAV value at baseline, and calculated by Sponsor or delegate.

The baseline normalized TAV value will be the normalized TAV obtained before the randomization.

The normalized TAV at Week 36 will be the normalized TAV obtained after ≥24 weeks of treatment after randomization.

9.1.2 Secondary endpoints

9.1.2.1 Key secondary efficacy endpoint

The key secondary efficacy endpoint is:

- Absolute change in PAV from baseline to Week 36.

9.1.2.2 Other secondary efficacy endpoints

The other secondary efficacy endpoints are:

- Absolute change in normalized TAV from baseline to Week 36.
- Absolute and percent changes in external elastic membrane (EEM) volume from baseline to Week 36.
- Absolute and percent changes in lumen volume from baseline to Week 36.
- Absolute and percent changes in calculated LDL-C from baseline to Week 12, and Week 36.
- Absolute and percent changes in Apo B from baseline to Week 36.
- Absolute and percent changes in non-HDL-C from baseline to Week 36.
- Absolute and percent changes in TC from baseline to Week 36.
- Absolute and percent changes in Lp(a) from baseline to Week 36.
- Absolute and percent changes in HDL-C from baseline to Week 36.
- Absolute and percent changes in fasting TGs from baseline to Week 36.

- Absolute and percent change in Apo A-1 from baseline to Week 36.

9.1.3 Efficacy assessment method

9.1.3.1 IVUS parameters

The EEM volume, lumen volume, TAV, normalized TAV, and PAV will be calculated by the Sponsor or delegate. These IVUS parameters will be calculated using the following equations defined using EEM_{CSA} and $Lumen_{CSA}$ taken at pre-determined interval between each image (δ =0.5 mm):

$$TAV\ (mm^3)= \sum (EEM_{CSA} - Lumen_{CSA})\delta\ ,$$

$$normalized\ TAV\ (mm^3)=TAV\times \frac{C}{n}\ ,$$

where Σ is the summation over all the analyzed frames, n is the number of analyzed frames per patient, C is the median of the number of analyzed frames in patients with available baseline TAV within randomized population. EEM_{CSA} is the cross-sectional area inside the EEM border, the $Lumen_{CSA}$ is the cross-sectional area inside the lumen border, and both parameters are measured by the central reading laboratory. Besides,

$$PAV\ (\%)=\left(\frac{\sum (EEM_{CSA} - Lumen_{CSA})}{\sum EEM_{CSA}} \right)\times 100\ ,$$

$$EEM\ volume\ (mm^3)= \sum (EEM_{CSA})\delta\ ,$$

$$Lumen\ volume\ (mm^3)= \sum (Lumen_{CSA})\delta\ ,$$

where Σ is the summation over all the analyzed frames.

The detailed procedures of IVUS image analysis and calculation of the parameters will be specified in the procedure manual of IVUS image analysis.

The detailed procedures of IVUS imaging will be described in the specific manual, which will be provided to study sites (see Section 10).

9.1.3.2 Lipid parameters

The TC, HDL-C, TG, Apo B, Apo A-1, and Lp(a) will be measured by the central laboratory as per the schedule in Section 1.2. The LDL-C will be calculated using the Friedewald formula (35). If TG values exceed 400 mg/dL (4.52 mmol/L), LDL-C level will not be calculated using the Friedewald formula, but will be provided using the direct method. Non-HDL-C will be calculated by subtracting HDL-C from TC. Apo B/Apo A-1 ratio will be calculated. Detailed procedures of

sample preparation, storage, and shipment will be described in the laboratory manual which will be provided to each study site.

Efficacy endpoints will not be considered as adverse events (AEs), such as those related to abnormalities in lipid parameters, unless meeting the criteria in Section 10.4.1.

9.2   SAFETY ENDPOINTS

Safety endpoints are as follows:

- Safety parameters (adverse events including CV events, laboratory data, and vital signs) will be assessed throughout the study.

Note: CV events include CHD death, non-fatal MI, fatal and non-fatal ischemic/hemorrhagic stroke, congestive heart failure requiring hospitalization, ischemia-driven coronary revascularization procedure.

The observation period of safety data is defined in Section 11.4.3.

9.2.1 Adverse events

All AEs diagnosed by the Investigator/sub-Investigator, irrespective of the result of the adjudication for CV events, will be reported and described.

- All AEs will be coded to "Lowest Level Term (LLT)", "Preferred Term (PT)", "High Level Term (HLT)", "High Level Group Term (HLGT)", and associated primary "System Organ Class (SOC)" using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sponsor or delegate at the time of the considered database lock.

- AESIs include events as the following:

  - General allergic events (refer to Section 10.6.2)

  - Local injection site reactions (using specific e-CRF pages, refer to Section 10.6.1 and Section 17, Appendix I)

  - Hemolytic anemia (using specific e-CRF pages, refer to Section 10.4.4.1 and Section 17, Appendix H)

  - Neurologic and Neurocognitive adverse events (refer to Section 10.4.4.1 and Section 17, Appendix F)

  - Ophthalmologic adverse events (using specific e-CRF pages, refer to Section 10.4.4.1 and Section 17, Appendix F)

  - Skeletal muscle-related adverse event (using specific e-CRF pages, refer to Section 17, Appendix F)

  - Symptomatic overdose with IMP (refer to Section 10.4.4.1 and Section 17, Appendix F and G)

-    Pregnancy (including male patient's partner) (refer to Section 10.4.4.1 and Section 17, Appendices A and F)

-    Elevation of ALT (refer to Section 10.4.5 and Section 17, Appendices F and G)

Adverse event observation period is as per observation period of safety data defined in Section 11.4.3.

Adjudicated CV events include all CV AEs and coronary revascularization positively adjudicated (refer to Section 10.6.3) occurring after obtaining the informed consent for study participation until the end of study. The adjudication classifications are the following:

-    CHD death

-    Non-fatal MI

-    Fatal and non-fatal ischemic and/or hemorrhagic stroke

-    Unstable angina requiring hospitalization

-    Ischemia-driven coronary revascularization procedure

In addition, all deaths will be classified.

Note: Observation period for death are as per the adverse event observation period. *In addition, "post-study" death includes all deaths reported after the end of the study (refer to definition of end of study per patient in Section 6.2.2).*

9.2.2 Laboratory safety variables

The clinical laboratory data consist of hematology (red blood cell count, hematocrit, hemoglobin, white blood cell count with differential count, platelet count), blood chemistry (glucose, sodium, potassium, chloride, creatinine, uric acid, lactate dehydrogenase [LDH], total protein, albumin, gamma-glutamyl transpeptidase [γGT], CPK, alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP] and total bilirubin), and hepatitis C virus antibody (refer to Section 1.2).

Additional safety laboratory parameters may be reflexively measured based on the resultant laboratory data (refer to Section 10.4.5 and Section 17, Appendix F).

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

9.2.3 Vital signs

Vital signs include heart rate, and systolic/diastolic blood pressure in the sitting position.

9.3   OTHER ENDPOINTS

9.3.1   Hemoglobin A1c

The absolute change in hemoglobin A1c (HbA1c) (%) from the baseline (Week 0) to Week 12, Week 24, and Week 36 (EOT visit) will be assessed.

9.3.2   High sensitivity C-reactive protein

The percent change in high sensitivity C-reactive protein (hs-CRP) from baseline (Week 0) to Week 36 (EOT visit) will be assessed.

9.3.3   EQ-5D Patient Questionnaire

EQ-5D is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D as a measure of health-related quality of life, defines health in terms of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension can take one of three responses (3 ordinal levels of severity): "no problem" (1); "some problems" (2); "severe problems" (3). Overall health state is defined as a 5-digit number. Health states defined by the 5-dimensional classification can be converted into corresponding index scores that quantify health status, where 0 represents "death" and 1 represents "perfect health" (see Section 17, Appendix J) (36). If response to one or more dimension is missing, the index score will be missing.

EQ-5D variables include response of each EQ-5D items, index score, and absolute change of index score from the randomization visit (Week 0) (36).

9.4   APPROPRIATENESS OF MEASUREMENTS

The efficacy and safety endpoints used in this study are standard for the evaluation of post-ACS patients with hypercholesterolemia (refer to Section 4 for details).

10   STUDY PROCEDURES

For all study site visits except the randomization visit (Visit 1/Week 0), a time frame of 7 days before and after the scheduled study site visit will be allowed. For all study site visits after the randomization visit (Visit 1/Week 0), if a visit date is not kept, the next visit is scheduled according to the original schedule as outlined in Section 1.2.

Evaluation IVUS imaging:

The evaluation IVUS imaging will be performed in the same vessels of the initial IVUS imaging at the ACS diagnosis. The Investigator can schedule the evaluation IVUS imaging within 2 weeks before and after the EOT (Week 36; between Week 34 and Week 38). The detailed procedures of IVUS imaging are described in the specific manual. If the evaluation IVUS study cannot be performed by the EOT visit (Week 36) in patients of the alirocumab arm, Praluent® will be administered at Week 36 after data collection listed in the EOT visit (see Section 10.1.1.1.5), and the evaluation IVUS imaging can be performed before Week 38, while the effect of alirocumab remains. For patients in the SoC arm, the evaluation IVUS imaging should be performed between Week 34 and Week 36 as in the alirocumab arm. If patients cannot undergo the evaluation IVUS imaging by Week 36, all efforts should be made to perform the evaluation IVUS imaging by Week 38.

Blood sampling:

The blood sampling has to be performed in the morning under fasting conditions, which is defined as an overnight fast no less than 8 hours that consist of no food or liquid intake other than water with exception of to do so otherwise by Investigator/sub-Investigator's medical judgment, throughout the study.

The blood sample will be used to measure lipid parameters [TC, LDL-C, HDL-C, TG, non-HDL-C, Apo B, Apo A-1, Apo B/Apo A-1 ratio, Lp(a)], hematology (red blood cell count, hemoglobin, hematocrit, white blood cell count and differential count, platelet count), blood chemistry, HbA1c, hs-CRP, hepatitis B virus antibody, hepatitis C virus antibody, etc (see also Section 1.2).

Alcohol consumption within 48 hours and intense physical activities within 24 hours preceding the blood sampling are discouraged.

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

Laboratory tests:

The laboratory data are collected in accordance with the study schedule described in Section 1.2. It is noted that the lipid panels 1, 2, hepatitis C virus antibody, hepatitis B total core antibody (HBc-ab), hs-CRP, and HbA1c will be measured by the central laboratory (and at each study site if necessary).

(electronic 1.0)

- Hematology

- Chemistry including liver function enzymes, LDH, and CPK

- Lipid panel 1: TC, calculated and directly measured LDL-C, HDL-C, TG, and non-HDL-C

- Lipid panel 2: Apo B, Apo A-1, Apo B/Apo A-1, and Lp(a)

- Hepatitis C virus antibody: positive test will be confirmed with reflexive testing at each study site

- Hepatitis B virus surface antigen, surface antibody, and total core antibody: positive test that suggests active infection (positive surface antigen and antibody) or viral carrier (positive total core antibody) will be confirmed with reflexive testing at each study site.

  Note: The results of hepatitis B virus surface antigen and antibody results will be collected from each study site. Hepatitis B virus total core antibody will be measured by the central laboratory at the randomization visit (Week 0). Hepatitis B virus DNA will be measured immediately if positive hepatitis B virus total core antibody results.

- HbA1c

- hs-CRP

- Urine pregnancy test

- Serum pregnancy test

Decision trees for the management of certain laboratory abnormalities by Sponsor are provided in Section 17, Appendix F, and Appendix G, and should be followed by Investigators/sub-Investigators.

Other endpoint assessment methods:

All other blood parameters will also be measured at each study site during the study (as per the schedule in Section 1.2, on blood samples taken preferably in the morning in fasting conditions described above [see Section 10.1.1]). Alcohol consumption within 48 hours and intense physical activities within 24 hours preceding the blood sampling are discouraged.

Physical examination:

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

Blood pressure / heart rate:

It is recommended that blood pressure is measured in the sitting position under the same conditions each time, approximately at the same time of the day, on the same arm, with the same

apparatus (after the patient has rested in sitting position for at least 5 minutes). Both systolic and diastolic blood pressure should be recorded. It should be noted that blood pressure should be measured in both arms at the randomization visit (Week 0). The arm with the highest diastolic blood pressure will be used to measure the blood pressure throughout the study. The highest blood pressure value will be recorded in the e-CRF.

The heart rate will also be measured at the time of blood pressure measurement.

Note: In cases with hypertension (high blood pressure values) (within 4 weeks prior to the randomization or after ACS onset and prior to the randomization) the Investigator/sub-Investigators is responsible for the optimization of the patient's treatment to achieve blood pressure target as defined by local guidelines (Japanese Society of Hypertension) or the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7).

Body weight and height:

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

EQ-5D patient questionnaire:

Collection of EQ-5D patient questionnaire will be carried out in all patients at each scheduled visit (5 visits) by Investigator, or a person designated by the Investigator.

10.1   VISIT SCHEDULE

Patients with hypercholesterolemia, who develop ACS and undergo successful therapeutic intervention such as PCI (stent placement), and IVUS imaging, are the target subjects of the current study. All patients have to have been received stable statin therapy with either atorvastatin ≥10 mg/day or rosuvastatin ≥5 mg/day for at least 2 weeks prior to the randomization visit (Visit 1).

Between the onset of ACS and the randomization visit (within 4 weeks prior to the randomization visit), the patient will receive verbal information concerning the aims and methods of the study, its constraints and risks, and the study duration, and will be provided of a written summary. The written informed consent must be signed by the patient and the Investigator prior to any study activity. Only patients who meet the inclusion/exclusion criteria as noted in Section 7 will be enrolled to the study. Women of childbearing potential will be instructed to use a medically approved contraceptive method throughout the entire study period.

10.1.1 Open-label treatment period

For each on-site visit, the patient should visit the study site in the morning under fasting conditions, which is defined as an overnight fasting no less than 8 hours that consist of no food or liquid intake other than water with the exception made by Investigator's medical judgment.

During the open-label treatment period, the patient will have 5 on-site visits, and 14 Praluent® administration visits§ for patients in the alirocumab arm or 5 phone-call interviews for patient in the SoC arm. Data on IMP/NIMP compliance and any AE/SAE including CV events will be recorded in both study arms after the randomization visit (Week 0) to the EOT visit (Week 36).

- 5 on-site visits: Weeks 0, 4, 12, 24, and 36.

- 14 Praluent® administration visits (alirocumab arm only)§: Weeks 2, 6, 8, 10, 14, 16, 18, 20, 22, 26, 28, 30, 32, and 34.

  §: If the evaluation IVUS imaging cannot be performed by Week 36, patients will receive an additional Praluent® dose at Week 36. The evaluation IVUS imaging must be performed within 2 weeks of Week 36 on-site visit.

- If patients perform self-injection of Praluent® at home, they must visit the study site at least every 4 weeks, and at Weeks 0, 4, 12, 14, 24, and 36 regardless of the timing of the first self-injection.

- 5 phone-call interviews (SoC arm only); Weeks 8, 16, 20, 28, and 32.

10.1.1.1 Study site visit

10.1.1.1.1 Randomization visit (Visit 1 / Week 0 / D1)

Blood sampling should be completed before IMP administration.

This visit includes:

- On-site visit.

- Complete and collect written informed consent for the study by the randomization visit. Patient number will be allocated by the registration center. The patient number is composed of a 9-digit number containing the 3-digit country code, the 3-digit center code, and the 3-digit patient chronological number (3-digit patient chronological number is 001 for the first patient screened in a center, 002 for the second patient screened in the same center).

  Note: The written informed consent can be obtained any time between ACS diagnosis and the randomization visit (see Section 1.2).

- Confirm inclusion and exclusion criteria.

- Collect information about therapeutic intervention such as ACS culprit vessels, IVUS imaging locations (refer to Section 17, Appendix D for vessel locations), and types of stent placed at the PCI (BMS or DES).

- Contact the registration center to notify the patient enrollment. After the final confirmation of inclusion and exclusion criteria at the registration center, the arm to which the patient randomized to is communicated.

- Demographics (age, gender, race, ethnicity).

- Collect contact information (address, email, home and cell phone numbers) of the patient, patient's family members, and patient's primary care physician / cardiologist.

- Patient's medical and surgical history (including menopausal status, and family history), alcohol habits, smoking habits, lipid parameters including LDL-C used for the study eligibility, and HbA1c.

- Collect patient's history of CV disease.

- Record use of LMT including statins and prescription or over-the-counter non-statin LMTs within 1 month prior to Visit 1.

- Record of all concomitant medications including CV medications.

- Collection of adverse events including CV events (if any).

- Collection of results of hepatitis B virus surface antigen and antibody tested at the time of ACS diagnosis and PCI.

    Note: If the hepatitis B virus surface antigen and antibody titers are not checked, they must be measured prior to the randomization visit and the results must be recorded at the randomization visit (see Section 7.1).

- Physical examination including vital signs: heart rate and sitting SBP and DBP.

- Body weight and height.

- EQ-5D patient questionnaire.

- Serum and urine pregnancy tests (women of childbearing potential [WOCBP]).

- Confirm and record compliance with background LMT regimen including NIMPs.

- Fasting blood sample listed below will be collected and measured.

- Hematology and chemistry.

  - TC, calculated and directly measured LDL-C, HDL-C, TG, non-HDL-C (central laboratory).

  - Apo B, Apo A-1, Apo B/Apo A-1, Lp(a) (central laboratory).

  - HbA1c (central laboratory).

  - hs-CRP (central laboratory).

  - Hepatitis B virus antibody (Hepatitis B virus total core antibody is tested at the central laboratory).

  - Hepatitis C virus antibody titer (central laboratory).

Note: Additional blood samples can be obtained for measurement of above listed items and others at the study site by Investigator's judgment as needed.

- If the patient's eligibility (and fasting status) is confirmed, contact the registration center for randomization. The Investigator/sub-Investigator must not administer IMP without notifying the registration center.

- When the Investigator confirms the patient is randomized to the alirocumab arm and has completed fasting blood sample collection and assessments of all evaluations planned at this randomization visit (Visit 1), the first Praluent® injection will be performed at the study site following the patient injection instruction.

- The patient should be observed for at least 30 minutes after Praluent® administration.

- If patient is randomized to the SoC arm, ongoing LMTs will be continued unless modification of LMTs is made by the Investigator's medical judgment.

- For the patient who is randomized to the alirocumab arm, an appointment will be given for next Praluent® administration visit (Week 2 / D15).

- For the patient who is randomized to the SoC arm, an appointment will be given for next on-site visit (Visit 2 / Week 4 / D29). The patient should be instructed to visit the study site in the morning under fasting conditions, which is defined as an overnight fasting no less than 8 hours that consist of no food or liquid intake, other than water unless exception made by Investigator's medical judgment.

- Transfer IVUS imaging data to the central reading laboratory.

10.1.1.1.2 Study Site Visit 2 (Week 4 / D29 ± 7 days)

This visit includes:

- On-site visit.

- EQ-5D patient questionnaire

- IMP/NIMP compliance check including diet therapy (Patients should be on a diet following JAS guideline or equivalent).

- Vital signs: heart rate and sitting SBP and DBP.

- Record of all concomitant medications including CV medications.

- Collection of adverse events including CV events (if any).

- Fasting blood sample listed below will be collected and measured.

  - Hematology and chemistry.

  - TC, calculated and directly measured LDL-C, HDL-C, TG, non-HDL-C (central laboratory).

  Note: Additional blood samples can be obtained for measurement of above listed items and others at the study site by Investigator's judgment as needed.

- When the Investigator or the site medical staff confirms all required measurements are completed, the patient in the alirocumab arm will receive Praluent® administration.

- The patient should be observed for at least 30 minutes after Praluent® administration.

- If patient is in the SoC arm, ongoing LMTs will be continued unless modification of LMTs is made by the Investigator's medical judgment.

- For the patient in the alirocumab arm, an appointment will be given for next Praluent® administration visit (Week 6 / D43).

- For the patient in the SoC arm, an appointment will be given for the first phone-call interview (Week 8 / D57).

10.1.1.1.3 Study Site Visit 3 (Week 12 / D85 ± 7 days)

This visit includes:

- On-site visit.

- EQ-5D patient questionnaire.

- IMP/NIMP compliance check including diet therapy (Patients should be on a diet following JAS guideline or equivalent).

- Body weight.

- Vital signs: heart rate and sitting SBP and DBP.

- Record of all concomitant medications including CV medications.

- Collection of adverse events including CV events (if any).

- Fasting blood sample listed below will be collected and measured.

    - Hematology and chemistry.

    - TC, calculated and directly measured LDL-C, HDL-C, TG, non-HDL-C (central laboratory).

    - HbA1c (central laboratory).

    Note: Additional blood samples can be obtained for measurement of above listed items and others at the study site by Investigator's judgment as needed.

- When the Investigator or the site medical staff confirms all required measurements are completed, the patient in the alirocumab arm will receive Praluent® administration.

- The patient should be observed for at least 30 minutes after Praluent® administration.

- If patient is in the SoC arm, ongoing LMTs will be continued unless modification of LMTs is made by the Investigator's medical judgment.

- For the patient in the alirocumab arm, an appointment will be given for next Praluent® administration visit (Week 14 / D99).

- For the patient in the SoC arm, an appointment will be given for next phone-call interview (Week 16 / D113).

10.1.1.1.4 Study Site Visit 4 (Week 24 / D169 ± 7 days)

This visit includes:

- On-site visit.

- EQ-5D patient questionnaire.

- IMP/NIMP compliance check including diet therapy (Patients should be on a diet following JAS guideline or equivalent).

- Body weight.

- Vital signs: heart rate and sitting SBP and DBP.

- Record of all concomitant medications including CV medications.

- Collection of adverse events including CV events (if any).

- Fasting blood sample listed below will be collected and measured.

  - Hematology and chemistry.

  - TC, calculated and directly measured LDL-C, HDL-C, TG, non-HDL-C (central laboratory).

  - HbA1c (central laboratory).

    Note: Additional blood samples can be obtained for measurement of above listed items and others at the study site by Investigator's judgment as needed.

- When the Investigator or the site medical staff confirms all required measurements are completed, the patient in the alirocumab arm will receive Praluent® administration.

- The patient should be observed for at least 30 minutes after Praluent® administration.

- If patient is in the SoC arm, ongoing LMTs will be continued unless modification of LMTs is made by the Investigator's medical judgment.

- For the patient in the alirocumab arm, an appointment will be given for next Praluent® administration visit (Week 26 / D183).

- For the patient in the SoC arm, an appointment will be given for next phone-call interview (Week 28 / D197).

- The Investigator should make a schedule with the patient for the evaluation IVUS study at the EOT (Week 36 ± 2 weeks) by this on-site study visit if possible.

10.1.1.1.5 Study Site Visit 5 (End of Treatment Visit, Week 36 / D253 ± 14 days)

This study visit includes:

- On-site visit.

(electronic 1.0)

- Contact the registration center to document the end of study.

  Note: If the evaluation IVUS imaging is completed in this visit, EOT will be the end of study. If the evaluation IVUS imaging is scheduled after this visit, the contact with the registration center will be made when the evaluation IVUS imaging has been completed and this point is considered the end of study.

- EQ-5D patient questionnaire.

- IMP/NIMP compliance check including diet therapy (Patients should be on a diet following JAS guideline or equivalent).

- Body weight.

- Vital signs: heart rate and sitting SBP and DBP.

- Record of all concomitant medications including CV medications.

- Collection of adverse events including CV events (if any).

- Urine pregnancy tests (WOCBP).

- Fasting blood sample listed below will be collected and measured.

  - Hematology and chemistry.

  - TC, calculated and directly measured LDL-C, HDL-C, TG, non-HDL-C (central laboratory).

  - Apo B, Apo A-1, Apo B/Apo A-1, Lp(a) (central laboratory).

  - HbA1c (central laboratory).

  - hs-CRP (central laboratory).

  - Hepatitis C virus antibody levels (central laboratory).

  Note: Additional blood samples can be obtained for measurement of above listed items and others at the study site by Investigator's judgment as needed.

- If patient is in the SoC arm, ongoing LMTs will be continued unless modification of LMTs is made by the Investigator's medical judgment.

- Evaluation IVUS study should performed out by this visit ± 14 days and the IVUS images are transferred to the central reading laboratory immediately after the IVUS study.

- The notification of the end of study should be communicated to the registration center.

10.1.1.2 Praluent® administration visit (alirocumab arm only)

When patients are randomized to the alirocumab arm, they have to visit the study sites every 2 weeks for Praluent® administration in addition to on-site visits as indicated below:

- Week 2 / D15 ± 7 days

- Week 6 / D43 ± 7 days

- Week 8 / D57 $\pm$ 7 days: IMP/NIMP compliance recording including diet therapy (based on JAS guideline or the equivalent)

- Week 10 / D71 $\pm$ 7 days

- Week 14 / D99 $\pm$ 7 days

- Week 16 / D113 $\pm$ 7 days: IMP/NIMP compliance recording including diet therapy (based on JAS guideline or the equivalent)

- Week 18 / D127 $\pm$ 7 days

- Week 20 / D141 $\pm$ 7 days: IMP/NIMP compliance recording including diet therapy (based on JAS guideline or the equivalent)

- Week 22 / D155 $\pm$ 7 days

- Week 26 / D183 $\pm$ 7 days

- Week 28 / D197 $\pm$ 7 days: IMP/NIMP compliance recording including diet therapy (based on JAS guideline or the equivalent)

- Week 30 / D211 $\pm$ 7 days

- Week 32 / D225 $\pm$ 7 days: IMP/NIMP compliance recording including diet therapy (based on JAS guideline or the equivalent)

- Week 34 / D239 $\pm$ 7 days

  Note: IMP/NIMP compliance, diet therapy and AE/SAE will be assessed and recorded at Week 8, Week 16, Week 20, Week 28, and Week 32 as indicated above.

  Note 2: During Praluent® injection visits at Week 2, Week 10, Week 22, and Week 34, the appointment will be given for next on-site visits (Week 4, Week 12, Week 24, and Week 36, respectively). The patient should be instructed to visit the study site in the morning under fasting conditions, which is defined as an overnight fasting no less than 8 hours that consist of no food or liquid intake, other than water unless exception made by Investigator's medical judgment.

10.1.1.3 Phone-call interview (SoC arm only)

When patients are randomized to the SoC arm, they will have phone-call interview every 4 weeks for NIMPs compliance including diet therapy, CV medications, and AE/SAE recording in addition to on-site visits as indicated below:

- Week 8 / D57 $\pm$ 7 days

- Week 16 / D113 $\pm$ 7 days

- Week 20 / D141 $\pm$ 7 days

- Week 28 / D197 $\pm$ 7 days

- Week 32 / D225 $\pm$ 7 days

  Note: During the phone-call interviews at Week 8, Week 20, and Week 32, the appointment will be given for next on-site visits (Week 12, Week 24, and Week 36, respectively). The patient should be instructed to visit the study site in the morning under fasting conditions, which is defined as an overnight fasting no less than 8 hours that consist of no food or liquid intake, other than water unless exception made by Investigator's medical judgment.

10.2   DEFINITION OF SOURCE DATA

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

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

Source documentation may be found in the followings:

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

- Physician's notes.
- Laboratory reports.

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

Study treatment should be continued whenever possible. In case the treatment is discontinued, it should be determined whether the discontinuation can be made temporarily; permanent treatment discontinuation should be a last resort. Any treatment discontinuation should be fully documented in the Case Report Form (CRF). In any case, the patient should remain in the study as long as possible.

10.3.1 Temporary treatment discontinuation

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

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

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

10.3.2 Permanent treatment discontinuation with investigational medicinal product(s)

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

10.3.3 List of criteria for permanent treatment discontinuation (SoC or IMP)

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

Patients should discontinue the study treatment for the following reasons:

- Pregnancy, intention for pregnancy, or no longer taking an effective contraceptive method (in female patients).
- Acute injection-site reaction of clinical concern.

- SAE (or non-serious but severe in intensity) of hypersensitivity reaction considered to be related to study treatment.

- At patient's request.

- If, in the Investigator/sub-Investigator's opinion, continuation of the study treatment is detrimental to the patient's well-being.

- Condition that requires discontinuation of study treatment (e.g., laboratory abnormalities, refer to decision tree Appendix F).

- At the specific request of the Sponsor.

- At the specific request of the Investigator with Sponsor's agreement.

Criteria of permanent treatment discontinuation due to insufficient adherence to medications are defined as followed:

- Alirocumab arm: IMP administration compliance is less than 50% for 12 weeks (3 months from the randomization visit).

- SoC arm: NIMP administration compliance is less than 50% for 6 months from the randomization visit.

  Note for SoC arm: If patients exhibit their NIMP administration compliance is less than 50% for the first 3 months after the randomization visit, Investigators/sub-Investigator can terminate the study based on their judgment considering patients' safety.

10.3.4 Handling of patients after permanent treatment discontinuation (SoC or IMP)

- 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. The registration center should be notified when a patient prematurely discontinues the study. Patients should be asked to stick to the visit schedule for measuring laboratory test values until the end of study (Week 36).

- When patients permanently discontinue the study (regardless of the reasons) before Week 24 (6 months), they will have an unscheduled on-site visit as soon as possible (preferably within 7 days from treatment discontinuation) with assessments originally planned at the EOT visit (Week 36).

- When patients in the alirocumab arm permanently discontinue the study (regardless of the reasons) on Week 24 (6 months) or after, the Investigator should make the best effort to schedule the evaluation IVUS imaging with assessments originally planned at the EOT visit (Week 36) within 2 weeks from the last IMP administration (the earliest last IMP administration occurs on Week 22). If the patients decline the evaluation IVUS imaging after the study discontinuation, they will have an unscheduled on-site visit as soon as possible (preferably within 7 days from treatment discontinuation) with assessments originally planned at the EOT visit (Week 36).

- When patients in the SoC arm permanently discontinue the study (regardless of the reasons) on Week 24 (6 months) or after, the Investigator should make the best effort to

schedule the evaluation IVUS imaging with assessments originally planned at the EOT visit (Week 36) within 2 weeks from the determination date of the study discontinuation. If the patients decline the evaluation IVUS imaging after the study discontinuation, they will have an unscheduled on-site visit as soon as possible (preferably within 7 days from treatment discontinuation) with assessments originally planned at the EOT visit (Week 36).

- When patients, who develop AEs including AESIs and/or SAEs and need to be followed up as specified in this protocol, permanently discontinue the study, they will be followed up until recovery or stabilization of the AEs.

Note: If the evaluation IVUS imaging cannot be performed within 2 weeks from the last Praluent® administration in the alirocumab arm or 2 weeks after the day when the study discontinuation is determined in the SoC arm, lipid values measured at the study site should be recorded at the evaluation IVUS imaging.

10.3.5 Procedure and consequence for patient withdrawal from study

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

If possible, the patients should be assessed using the usual scheduled procedure on the visit day of the end of study.

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

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

10.4   OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

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

- All AE diagnosed by the Investigator, irrespective of the results of the adjudication for CV events, will be reported and described.

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- All AEs will be coded to "LLT", "PT", "HLT", "HLGT", and associated primary "SOC" using the version of MedDRA currently in effect at Sponsor or delegate at the time of the considered database lock.

10.4.1.2 Serious adverse event

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

- Results in death

- Life-threatening

  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

- Results in persistent or significant disability/incapacity

- Congenital anomalies/birth defects, or

- Other medically important event

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

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

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

- Cancers diagnosed during the study.

- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study.

10.4.1.3 Adverse event of special interest

An **adverse event of special interest** (AESI) is an AE (serious or non-serious) that need to be monitored, documented, and managed in a pre-specified manner described in the protocol. Please see Section 10.4.6 and Section 17, Appendix F for additional information.

10.4.2 General guidelines for reporting adverse events

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

Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator/sub-Investigator should specify the date of onset, intensity, action taken with respect to study treatment, 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 study treatment or by the study procedure(s).

The Investigator/sub-Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the Sponsor. When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.

Laboratory and vital signs are recorded as AEs only if:

- Symptomatic and/or

- Requiring either corrective treatment or consultation, and/or

- Leading to study treatment discontinuation or modification of dosing, and/or

- Fulfilling a seriousness criterion, and/or

- Defined as an AESI

See Section 17, Appendix F for summary of AE reporting guidelines.

10.4.3 Instructions for reporting serious adverse events

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

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send a notification to the Sponsor after approval of the Investigator/sub-Investigator within the e-CRF or after standard delay.

- SEND (within 24 hours, preferably by fax or e-mail) the signed and dated corresponding page(s) from the CRF to the representative of the monitoring team whose name, fax number, and e-mail address appear in the clinical trial protocol. Care must be taken to ensure that the patient's identify is protected and the Patient's identifiers in the study are properly mentioned on any copy of a source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.

- ATTACH a clear photocopy of all examinations carried out and the dates on which these examinations were performed. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.

- All further data updates should be recorded in the e-CRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status, etc) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life-threatening within a week (7 days) of the initial notification.

- A back-up plan (using a paper CRF process) will be used when the e-CRF system does not work.

- REPORT to head of the study site by document immediately.

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

10.4.4 Guidelines for reporting adverse events of special interest

10.4.4.1 Reporting of adverse events of special interest (AESI)

For AESIs, the Sponsor must be informed immediately (i.e., within 24 hours), as per SAE notification described in Section 10.4.3 and Section 17, Appendix F even if not fulfilling a seriousness criterion, using the corresponding screens in the e-CRF.

- Allergic events:
  - General allergic drug reactions and/or local injection site reactions deemed to be allergic (or have an allergic component) that require consultation with other physician(s) for further evaluation of hypersensitivity/allergy, as per the Investigator/sub-Investigator's medical judgement or as per Section 10.6.2, should be reported as an AESI with immediate notification.
  - All general allergic events, and all injection site reactions having an allergic component or deemed to be allergic, require completion of the specific e-CRF screen (see Section 10.6.2), regardless of requirements for immediate reporting.

- Hemolytic anemia (see Section 17, Appendix H):

  - If there is a decrease in hemoglobin and reflexive testing as per Section 17, Appendix H suggesting hemolysis, then report this as AESI with immediate notification. Special e-CRF screen will need to be completed.

- Pregnancy

  - Pregnancy occurring in a female patient or the partner of a male patient included in the clinical trial. Pregnancy will be recorded as an AESI with immediate notification in all cases. It will be qualified as an SAE only if it fulfills the SAE criteria.

  - In the event of pregnancy of a female patient included in the clinical trial, study treatment should be discontinued.

  - The follow-up of the pregnancy will be mandatory until the outcome has been determined.

- Overdose with IMP/NIMP

  - Only the symptomatic overdoses with IMP/NIMP are defined as AESI in the study.

  - An overdose (accidental or intentional) with the IMP/NIMP is an event suspected by the Investigator/sub-Investigator or spontaneously notified by the patient (not based on systematic injection counts).

  - An overdose with the IMP/NIMP is defined as at least twice of the intended dose within the intended therapeutic interval.

  - The overdose events should be reported using the corresponding screens in the e-CRF using the term "symptomatic overdose (accidental or intentional)". The circumstances of the overdose should be clearly specified in the verbatim and symptoms, if any, entered on separate AE forms.

  Of note, asymptomatic overdose should be reported using the corresponding screens in the e-CRF using the term "asymptomatic overdose (accidental or intentional)". The circumstances of the overdose (i.e., accidental or intentional) and asymptomatic condition should be clearly specified.

  - The patient should be monitored and receive appropriate corrective treatment.

- Neurological events:

  - Neurologic events that require additional examinations / procedures and/or referral to a specialist should be reported as an AESI with immediate notification (see Section 17, Appendix F).

- Neurocognitive events:

  - All neurocognitive events will be considered as AESI (see Section 17, Appendix F)

- Ophthalmologic events:

  - Ophthalmologic events that require additional examinations/procedures and/or referral to a specialist should be reported as an AESI with immediate notification.

- ALT >3 x ULN (see Section 17, Appendices F and G, Increase in ALT).

- Local injection site reaction as non-allergic event (see Section 10.6.1)

    - Local injection site reactions that are considered as non-allergic events should be further characterized by evaluation of the related symptoms comprising injection site reactions such as but not limited to redness, pain, etc. (see Section 17, Appendix I). Specific e-CRF screens will need to be completed. If such AEs do not occur, then do not report the individual components of the reaction but rather the term "local injection site reactions", the individual components being described in the specific e-CRF screen.

- Skeletal muscle-related events:

    - Any AEs related to skeletal muscle abnormalities, including myalgia, muscle spasms and stiffness, musculoskeletal discomfort and stiffness, back pain, muscular weakness, and muscle fatigue.

10.4.4.2 Device deficiency

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

Product complaints:

- A product complaint is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, durability, reliability, safety, efficacy, or performance of a product after it is released for distribution.

- All product complaints must be reported on a product complaint form when there is a reason to suspect a problem with the device.

- In case of a product complaint associated with the occurrence of an AE, the AE must be documented on an AE page in the CRF.

- In the case of a product complaint associated with the occurrence of a SAE, the SAE must be reported in accordance with the SAE reporting procedure (see Section 10.4.1.2 and Section 10.4.2).

- All product complaints require reporting within 24 hours

10.4.5 Guidelines for management of specific laboratory abnormalities

Laboratory abnormalities with pre-specified monitoring should be monitored, documented, and managed according to the flowchart shown in Section 17, Appendices G and H.

- Neutropenia

- Thrombocytopenia

- Increase in ALT

- Acute renal insufficiency

- Increase CPK and suspicion of rhabdomyolysis

- Decrease in hemoglobin (defined as ≥ 1.5 g/dL)

10.4.6 Summary of adverse event reporting instructions

Section 17, Appendix F shows the summary of the reporting instructions of adverse events.

10.5   OBLIGATIONS OF THE SPONSOR

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

- All SAEs that are both unexpected and at least reasonably related to the IMP (Suspected Unexpected Serious Adverse Reaction, SUSAR), to the Health Authorities, independent ethics committees (IECs) / institutional review board (IRB) as appropriate and to the Investigators.

- All SAEs that are expected and at least reasonably related to the IMP to the Health Authorities, according to local regulations.

Any AE not listed as an expected event in the Package Insert will be considered unexpected.

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

10.6   SAFETY INSTRUCTIONS

10.6.1 Local tolerability (local injection site reactions)

In case the Investigator/sub-Investigator or the patient recognize any sign of local intolerability, then this should be treated and followed up as per the Investigator/sub-Investigator's medical judgment. See Section 17, Appendix I for further information.

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

10.6.2 Allergic adverse events

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

Adverse events that are obviously not of allergic origin (e.g., local injection site reactions related to mechanics of injection) should only be recorded on the Local Injection Site Reaction Complementary Form. However, injection site reactions that progress/expand/worsen/etc. should

be evaluated as recommended in Section 10.6.2 and the General Allergic Reaction Complementary Form should be completed.

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

10.6.2.1 Allergic adverse events with cutaneous involvement

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

The Investigator/sub-Investigator should evaluate the patient for possible etiologies (new medications, etc.) and extra-cutaneous symptoms and signs. If possible, the Investigator/sub-Investigator will take pictures of skin lesions in order to provide the patient with the abnormal skin images for the dermatologist's visit. If the photographs of skin lesions are obtained, then photocopies should be kept as source documents which may be collected by the Sponsor later. The Investigator/sub-Investigator will provide summary of the patient's case, reason for consultation, and information being requested to the consulting dermatologist.

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

10.6.2.2 Acute allergic reactions of IMP injection

See also Section 10.4.

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

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

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

10.6.3 Cardiovascular events and all deaths

The following suspected or confirmed CV events that occur from randomization until end of the study visit should be reported in a corresponding specific e-CRF. The Investigator will submit the adjudication materials to the CEC through the Sponsor as needed:

- MI.

- Congestive heart failure requiring hospitalization.

- Cerebrovascular events (e.g., stroke, transient ischemic attack, intracranial hemorrhage, ischemia or bleeding of spine or retina).

- Unstable angina requiring an emergency room visit or requiring / prolonging hospitalization.

- All coronary revascularization procedures (e.g., PCI, coronary artery bypass graft).

- All death (including CHD death).

All suspected or confirmed CV events should be reported as SAEs. For coronary revascularization procedures, 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 (e.g., unstable angina leading to PCI should be reported as "unstable angina" instead of "PCI").

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

The process includes specific assessment and monitoring in all patients, who has the calculated LDL-C values <25 mg/dL (0.65 mmol/L) any time after the randomization:

- The patient will continue study treatment (both alirocumab and SoC arms).

- The Investigator closely monitors the patient and collects any AE including AEs potentially associated with low LDL-C.

- The Investigator/sub-Investigator decides whether patient should be immediately request to have an unscheduled on-site visit, or patient assessment could be done at the next scheduled on-site visit.

- At the on-site visit, plan for the following, based on the Investigator/sub-Investigator's medical judgment:

    - Assess the need for conducting clinical investigations, arranging specialist consultation(s) as needed, and any relevant additional work-up.

- Assess the need for temporary or permanent discontinuation of study treatment, or continuation of the study treatment. Regardless of the action taken regarding study treatment, the patient should continue the study as per Section 10.3.

11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

The study is expected to enroll approximately 200 patients. The sample size calculations are based on the primary efficacy variable of percent change in normalized TAV from baseline to Week 36.

Based on the results of ZEUS (1) and PRECISE-IVUS (2) studies, it is assumed that difference in percent change in normalized TAV from baseline between alirocumab arm and SoC arm is 8%, and the common standard deviation of percent change in normalized TAV is 15%.

Under the assumption, a sample size of 150 patients (75 in the alirocumab arm and 75 in the SoC arm) will have 90% power to detect the treatment difference with two-sided significance level of 5%. Assuming that proportion of non-evaluable primary endpoint is 25%, it is considered that 200 patients (100 in the alirocumab arm, 100 in the SoC arm) will be needed.

As the ANCOVA model will be used for primary analysis, the power should be somewhat higher due to reduced estimate variability versus the two-sample t-test.

Calculations were made using SAS 9.4

11.2 DISPOSITION OF PATIENTS

Patients who signed the informed consent are defined as the patients who signed the informed consent.

Randomized patients consist of all patients who have been allocated to a randomized treatment and recorded in the registration center database, regardless of whether a study drug was used or not.

Patients treated without being randomized will not be considered as randomized and will not be included in any analysis population.

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

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

11.3 ANALYSIS POPULATIONS

The randomized population includes all randomized patients defined in Section 11.2.

11.3.1 Efficacy populations

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

11.3.1.1 Modified intent-to-treat population

The modified intent-to-treat population is the randomized population which takes at least one dose or part of dose of study drug and has an available value of normalized TAV before randomization, and after 24 weeks of treatment. Patients will be analyzed in the treatment arm to which they are randomized.

11.3.2 Safety population

The safety population is defined as the randomized population which actually received at least 1 dose or part of a dose of the study drug, and analyzed according to the treatment actually received.

In addition:

- Non-randomized but treated patients will not be part of the safety population, but their safety data will be presented separately.

- Randomized patients for whom it is unclear whether they took the study drug will be included in the safety population as randomized.

- The treatment arm allocation for "as-treated analysis" will defined as follows:

  - Alirocumab arm if proportion of IMP injection is $\geq 50\%$.

  - SoC arm if proportion of IMP injection is $<50\%$.

- Proportion of IMP injection (%) is defined as 100 x (Number of IMP injection)/[(Date of end of treatment - Date of randomization)/14 + 1]

11.3.3 Quality-of-life (QOL) population

The analyses of QOL will be performed on all randomized and treated patients (safety population) with a baseline and at least 1 matching post-baseline evaluation for any of the 5 dimensions.

11.4   STATISTICAL METHODS

Statistical methods are briefly described here and will be detailed in the statistical analysis plan (SAP) of the study.

11.4.1 Extent of study treatment exposure and compliance

The extent of study treatment exposure and compliance will be assessed and summarized within the safety population. The extent of IMP exposure and compliance will be summarized for alirocumab arm (actual treatment received). Regarding to NIMP, it will be detailed in the SAP.

11.4.1.1 Extent of investigational medicinal product exposure

The total exposure will be assessed by:

- Duration of IMP exposure in weeks regardless of intermittent treatment is defined as: (last dose of IMP injection date – first dose of IMP injection date + 14 days)/7.

- Number (%) of patients with an up-titration from Praluent$^®$ 75 mg Q2W to Praluent$^®$ 150 mg Q2W.

11.4.1.2 Compliance of investigational medicinal product exposure

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

11.4.2 Analyses of efficacy endpoints

11.4.2.1 Analysis of primary efficacy endpoint

The primary efficacy endpoint, percent change in normalized TAV from baseline to Week 36 defined in Section 9.1.1 will be analyzed in the mITT population using an analysis of covariance (ANCOVA) model with treatment arm (SoC arm, alirocumab arm) and randomization strata (statin at ACS onset [Yes / No]), as fixed effects, and the baseline normalized TAV as covariate.

Throughout the ANCOVA model run using SAS Mixed procedure, alirocumab arm will be compared to SoC arm at the two-sided 0.05 level for superiority and providing baseline adjusted least squares means (LS means) estimates at Week 36 for each treatment arm with their corresponding standard errors (SEs) and the 95% confidence interval (CI) of the difference between the arms.

Let μ_0 and μ_1 be the population means of the percent change in normalized TAV from baseline to Week 36 under SoC arm and alirocumab arm, respectively. The null hypothesis that will be tested is "$H_0 : \mu_0 = \mu_1$" versus "$H_1 : \mu_0 \neq \mu_1$".

Robustness of this method will be also assessed via sensitivity analyses detailed in the SAP, including for handling of missing data.

11.4.2.2 Analyses of secondary efficacy endpoints

Method for controlling the overall type-I error rate when testing the key secondary efficacy endpoint is described in Section 11.4.2.3.

For the key secondary efficacy endpoint (defined in Section 9.1.2.1) and the other secondary efficacy endpoints (described in Section 9.1.2.2), descriptive summaries and analyses will be performed in the mITT population.

For descriptive summaries, percentage change (except ratio) and absolute change from baseline in calculated LDL-C, TC, HDL-C, TGs, non-HDL-C, Apo B, Apo A-1, Apo B/Apo A-1 ratio, and Lp(a) will be provided at each time point for each treatment arm. For lipids, all measurements, scheduled or unscheduled will be assigned to analysis windows defined in the SAP in order to provide an assessment for time points. Laboratory assessments other than the ones provided by the central laboratory will be excluded. For TGs, measurements on non-fasting patients will be excluded. The time profile of each parameter will be plotted by treatment arm with the corresponding SEs.

Continuous endpoints related to IVUS anticipated having a normal distribution

Continuous secondary endpoints related to IVUS anticipated having a normal distribution will be analyzed using the same ANCOVA model as for the primary endpoint with the continuous fixed covariates of corresponding baseline value.

Continuous endpoints of lipids anticipated having a normal distribution and collected at Week 0, Week 4, Week 12, Week 24 and Week 36

Continuous secondary endpoints of lipids defined in Section 9.1.2 are anticipated having a normal distribution and collected at Week 0, Week 4 Week 12, Week 24, and Week 36 (i.e., calculated LDL-C, TC, HDL-C, non-HDL-C) will be analyzed in the in the mITT population using a mixed-effect model with repeated measures (MMRM) approach. All post-baseline data available within Week 4, Week 12, Week 24, and Week 36 analysis windows will be used and missing data will be accounted for by the MMRM model. The model will include the fixed categorical effects of treatment arm (SoC arm, alirocumab arm), time point (Week 4, Week 12, Week 24, and Week 36), randomization strata (statin at ACS onset [Yes / No]), treatment-by-time point interaction, randomization strata-by-time point interaction, as well as, the continuous fixed covariates of corresponding baseline value and baseline value-by-time point interaction.

Continuous endpoints of lipids anticipated having a normal distribution and collected at Week 0 and Week 36

Continuous secondary endpoints of lipids defined in Section 9.1.2 are anticipated having a normal distribution and collected at Week 0 and Week 36 (i.e., Apo B, Apo A-1, Apo B/Apo A-1 ratio) will be analyzed using the same ANCOVA model as for the primary endpoint with the continuous fixed covariates of corresponding baseline value.

Continuous endpoints of lipids anticipated having a non-normal distribution

Continuous secondary efficacy endpoints of lipids defined in Section 9.1.2 are anticipated having a non-normal distribution (i.e., TGs and Lp(a)), will be analyzed in the mITT population using a robust regression model (37) (i.e., ROBUSTREG SAS procedure with M-estimation option) with treatment arm, and randomization strata (statin at ACS onset [Yes / No]) 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 arm combined means will be provided with respective SE estimates. The combined mean difference between the treatment arms will be provided with the SE, 95% confidence interval and p-value.

11.4.2.3 Multiplicity considerations

In order to handle the key secondary efficacy endpoint in addition to the primary efficacy endpoint, the overall type-I error will be controlled by the use of a sequential inferential approach. Statistical significance of the primary efficacy endpoint at the 0.05 alpha level is required before drawing inferential conclusions about the key secondary efficacy endpoint. 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 other than key secondary endpoints for which p-values will be provided for exploratory purpose only (no claim).

11.4.3 Analyses of safety data

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

Observation period

The observation period of safety data will be as follows:

- **Pre-treatment period** is defined as the time from the signed informed consent date up to the day of randomization.

- **TEAE period** is defined as the time from the day of randomization up to the last administration + 14 days (+ 7 days), or end of study, whichever comes first.

- **Post-treatment 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).

- **On-study observation period** is defined as the time from the day of randomization up to the end of the study (see definition in Section 6.2.1).

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

- 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 be determined which patients had at least 1 PCSA during the TEAE period, taking into account all evaluations performed during the TEAE period, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the PCSA percentage.

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 arm 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 arm. The selection of preferred terms will be based on standardized MedDRA query (SMQ) "Hepatic disorder."

11.4.3.1 Adverse events

The adverse events are defined as follows:

- Pre-treatment AEs are AEs that develop, worsen, or become serious during the pre-treatment period

- TEAEs are AEs that develop, worsen, or become serious during the TEAE period

- Post-treatment AEs are AEs that develop, worsen, or become serious during the post-treatment period

AE incidence tables will be presented by SOC (sorted by internationally agreed order), HLGT, HLT, and PT sorted in alphabetical order for each treatment arm, and 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.

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

Deaths

The following deaths summaries will be generated:

- Number (%) of patients who die during study period (TEAE, on-study, post-study) summarized on the safety population by treatment received

- Death in non-randomized patients or randomized and not treated patients

- TEAE leading to death (death as an outcome on the AE CRF page as reported by the Investigator/sub-Investigator) by primary SOC , HLGT, HLT, and PT showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT.

Adjudicated CV events

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

11.4.3.2 Laboratory data and vital signs

See also Section 9.2.2 and Section 9.2.3.

The descriptive statistics (including mean, median, Q1, Q3, SE, minimum and maximum) of all laboratory variables and all vital signs parameters (raw data and changes from baseline) will be calculated for each time point, last and worst values assessed during the treatment period and presented by treatment arm. For selected parameters, mean changes from baseline with the corresponding SE will be plotted over time (at same time points) in each treatment arm. The incidence of PCSAs at any time during the TEAE period (on-treatment PCSAs) will be summarized by treatment arm regardless of 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 are not defined, similar table(s) using the normal range could be provided.

Hepatitis C virus test:

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

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 randomization.

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

Exploratory variables defined in Section 9.3 will be summarized by time points for each treatment arm. For hs-CRP, the incidence of PCSA at any time during the TEAE period will be also summarized by treatment arm using descriptive statistics.

11.4.5 Analyses of quality of life/health economics variables

The analysis of QOL data will be performed on the QOL population. Baseline is defined as the visit 1 (week 0) evaluation.

Data on the 5 items

The responses of each EQ-5D items will be presented by visit for each treatment arm using tables. The tables will contain information on the frequency and proportion of the population reporting level 1 (no problems), level 2 (some problems) and level 3 (extreme problems) per item, by treatment arm.

Scoring the EQ-5D health states

The 5 dimensional 3-level system will be converted into a single index utility score: values for the 243 theoretically possible health states defined by the EuroQol classification are calculated using a regression model (36). The single index utility score will be described by visit and treatment arm.

Absolute change from Baseline to the following time points

The absolute change of health-related QOL (single index utility score) from baseline to following time points will be described in the QOL population for each treatment arm using the same MMRM model as for the continuous secondary efficacy endpoints of lipids anticipated to have a normal distribution and collected at Week 0, Week 4, Week12, Week 24 and Week 36 with corresponding baseline value as covariate.

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, and delegated Investigator staff and sub-Investigator, in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, and the ICH guidelines for Good Clinical Practice (GCP), all applicable laws, rules and regulations.

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

12.2 INFORMED CONSENT

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

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

If informed consent is obtained under special circumstances (emergency, from a guardian, minor, etc.), the method should be specified following the ICH requirements.

The informed consent form used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate ethics committee (IRB/IEC) for approval/favorable opinion.

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, should fully inform the patient of all pertinent aspects of the clinical trial including the written information given 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.

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

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

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

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

The 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 health authorities (competent regulatory authority), as required by local regulation, in addition to the IRB/IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the health authorities (competent regulatory authority) and the IRB/IEC should be informed as soon as possible. They should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the Investigator's Brochure or labeling information, will be sent to the IRB/IEC and to health authorities (competent regulatory authority), as required by local regulation.

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

13   STUDY MONITORING

13.1   RESPONSIBILITIES OF THE INVESTIGATOR(S)

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

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

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

13.2   RESPONSIBILITIES OF THE SPONSOR

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

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

13.3   SOURCE DOCUMENT REQUIREMENTS

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

personnel, the ethics committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the CRFs (eg, patient's medical file, appointment books, original laboratory records, etc). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

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

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

Should a correction be made, the 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 (discrepancy resolution forms [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-CRFs by the Investigator and the Sponsor.

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 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 sub-Investigator 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 CRFs, the Investigator's Brochure 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 sub-Investigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the sub-Investigators of the confidential nature of the clinical trial.

The Investigator and the sub-Investigators 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 /sub-Investigator 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 sub-Investigators 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

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

14.6 INSURANCE COMPENSATION

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

14.7   SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

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

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

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

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

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

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

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

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

14.8.1 By the Sponsor

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

- The information on the product leads to doubt as to the benefit/risk ratio
- Patient enrollment is unsatisfactory
- The Investigator has received from the Sponsor all IMP, means, and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon
- Noncompliance of the Investigator or sub-Investigator, 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 to the clinical trial protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC and/or notification/approval of health authorities (competent regulatory authority) of an amendment, as required by local regulation, 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 case of substantial amendment to the clinical trial protocol, approval from the health authorities (competent regulatory authority) will be sought before implementation.

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

16   BIBLIOGRAPHIC REFERENCES

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3. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001;345(7):494–502.

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