AMENDED CLINICAL TRIAL PROTOCOL NO. 11

COMPOUND: alirocumab (SAR236553/REGN727)

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Effect of Alirocumab (SAR236553/REGN727) on the Occurrence of Cardiovascular Events in Patients Who Have Recently Experienced an Acute Coronary Syndrome

STUDY NUMBER: EFC11570

VERSION DATE/STATUS: 25-Feb-2016

STUDY NAME: ODYSSEY Outcomes

NCT01663402

Version Number:	1	EudraCT IND Number(s)	2011-005698-21 105574
Date:	25-Feb-2016	Total number of pages:	171

HISTORY

Amended Clinical Trial Protocol 11	Version number: 1	Date: 25-Feb-2016
Protocol Amendment 11	Version number: 1	Date: 25-Feb-2016
Amended Clinical Trial Protocol 10 - Colombia	Version number: 1	Date: 27-Jan-2016
Protocol Amendment 10 - Colombia	Version number: 1	Date: 27-Jan-2016
Amended Clinical Trial Protocol 09 - China	Version number: 1	Date: 10-Dec-2015
Protocol Amendment 09 - China	Version number: 1	Date: 10-Dec-2015
Amended Clinical Trial Protocol 08 - Germany	Version number: 1	Date: 08-Dec-2015
Amended Clinical Trial Protocol 08 - Latvia	Version number: 1	Date: 08-Dec-2015
Amended Clinical Trial Protocol 08 - France	Version number: 1	Date: 08-Dec-2015
Amended Clinical Trial Protocol 08	Version number: 1	Date: 16-Apr-2015
Protocol Amendment 08	Version number: 1	Date: 16-Apr-2015
Amended Clinical Trial Protocol 07 - China	Version number: 1	Date: 11-Apr-2014
Protocol Amendment 07 - China	Version number: 1	Date: 11-Apr-2014
Amended Clinical Trial Protocol 06 - Germany	Version number: 1	Date: 13-Jan-2014
Amended Clinical Trial Protocol 06 - Latvia	Version number: 1	Date: 13-Jan-2014
Amended Clinical Trial Protocol 06 - France	Version number: 1	Date: 13-Jan-2014
Amended Clinical Trial Protocol 06	Version number: 2	Date: 05-Dec-2013
Protocol Amendment 06	Version number: 2	Date: 05-Dec-2013
Amended Clinical Trial Protocol 05 - China	Version number: 1	Date: 29-Jul-2013
Protocol Amendment 05 - China	Version number: 1	Date: 29-Jul-2013
Amended Clinical Trial Protocol 04 - Germany	Version number: 1	Date: 25-Mar-2013
Protocol Amendment 04 - Germany	Version number: 1	Date: 25-Mar-2013
Amended Clinical Trial Protocol 03 - Latvia	Version number: 1	Date: 22-Mar-2013
Protocol Amendment 03 - Latvia	Version number: 1	Date: 22-Mar-2013
Amended Clinical Trial Protocol 02 - France	Version number: 1	Date: 01-Mar-2013
Protocol Amendment 02 - France	Version number: 1	Date: 01-Mar-2013
Amended Clinical Trial Protocol 01	Version number: 1	Date: 17-Sep-2012
Protocol Amendment 01	Version number: 1	Date: 17-Sep-2012
Clinical Trial Protocol	Version number: 1	Date: 19-Jul-2012

NAMES AND ADDRESSES

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CLINICAL TRIAL SUMMARY

COMPOUND: ALIROCUMAB (SAR236553/REGN727) **STUDY No: EFC11570** **STUDY NAME: ODYSSEY Outcomes**	
TITLE	A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Effect of Alirocumab (SAR236553/REGN727) on the Occurrence of Cardiovascular Events in Patients Who Have Recently Experienced an Acute Coronary Syndrome
INVESTIGATOR/TRIAL LOCATION	Worldwide – multicenter study
PHASE OF DEVELOPMENT	IIIb
STUDY OBJECTIVE(S)	**Primary objective** The primary objective of this study is to compare the effect of alirocumab with placebo on the occurrence of cardiovascular events (composite endpoint of coronary heart disease (CHD) death, non-fatal myocardial infarction (MI), fatal and non-fatal ischemic stroke, unstable angina requiring hospitalization) in patients who have experienced an acute coronary syndrome (ACS) event 4 to 52 weeks prior to randomization and are treated with an LMT regimen that is statin-intensive (defined as atorvastatin 40 or 80 mg, or rosuvastatin 20 or 40 mg) or at maximally tolerated dose of these given statins and optimized for long-term chronic use with other non-statin LMT(s) at investigator's discretion. **Secondary objective(s)** To compare the efficacy of alirocumab versus placebo on secondary endpoints (any CHD event, major CHD event, any CV event, composite of all-cause mortality/non-fatal MI/non-fatal ischemic stroke, all-cause mortality). *A Clinical Events Committee (CEC) will be established to adjudicate, in a blinded fashion, events corresponding to the primary and secondary cardiovascular endpoints as well as all causes of death.* • To evaluate the safety and tolerability of alirocumab throughout the study. • To evaluate the development of anti- alirocumab antibodies. • To evaluate the effect of alirocumab on low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (ApoB), and non-high-density lipoprotein cholesterol (non-HDL-C).

STUDY DESIGN	This is a double-blind, randomized, placebo-controlled, parallel-group study, multi-national, multicenter study. Randomization will be stratified according to country. The study will comprise 2 periods: • A run-in period (~2 to 16 weeks) during which the background lipid-modifying therapy (LMT) will be adjusted as needed, to ascertain the patient is receiving the required intensive statin treatment (defined as atorvastatin 40 or 80 mg, or rosuvastatin 20 or 40 mg) or the maximally tolerated doses of these given statins, or other non-statin LMTs prior to randomization, and to stabilize this treatment. • A double-blind treatment period (~2 to 5 years) during which the following should be emphasized and reinforced: - compliance with study visits and assessments (all randomized patients, including those who permanently discontinued treatment early, must remain in the study and be followed until the end of the study) - compliance with blinded study treatment (IMP) - compliance with required background LMT regimen (which should be continued for as long as it remains well tolerated) - compliance with requirement to not check cholesterol levels **1/ The Run-in period** starts with a screening visit (V1), continues with a qualifying visit (V2), and ends with a randomization visit (V3). V1 and V2 visits can be separate or combined. The main goals of the run-in period are to ensure that: • patient has received prior to V2 a required LMT regimen that is - statin-intensive (defined as atorvastatin 40 or 80 mg or rosuvastatin 20 or 40 mg) or maximal tolerated dose of one these 2 statins - optimized for long-term chronic use with addition of non-statin LMTs (at Investigator's discretion) - well tolerated after at least 2 weeks of stable dose • lipid criteria outlined in the inclusion criteria are met at V2 • patient (and family) has been adequately informed and agrees to participate in a long-term study with an injection every 2 weeks • patient has been trained to self-administer study drug injections • there are no exclusion criteria The run-in period should be planned carefully, keeping in mind 3 elements: • The visit and time interval requirements with respect to: - Index ACS event - V1 (start of run-in period) - V2/V2b (collection of lipid qualifying labs) - V3 (randomization) • The required background lipid-modifying therapy (LMT) • The coronary revascularization strategy

	Visit and Time Intervals during Run-In Period • Interval between index ACS event and V1 is flexible: - V1 can be performed as early as on the day of the index ACS event and no later than 50 weeks after the index ACS event if V1 and V2 are separate visits (or 50 weeks + 5 days after ACS event, if combined V1/V2) • Run-In Period (from V1 to V3) includes 2 time interval requirements (and both should be met): - Time from V1 to V3 (i.e. from start of run-in period to randomization): this is the duration of the overall run-in period. It should be between 2 weeks (14 days) and 16 weeks (+5 days). - Time from index ACS event to randomization (V3): this includes the time between index ACS event and V1 (start of run-in period) plus time from V1 to V3 (randomization). V3 (randomization) should occur no earlier than 4 weeks (28 days) and no later than 52 weeks (+ 5 days) post index ACS event The run-in period can be conducted in one of 2 ways, depending on whether the required LMT regimen prior to V2 was already administered for at least 2 weeks (and found well tolerated) prior to V1 or not. - If required LMT regimen was not already administered for at least 2 weeks prior to V1, then V1 and V2 should be separate visits with an interval of at least 2 weeks, during which required LMT regimen is administered. V3 (randomization) can occur as soon as the qualifying lipid lab results from V2 are obtained from the central lab (typically within 2-5 days of collection), pending patients meets all eligibility criteria - If it is documented that required LMT regimen was already administered for at least 2 weeks (and found well tolerated) prior to V1, then V1 and V2 can be combined. V3 (randomization) should then occur at least 2 weeks (14 days) after the combined V1/V2 visit An optional additional V2 visit (V2b) with repeat central laboratory lipid assessments may be scheduled if needed. Required background LMT during the run-in period Investigator must have identified prior to V2 (or combined V1/V2), a background LMT regimen that is: • Statin-intensive (defined as atorvastatin 40 or 80 mg, or rosuvastatin 20 or 40 mg), or maximally tolerated dose of these given statins; statins other than atorvastatin, rosuvastatin are not allowed • Optimized for long-term chronic use, with addition of non-statin LMT(s), as per Investigator's discretion; no fibrate allowed (other than fenofibrate or fenofibric acid) - In statin-intolerant patients (defined as intolerance to 2 or more statins), LMT can be optimized with non-statins LMT only (e.g. ezetimibe, or other non-statin LMT) • Well tolerated for at least 2 weeks (at stable dose) prior to V2

	Coronary revascularization strategy When indicated for the treatment of the qualifying index ACS event, a coronary revascularization (PCI, CABG) may have taken place before V1, but may also occur during the run-in period. If a PCI and/or CABG occur during the run-in period, randomization should be scheduled to allow for a minimum 2 week interval between the last coronary procedure and the randomization visit V3. Rescreening A patient who fails screening and left the study may undergo rescreening and re-enter the study (only once) - see Section 6.1.3. **2/ The double-blind treatment period** will continue for 24 months after the closing of randomization ex-China (ie, last date of randomization in all countries except China) or until the target number of events (1613) is reached whichever comes last. • *Closing of randomization ex-China* will occur shortly after a total of 18,000 patients have been randomized (these may or may not include some patients randomized in China). • *Closing of randomization in China* will occur shortly after a total of 600 patients have been randomized in China or at the common study end date (see Section 6.2.2), whichever comes first. Therefore, at the end of the double-blind treatment period, the overall population will include about 18,000 randomized patients who have either died or been followed for a minimum of 24 months, supplemented with an additional subset of patients from China (~600) who may be followed for less than 24 months. The corresponding estimated study duration is 64 months (as described in the sample size considerations – Section 11.1). During this double-blind treatment period, the dosing of alirocumab is intended to achieve LDL-C levels of 30-50 mg/dL (0.78-1.29 mmol/L) which is considered as the physiologic ideal level and to avoid levels of LDL-C that are clearly below the physiologic range (ie,<15 mg/dL or 0.39 mmol/L)). To achieve this goal the following up-titration or down-titration scheme (including discontinuation if needed) will be applied: • At randomization Visit (V3), the starting dose of alirocumab will be 75 mg every 2 weeks (Q2W). At Month 2, patients randomized to alirocumab will, in a blinded manner, either: - Continue alirocumab 75 mg Q2W, if the Month 1 LDL-C is <50 mg/dL (1.29 mmol/L) **OR** - Be up-titrated to alirocumab 150 mg Q2W, if the Month 1 LDL-C is ≥50 mg/dL (1.29 mmol/L). • At subsequent visits, for patients on alirocumab, the following adjustments may be applied depending on the dose received: - For patients receiving 150 mg Q2W: if LDL-C <25 mg/dL (0.65 mmol/L) (including LDL-C < 15 mg/dL [0.39 mmol/L]) on 2 consecutive measurements, down-titration to 75 mg Q2W will be done in a blinded manner at the next visit. Additional monitoring will be implemented until the down-titration is done.

	- For patients receiving 75 mg Q2W:
	  o If LDL-C <25 mg/dL (0.65 mmol/L) but ≥ 15 mg/dL (0.39 mmol/L) on 2 consecutive measurements: alirocumab will be continued but additional monitoring will be implemented, to further confirm the safety of low LDL-C levels.
	  o If LDL-C <15 mg/dL (0.39 mmol/L) on 2 consecutive measurements: alirocumab treatment will be discontinued at the next visit. In order to maintain the blind there will be blinded substitution to placebo injections for the remaining duration of the study. Additional monitoring will be implemented until the study treatment discontinuation is done.
	As lipid values will not be communicated to investigators after randomization to maintain the blind, the continuation of the 75 mg dose, the up-titration to the 150 mg dose, the down-titration from 150 to 75 mg, or discontinuation will occur automatically, without site or patient awareness. Moreover, blinded dose adjustment will avoid the need for dummy titrations in the placebo group.
	Atorvastatin or rosuvastatin daily dose, as well as dose of other non-statin LMT (if applicable), is required to be stable from randomization up to the end of the study, unless safety reasons prompt dose reduction or discontinuation.
	Patients should be on stable diet (NCEP-ATPIII TLC diet or equivalent) throughout the entire study duration from screening to the end of the study.

STUDY POPULATION
Main selection criteria
	Inclusion criteria
	• Hospitalization for ACS (ST-elevation MI, non-ST elevation MI or high-risk unstable angina) defined by:
	  - Ischemic symptoms with unstable pattern, occurring at rest or minimal exertion within 72 hrs of an unscheduled hospital admission, due to presumed or proven obstructive coronary disease **AND at least one of the following:**
	  o Elevated cardiac biomarkers, **OR**
	  o Resting ECG changes consistent with ischemia or infarction AND additional evidence of obstructive coronary disease
	• Patient lipid levels not adequately controlled at V2 (qualifying visit), despite evidence-based lipid lowering therapy (including intensive atorvastatin/rosuvastatin therapy or maximally tolerated dose of either of these 2 statins), or other non-statin LMTs. Inadequate lipid control means that patient must meet <u>at least one</u> of the following criteria at V2 to qualify:
	  - LDL-C ≥ 70 mg/dL (≥1.81 mmol/L), or
	  - ApoB ≥ 80 mg/dL (≥ 0.8 g/L), or
	  - non-HDL-C ≥ 100 mg/dL (≥2.59 mmol/L)
	Exclusion criteria
	• All of the 3 following criteria are concomitantly present at the qualifying visit (V2):
	  - LDL-C <70 mg/dL (<1.81 mmol/L), and
	  - ApoB < 80 mg/dL (< 0.8 g/L), and
	  - non-HDL-C <100 mg/dL (<2.59 mmol/L)

	NOTE: *If not all 3 but only 1 or 2 criteria are present then the patient may qualify.* • Age < 40 years • Patients in whom the qualifying index ACS event occurred less than 4 weeks (28 days) or more than 52 weeks (+ 5 days) prior to randomization visit (V3) • Not on stable LMT doses (statin and/or non-statin LMT) for at least 2 weeks prior to qualifying visit (V2) • Uncontrolled hypertension (multiple readings with SBP > 180 mmHg or DBP > 110 mmHg) at V3 • New York Heart Association Class III or IV congestive heart failure persisting despite treatment or if measured LVEF <25% • Known history of hemorrhagic stroke • Fasting serum triglycerides (TG) >400 mg/dL (>4.52 mmol/L) prior to randomization • New ACS event occurring within 2 weeks prior to the randomization Visit (V3) • Coronary revascularization (PCI or CABG) planned after randomization and/or performed within 2 weeks prior to the randomization Visit (V3)
Total expected number of patients	Approximately 18,600 patients should be randomized (9,300 patients / group). Approximately 1400 sites
STUDY TREATMENT(s) **Investigational medicinal product(s)** **Formulation**	Alirocumab Sterile alirocumab drug product supplied at a concentration of 75 mg/mL or 150 mg/mL in histidine, pH 6.0, polysorbate 20, and sucrose
Route(s) of administration	Subcutaneous (SC) injection in the abdomen, thigh or outer area of upper arm
Dose regimen	75 mg every 2 weeks **OR** 75 mg every 2 weeks up to Month 2 followed by 150 mg every 2 weeks at Month 2 onwards (with criteria for up-titration and down-titration as indicated above)
INJECTION FOR TRAINING AND PLACEBO COMPARATOR **Investigational medicinal product(s) (if applicable)** **Formulation**	Placebo Same formulation as alirocumab without the addition of protein.
Route(s) of administration	Subcutaneous (SC) injection in the abdomen, thigh or outer area of upper arm.

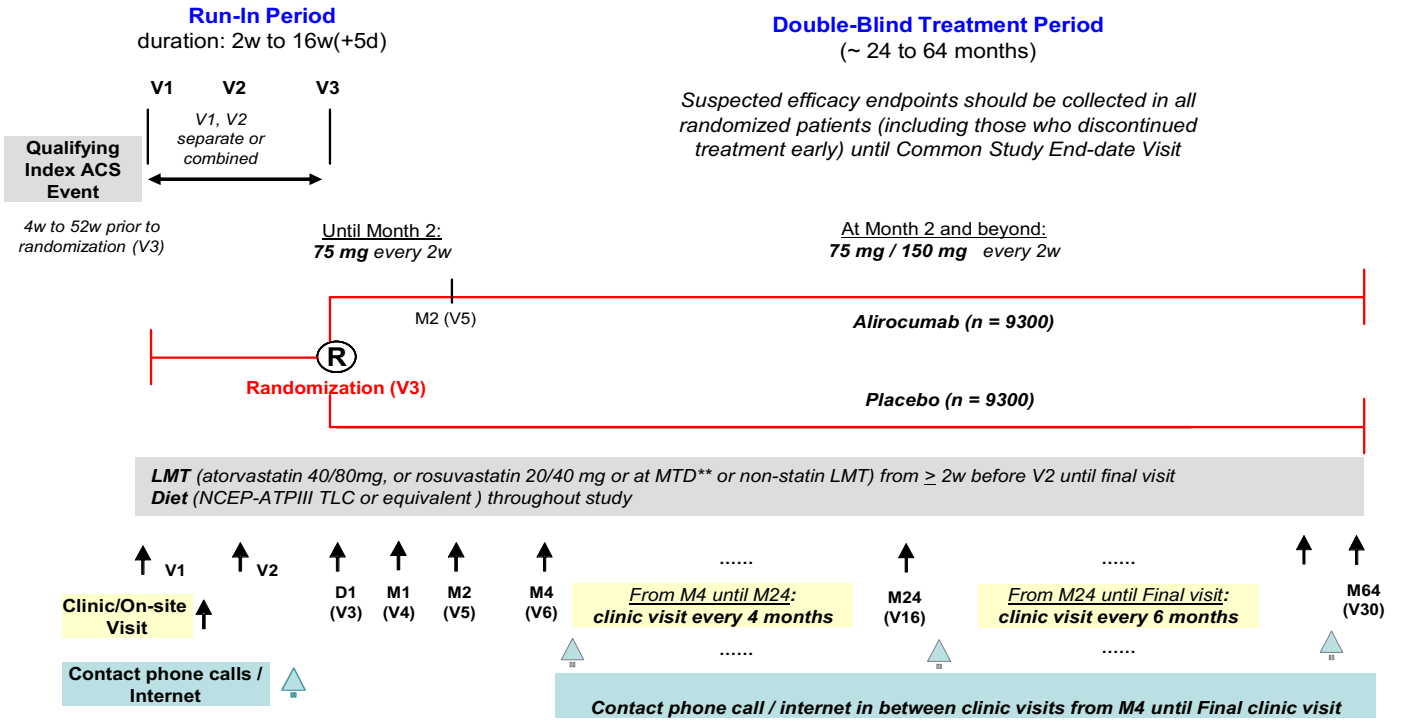
ENDPOINT(S)	**Primary endpoint** • Time from randomization to first occurrence of one of the following Clinical Events, as determined by the CEC: - CHD death - Any non-fatal MI - Fatal and non-fatal ischemic stroke - Unstable angina requiring hospitalization **Main Secondary Efficacy Endpoint(s):** • Time from randomization to first occurrence of any CHD event (major CHD event, unstable angina requiring hospitalization, ischemia-driven coronary revascularization procedure) • Time from randomization to first occurrence of any major CHD event (CHD death, non-fatal MI) • Time from randomization to first occurrence of any CV event defined as follows: any non-fatal CHD event, any CV death, and non-fatal ischemic stroke • Time from randomization to first occurrence of all-cause mortality, non-fatal MI, non-fatal ischemic stroke • Time from randomization to death (all-cause mortality) **Other Secondary Efficacy Endpoint(s):** • Components of the primary end point considered individually: CHD death, or non-fatal MI, or fatal and non-fatal ischemic stroke, unstable angina requiring hospitalization • Ischemia-driven coronary revascularization procedure • Congestive heart failure requiring hospitalization **Safety Endpoint(s):** • Safety endpoints: all adverse events, heart rate and blood pressure, hematology and biochemistry assessments **Other Endpoint(s):** • Anti- alirocumab antibodies assessed throughout the study • The percent change in calculated LDL-C, in ApoB and non HDL-C

ASSESSMENT SCHEDULE	**Visits scheduled during the run-in period:** Please refer to Run-In Period section under 'Study Design' **Visits schedule during the double-blind treatment period:** • Clinic/On-site visits: - For the first year: visit at Month1, Month 2, Month 4 and then every 4 months (Month 8, Month 12) - For the second year: visit every 4 months - For the subsequent years: visit every 6 months up to the end of the study **Contacts schedule during the double-blind treatment period:** • A phone call or contact via internet (as permitted by institutional privacy policies) should occur in between clinic visits throughout the study with the goal of maintaining a contact with the patient about every 2 months during first 24 months, and about every 3 months thereafter.
STATISTICAL CONSIDERATIONS	**Sample size determination:** Based on the targeted population for the study, a Kaplan-Meier event rate in placebo group of 11.4% at 48 months (3.8% at 12 months, 6.4% at 24 months, 9.0% at 36 months) is assumed. With a 40-month recruitment period, a 64-month total study duration, 9300 patients per group (total 18,600), and 1,613 patients experiencing at least one primary endpoint event, the study has 90% power (one-sided Logrank test at the overall 0.025 alpha level) assuming a 15% risk reduction associated with alirocumab treatment. The sample size calculation takes into account two interim analyses. **Analysis Populations:** Randomized population includes any patients who have been allocated to a randomized treatment regardless of whether the treatment kit was used or not. Efficacy analyses will be performed on the intention-to-treat (ITT) population, consisting of all randomized patients. Patients in the ITT population will be analyzed according to the treatment group allocated by randomization. The safety population consists of the randomized population who actually received at least one dose or partial dose of IMP analyzed according to the treatment actually received. **Primary Analysis:** The primary endpoint will be compared between treatment groups by a log-rank test, stratified by region (North America, South America, Western Europe, Eastern Europe, Asia, other region). The distribution will be estimated by treatment group with Kaplan-Meier methodology. Treatment hazard ratios (HRs) for the primary endpoint will be estimated from Cox regression models stratified by region. **Analysis of the main secondary endpoints** A hierarchical procedure will be used to control the type I error and handle multiple endpoints. If the primary endpoint analysis is significant (at the 0.0001 one-sided alpha level at the second interim analysis or at the 0.0249 one-sided alpha level at the final analysis), main secondary efficacy endpoints will be tested sequentially, using the order defined in section "Primary and secondary

	endpoints". Secondary endpoints will be analyzed in the ITT population using the same statistical methodology as for the primary endpoint (time-to-event analysis). **Safety analysis** Safety analysis (adverse events, laboratory, and vital signs) will be descriptive, based on the safety population. The safety analysis will focus on the Treatment Emergent Adverse Event (TEAE) period. This period is defined as the time from the first to the last dose of double-blind IMP + 70 days (10 weeks). **Interim analyses:** Patients will be followed until 1,613 patients experience at least one primary endpoint event or for approximately 24 months after the closing of randomization ex-China, whichever comes last. Interim analyses for futility will be performed, under the supervision of the CV DMC, when 50% and 75% of events have occurred. An interim analysis for efficacy will be performed when 75% of events have occurred. Control of the type I and type II error will be ensured using gamma (-5) spending function for type II error (futility) and Gamma (-22) for type I error (efficacy). Stopping rules details are further described in Section 11.5.
DURATION OF STUDY PERIOD (per patient)	The duration of the run-in period (V1 to V3) should be between 2 weeks (14 days) and 16 weeks (+ 5 days). Randomization must occur no earlier than 4 weeks (28 days) and no later than 52 weeks (+ 5 days) after the index ACS event. The double-blind treatment period will continue for 24 months after the closing of randomization ex-China (last date for randomization in all countries except China) or until the target number of events (1613) is reached whichever comes last. The corresponding estimated study duration is 64 months (as described in the sample size considerations). All patients, even those who have achieved an endpoint or prematurely discontinued study treatment, will be followed from randomization until the common study end date.

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



Run-In Period (duration between 2w and 16w+5d)
- **V1:** earliest is on day of ACS; latest is 50w post ACS (if V1, V2 separate) or 50w (+5d) post ACS (if combined V1/V2)
- **V2:** collection qualifying lipid labs after receiving lipid-modifying therapy (LMT) that is statin-intensive (atorvastatin 40/80mg, or rosuvastatin 20/40 mg or at max. tolerated dose), optimized for long-term chronic use (with addition of non-statin LMT at Inv. Discretion) and well tolerated after ≥ 2w of stable LMT dose
- **V3**: earliest is 4w and latest is 52w(+5d) post-index ACS

After randomization
- Final clinic visit (Common Study End Date Visit, V30 M64) should be completed in all randomized patients (regardless of whether they are still on treatment or had discontinued treatment early) and should occur between Common Study End Date (CSED) and CSED+30days.

ACS: acute coronary syndrome, LMT: lipid-modifying therapy, MTD: maximal tolerated dose

1.2 STUDY FLOW CHART

1.2.1 On-site/Clinic visits during the study

	Screening (run-in period)		Double-blind period										
On-site / Clinic Visit	V1 (or combined V1/V2)	V2[b]	V3	V4	V5	V6	V8	V10	V12/V14/V18/V22/V26	V16/V20/V24/V28	V30[m]		V70[n]
Week(W) / Month(M)[a]	≥ 2w prior to V3 AND 0 to 50w post index ACS	W-2 After ≥2w required LMT	M0 (D1) 4 to 52w post index ACS	M1	M2	M4	M8	M12	M16/M20/M30/M42/M54	M24/M36/M48/M60	M64 Final visit (common study end date visit)		Early end of treatment visit
											Study completers	Prematurely discontinued patients[m]	
Design:													
Informed Consent / Patient Demography	X												
Inclusion / Exclusion Criteria	X	X	X										
Medical / surgical history (incl. relevant family history e.g. allergy), alcohol / smoking habits	X												
Prior Medication History[c]	X												
Physical Examination	X		X					X		X	X		X
Body weight	X		X			X	X	X	X	X	X		X
Height	X												
Randomization			X										

	Screening (run-in period)		Double-blind period										
On-site / Clinic Visit	V1 (or combined V1/V2)	V2[b]	V3	V4	V5	V6	V8	V10	V12/V14/V18/V22/V26	V16/V20/V24/V28	V30[m]		V70[n]
Week(W) / Month(M)[a]	≥ 2w prior to V3 AND 0 to 50w post index ACS	W-2 After ≥2w required LMT	M0 (D1) 4 to 52w post index ACS	M1	M2	M4	M8	M12	M16/M20/M30/M42/M54	M24/M36/M48/M60	M64 Final visit (common study end date visit)		Early end of treatment visit
											Study completers	Prematurely discontinued patients[m]	
Patient diary dispensation/ review / collection[d]			X	X	X	X	X	X	X	X	X		X
IVRS/IWRS contact	X	X	X		X	X	X	X	X	X	X	X	X
Treatment:													
Injection training	X[e]	X[e]	X[f]										
Double Blind Investigational Medicinal Product (IMP) kit dispensation			X		X	X	X	X	X	X			
Compliance check of IMP (review patient diary and treatment kit) and data collection on IMP administration				X	X	X	X	X	X	X	X		X
Compliance check for atorvastatin, rosuvastatin, ± other LMTs		X	X	X	X	X	X	X	X	X	X	X (statin, ezetimibe only)	X
Concomitant Medication[c]	X	X	X	X	X	X	X	X	X	X	X		X

	Screening (run-in period)		Double-blind period										
On-site / Clinic Visit	V1 (or combined V1/V2)	V2[b]	V3	V4	V5	V6	V8	V10	V12/V14/V18/V22/V26	V16/V20/V24/V28	V30[m]		V70[n]
Week(W) / Month(M)[a]	≥ 2w prior to V3 AND 0 to 50w post index ACS	W-2 After ≥2w required LMT	M0 (D1) 4 to 52w post index ACS	M1	M2	M4	M8	M12	M16/M20/M30/M42/M54	M24/M36/M48/M60	M64 Final visit (common study end date visit)		Early end of treatment visit
											Study completers	Prematurely discontinued patients[m]	
Vital signs:													
Heart rate, blood pressure	X	X	X	X	X	X	X	X	X	X	X		X
Efficacy Endpoints (primary and secondary) and **Cardiovascular Events of Interest (other than efficacy endpoints)**													
Update patient contact information (incl. patient's family, patient's GP/cardiologist)	X	X	X	X	X	X	X	X	X	X			X
Check patient card (with mention of study participation and site contact information)			X	X	X	X	X	X	X	X			X
Collect information on suspected efficacy endpoints				X	X	X	X	X	X	X	X	X	X

	Screening (run-in period)		Double-blind period										
On-site / Clinic Visit	V1 (or combined V1/V2)	V2[b]	V3	V4	V5	V6	V8	V10	V12/V14/V18/V22/V26	V16/V20/V24/V28	V30[m]		V70[n]
Week(W) / Month(M)[a]	≥ 2w prior to V3 AND 0 to 50w post index ACS	W-2 After ≥2w required LMT	M0 (D1) 4 to 52w post index ACS	M1	M2	M4	M8	M12	M16/M20/M30/M42/M54	M24/M36/M48/M60	M64 Final visit (common study end date visit)		Early end of treatment visit
											Study completers	Prematurely discontinued patients[m]	
Collect cardiovascular events of interest other than efficacy endpoints (related to peripheral arterial disease, venous thromboembolic events)				X	X	X	X	X	X	X	X	X	X
Safety:													
AE /SAE recording	X	X	X	X	X	X	X	X	X	X	X	X (related and/or serious AE)	X
12-lead ECG			X								X		X
Laboratory Testing / Efficacy:													
TC, LDL-C, HDL-C, TG, non-HDL-C	X	X	X	X	X	X	X	X	X	X	X	X	X
ApoB	X	X	X			X		X		X (M24 only)	X	X	X
ApoA-1, ratio ApoB/ApoA-1, Lp (a)			X			X		X			X		X

	Screening (run-in period)		Double-blind period										
On-site / Clinic Visit	V1 (or combined V1/V2)	V2[b]	V3	V4	V5	V6	V8	V10	V12/V14/V18/V22/V26	V16/V20/V24/V28	V30[m]		V70[n]
Week(W) / Month(M)[a]	≥ 2w prior to V3 AND 0 to 50w post index ACS	W-2 After ≥2w required LMT	M0 (D1) 4 to 52w post index ACS	M1	M2	M4	M8	M12	M16/M20/M30/M42/M54	M24/M36/M48/M60	M64 Final visit (common study end date visit)		Early end of treatment visit
											Study completers	Prematurely discontinued patients[m]	
Laboratory Testing / Safety:													
Hematology and chemistry[g]	X		X					X		X	X		X
Creatine phosphokinase (CPK)	X		X	X		X		X	X	X	X		X
Liver panel[h]	X		X	X		X		X	X	X	X		X
Hepatitis B surface antigen	X												
Hepatitis C antibody[h]	X		X								X		X
Serum pregnancy test[h]	X												
Urine pregnancy test[h]			X			X	X	X	X	X	X		X
Urinalysis (at selected sites only) [h]			X					X		X	X		X

	Screening (run-in period)		Double-blind period										
On-site / Clinic Visit	V1 (or combined V1/V2)	V2[b]	V3	V4	V5	V6	V8	V10	V12/V14/V18/V22/V26	V16/V20/V24/V28	V30[m]		V70[n]
Week(W) / Month(M)[a]	≥ 2w prior to V3 AND 0 to 50w post index ACS	W-2 After ≥2w required LMT	M0 (D1) 4 to 52w post index ACS	M1	M2	M4	M8	M12	M16/M20/M30/M42/M54	M24/M36/M48/M60	M64 Final visit (common study end date visit)		Early end of treatment visit
											Study completers	Prematurely discontinued patients[m]	
Laboratory Testing / Other:													
HbA_{1c}	X		X					X		X	X	X	X
High sensitivity C-reactive protein (hs-CRP)			X			X		X			X		X
Anti- alirocumab antibodies			X		X	X		X		X	X	X	X
Library samples[j]			X			X		X			X		X
Genomics													
Genomics consent (optional)			X										
Collect specimen (if genomics consent)[k]			X										
Quality of Life Variables													
EQ-5D patient questionnaire[l]			X		X	X	X	X	X	X	X		X

a Window period for visits: randomization visit (V3) should be performed no earlier than 4w(28d) post-index ACS, and no later than 52w(+5d) post index ACS, window at Months 1 and 2 is ± 7 days, and for all other subsequent visits it is ± 14 days (in case of major IMP issue, please refer to Section 8.9).

b V2 is main visit for collection of qualifying lipid labs (sent to Central Labs) following ≥ 2w of well tolerated, stable required LMT (i.e. statin-intensive, and optimized for long-term chronic use with addition of non-statin LMT, at Investigator's discretion). If required LMT treatment was already administered prior to V1 for ≥ 2w, V1 and V2 visits can be combined as one visit. Otherwise, interval between V1 and V2 should be ≥2w. After 2 to 5 days, V2 lab results are obtained, and patient may be randomized if all eligibility criteria are met. Overall, duration of run-in period (between V1 and V3, or between combined V1/V2 and V3) should be between 2w (14 days) and 16w(+5 days). V3 (randomization) should occur no earlier than 4w (28 days) and no later than 52w (+5days) post ACS index event. An optional visit (V2b) with repeat Central Laboratory assessments may be scheduled during run-in after V2 in the following scenario: V2 labs are not met, however patient was kept in run-in period after 'failed' V2 and subsequently develops intolerance to statin leading to lower statin dose; patient may then be retested with lower statin dose. A V2b visit should be performed if V2 labs are met but statin dose (or non-statin LMT regimen) was subsequently increased, after V2.

c Prior medication: prior to screening visit V1 and randomization (IMP administration); only restrictions pertain to fibrates (other than fenofibrate, fenofibric acid) and statins (other than atorvastatin, rosuvastatin) which should be discontinued at V1. Concomitant medication: received concomitantly to the IMP, from first IMP to the end of treatment + 70 days.

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

e At least 2 training injections are required on 2 different occasions. These can take place at V1, V2, Combined V1/V2, or V3 at the discretion of the study site. First training injection (with placebo) must be done before V3. The initial IMP double-blind injection (active or placebo) performed at V3 may serve as second training injection. If needed, additional training injections (with placebo) are available

f Injection is performed at randomization Visit Month 0/Day 1 on site with double-blind study treatment kit allocated by IVRS (can serve as training injection).

g Hematology includes: complete blood cell count (CBC) including hematocrit, hemoglobin, red blood cell count, reticulocyte count, white blood cell count with differential count, and platelets (Note: reticulocyte not done at V1). Chemistry includes: glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, uric acid, LDH, total protein, albumin, and γGT.

h Liver panel: ALT, AST, alkaline phosphatase (ALP), and total bilirubin. Hepatitis C antibody: In case of positive hepatitis C antibody test, a blood sample will be collected at a subsequent visit and sent to Covance Central Lab for further confirmatory testing

i Pregnancy tests (serum, urine) in Women of Child Bearing Potential (WOCBP) only. Urinalysis to be performed only at selected sites (see Section 10).

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

k If blood sample not collected at randomization, could be collected at any time during the study.

l EQ-5D patient questionnaire will only be administered in patients still on treatment, for prematurely (permanently) discontinued patients the last administration will be done at the early end of treatment visit.

m Common study end date (CSED) will occur 24 months after the closing of randomization ex-China or after the target number of events (1613) is reached whichever comes last. A final clinic visit V30 (CSED visit, Month 64) should be completed within 30 days of CSED for all randomized patients regardless of the compliance with study treatment (see Section 10.1.5.1.4). Reduced assessments in 'Prematurely discontinued patients' column apply only if V30 occurs more than 6 months after V70 (see Section 10.3.4).

n For patients who prematurely discontinue blinded study treatment (IMP): as a general rule, any IMP treatment discontinuation should be initially considered temporary, and Investigator should make best effort to resume IMP treatment as early as practically possible, after several weeks or months (pending there are no safety concerns), and perform all study visits and assessments as usual. Investigator is strongly encouraged to discuss with monitoring team before considering any treatment discontinuation as permanent. A discussion with National Coordinator may occur regarding other possible options If and when a treatment discontinuation is considered 'permanent', an extra visit (early end of treatment visit V70) should be performed as soon as practically possible (within 1 month) after IMP discontinuation is considered permanent by Investigator. Such patients (with premature permanent treatment discontinuation) must continue to remain in the study and should return for all study visits until the common study end date (final visit V30). Complete usual study assessments should be performed for 6 months following V70. Thereafter, assessments are reduced to collection of suspected efficacy endpoints, cardiovascular events of interest other than efficacy endpoints (peripheral arterial disease, venous thromboembolic events – see Section 9.3.7), related and/or serious AEs , selected concomitant medications (statins, ezetimibe) and selected labs (anti- alirocumab antibodies, lipid panel, ApoB, HbA1c) (See Section 10.3.4).

1.2.2 Contacts (phone calls or contacts via internet) during the study

Month (M)[a]	**M6/ M10/ M14/ M18/ M22/ M27/ M33/ M39/ M45/ M51/ M57/ M62**
Visit	V7/ V9/ V11/ V13/ V15/ V17/ V19/ V21/ V23/ V25/ V27/ V29
Phone Call	☎ or Internet contact [b]
Update patient contact information (incl.patient's family, patient's GP/cardiologist) [d]	X
Review compliance with statins, other LMTs [d]	X
Collect information on IMP administration (and remind patient to complete diary)	X
Collect information on possible occurrence of efficacy endpoints (and remind patient to call site in case of hospitalization and not wait until next visit) [d]	X
Reminders [c]	X

a Although flexibility is allowed in the timing of phone call in between the on-site/clinic visits, it should be scheduled with the goal of maintaining a contact with the patient about every 2 months during first 24 months, and about every 3 months thereafter. Having no phone or e mail contact with a patient for a prolonged period (>4 months) should be avoided as much as possible. Some additional instructions for scheduling phone call may be provided at time of interim analysis.

b In addition, an optional service will be made available for sites to send via SMS/text messages appointment and injection reminders to any patient who wishes to and is able to receive them. These contacts will conform with privacy regulations at each site.

c Reminders as applicable for IMP administration schedule, timing of next appointments, fasting conditions for next lab assessments, bring the diary, and used and unused kits at the next study site visit.

d In patients who have permanently discontinued treatment, contacts will include: update of patient contact information (incl. family and patient's GP/cardiologist), collection of suspected efficacy endpoints during entire study until common study end-date, and review of compliance with statin and other LMT for 6 months following V70, and with statin and ezetimibe thereafter.

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3 LIST OF ABBREVIATIONS

ACS	Acute coronary syndrome
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
Apo	Apolipoprotein
ARF	Acute renal failure
AST	Aspartate aminotransferase
BMI	Body mass index
BP	Blood pressure
CABG	Coronary artery bypass graft surgery
CEC	Clinical Events Committee
CHD	Coronary Heart Disease
CI	Confidence interval
CIB	Clinical Investigator's brochure
CPK	Creatine Phosphokinase
CSED	Common Study End Date
CSR	Clinical Study Report
CV	Cardiovascular
DBTP	Double Blind Treatment Period
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DRF	Discrepancy resolution form
ECG	Electrocardiogram
eg	Exempli gratia = for example
e-SMS	Emergency Scientific & Medical Services
eCRF	Electronic case report form
EDTA	Ethylene diamine tetra-acetic acid
eGFR	Estimated Glomerular Filtration Rate
FH	Familial hypercholesterolemia
FPI	First patient in
FU	Follow-up
GCP	Good Clinical Practice
γGT	Gamma-glutamyl Transferase
HbA_{1c}	Glycated hemoglobin A_{1c}
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
HLGT	High Level Group Term
HLT	High level term

HR	Hazard ratio
hs-CRP	High-sensitivity C-reactive protein
IA	Interim Analysis
ICF	Informed consent form
ICH	International Conference on Harmonization
ie	Id est = that is
IEC	Independent ethics committee
IMP	Investigational Medicinal Product
IRB	Institutional review board
ITT	Intent-to-treat
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LDH	Lactate dehydrogenase
LDL-C	Low-density lipoprotein cholesterol
LDL-R	Low-density lipoprotein receptor
LLN	Lower limit of normal range
LMT	Lipid modifying therapy
Lp(a)	Lipoprotein a
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
mmHg	Millimeter of mercury
NCEPATPIII	National Cholesterol Education Program Adult Treatment Panel III
NYHA	New York heart association
NIMP	Non-Investigational Medicinal Product
PAD	Peripheral Arterial Disease
PCI	Percutaneous coronary intervention
PCSA	Potentially Clinically Significant Abnormality
PCSK9	Proprotein convertase subtilisin/kexin type 9
PD	Pharmacodynamics
PK	Pharmacokinetics
PT	Preferred term
PTC	Product technical complaint
Q2W	every 2 weeks
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SNP	Single nucleotide polymorphisms
SOC	System organ class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TOTAL-C	Total cholesterol
TEAE	Treatment Emergent Adverse Event
TG	Triglycerides

TLC	Therapeutic lifestyle changes
ULN	Upper limit of normal range
WBC	White blood cell
WOCBP	Women of childbearing potential

4 INTRODUCTION AND RATIONALE

Alirocumab is a fully human monoclonal antibody that binds PCSK9. All relevant information concerning the compound is available in the latest version of the Clinical Investigator's Brochure (CIB) (1).

Alirocumab is also referred to as SAR236557/REGN727. However, for this study protocol ODYSSEY Outcomes (EFC11570), it will be referred to as alirocumab.

Patients with recent acute coronary syndrome (ACS) are at very high risk for suffering recurrent coronary events in the near term. In approximately 10% of patients with ACS, cardiovascular death, recurrent myocardial infarction (MI), or stroke, occur within 1 year (2). Based on the results of large clinical trials, early intensive statin therapy has become formally endorsed as a treatment recommendation (3) (4) for patients with ACS (5). The use of high-dose statins has been largely demonstrated to be safe and well tolerated (6).

Both epidemiological and pharmacological intervention trials have demonstrated a strong and linear relationship between the levels of low-density lipoprotein cholesterol (LDL-C) and cardiovascular (CV) events. Three of the most recent statin trials, the TNT trial (7), the PROVE-IT trial (8), and the JUPITER trial (9), have provided new information on the relationship between low levels of LDL-C and CV event rates, with demonstration that treatment of LDL-C to a mean level of 77 mg/dL, 62 mg/dL, or 55 mg/dL was associated with a greater reduction in CV events.

The overall results of these trials have helped to demonstrate the continued linear relationship between LDL-C and CV events to these levels and to support the establishment of 70 mg/dL as a treatment goal for high-risk patients (10) (11). The lack of a demonstrated existing threshold or plateau between LDL-C and CV risk from these studies begs the question that even further reductions beyond the 55-77 mg/dL observed in these trials could provide additional benefits in CV event reduction. In the above three trials post-hoc analyses were conducted analyzing both the efficacy (in regards to CV event rates) and safety of achieving LDL-C levels at the lower end of the treatment spectrum.

- The PROVE-IT/TIMI-22 trial examined patients with LDL-C <100 mg/dL in the atorvastatin arm and found a lower rate of CV events in the patients with achieved LDL-C levels in the <40 mg/dL and the 40-60 mg/dL groups than those patients with higher achieved LDL-C levels (12).
- In the TNT trial, patients in the lowest quartile of achieved LDL-C had value <64 mg/dL and a mean LDL-C level of 54 mg/dL as compared to means of 70, 83, 97 and 122 mg/dL in the remaining quintiles. Within these quintiles, there was a strong and significant relationship between the lower achieved LDL-C levels and lower rates of major CV events ($p<0.0001$) (13).

- In the JUPITER trial, the investigators split the patients in the rosuvastatin group into two cohorts of achieved LDL-C <50 mg/dL (n=4154) and >50 mg/dL (n=4000) and compared them to the placebo group. Those that had achieved LDL-C <50 mg/dL demonstrated significantly lower rates of CV events than either of the other two groups (14).

In none of these three analyses there was evidence of an adverse safety signal observed with patients that achieved these lower levels of LDL-C. A recent communication compared patients who achieved a LDL-C ≤30 mg/dL (n=621) versus those with LDL-C >30 mg/dL (n=7533) (15). No differences in overall TEAEs and many other specific AEs were observed, with the exception of a greater incidence in insomnia (1.6/100 PY versus. 1.2/100 PY; p=0.031) and hematuria (1.8 /100 PY versus. 1.1/100 PY; p=0.0007) among patients with LDL-C ≤30 mg/dL. The rate of clinically relevant declines in eGFR (≥30%) tended to be lower among patients with lower reduction in LDL-C.

Similar findings have been observed in a patient-level meta-analysis conducted by the Cholesterol Trialists Treatment Collaboration. This examination of 26 large statin CV event trials encompassing approximately 170,000 patients has demonstrated that 20% reduction in major CV events can be derived for every 1 mmol/L (38.6 mg/dl) reduction in LDL-C, even in patients whose starting LDL-C levels are less than 2 mmol/L (77 mg/dl) (16). This meta-analysis has also demonstrated no significant safety risks with long-term cholesterol reduction treatment, including cancer (17).

These data provide strong support for the concept that high risk patients may derive further benefits of reductions in LDL-C to levels <50 mg/dl (1.29 mmol/L). A number of lipid and cardiovascular experts have begun to consider lower LDL-C values as the ideal level for humans with the concept that LDL-C levels of 30-50 mg/dL (0.78-1.29 mmol/L) represent the physiological ideal. This is based upon the findings from both the observed LDL-C levels in human newborns as well as in humans with more primitive/paleolithic lifestyles (18) (19) (20).

However, many high CV risk patients cannot achieve such levels with currently available lipid-lowering drugs. Furthermore, a significant number of high-risk patients even fail to achieve their recommended LDL-C target levels (21) (22) and most CV events are actually not prevented, leaving a substantial “residual risk” for patients and thus additional pharmacologic therapies for the prevention of coronary heart disease (CHD) remains essential, particularly for high-risk patients with ACS.

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

Proprotein convertase subtilisin kexin type 9 (PCSK9) belongs to the subtilisin family of serine proteases and is highly expressed in the liver. PCSK9 is involved in regulating the levels of the low-density lipoprotein receptor (LDL-R) protein (23) (24). Once PCSK9 is secreted into plasma it directly binds to the LDL-R and promotes its degradation. The increased degradation of LDLRs leads to a reduced LDL-C removal, and therefore higher LDL-C circulating levels. Experiments with mice have shown that increasing PCSK9 protein levels decreases levels of LDL-R protein in the liver while PCSK9 knockout mice have increased levels of LDL-R in the liver (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 CHD (27) (28).

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 (29).

Summary of selected clinical studies with alirocumab:

Phase 1 studies

Three Phase 1 studies have been conducted with alirocumab and evaluated the safety, tolerability and pharmacokinetics/pharmacodynamics (PK/PD) profile. Two studies were single dose administration (R727-CL-0902 study with intravenous (IV) administration of doses from 0.3 to 12 mg/kg and R727-CL-0904 study with SC administration of doses from 50 to 250 mg) conducted in healthy volunteers with LDL-C >100 mg/dL for whom statin therapy was not indicated. The third study (R727-CL-1001 study) was conducted in hypercholesterolemic patients (familial or non-familial) with single to multiple subcutaneous (SC) administration of 50 mg, 100 mg, 150 mg and 200 mg either as add-on to stable doses of atorvastatin from 10 to 40 mg/day or as monotherapy.

Results of these Phase 1 studies showed that alirocumab administered to healthy volunteers and patients either by IV or SC administration was generally well tolerated at all doses; treatment emergent adverse events (TEAEs) did not display a dose relationship. No pattern of adverse events related to the drug was identified. In all these Phase 1 studies, administration of alirocumab induced rapid, substantial, and sustained reductions from baseline in LDL-C, up to 60%. The magnitude and duration of these reductions were positively related to the dose administered. It should also be noted that in the R727-CL-1001 study, results were similar in the familial and non-familial hypercholesterolemic patients.

Overall, a total of 109 subjects were exposed to at least one dose of alirocumab in these three Phases 1 studies.

Phase 2 studies:

Three Phase 2 studies have been conducted:

- Two dose / dose regimen finding studies (DFI11565 and R727-CL-1003) with the main objective to assess, over a 12 week-treatment duration, the effects on LDL-C level reduction of several doses of alirocumab and 2 dose-regimens (50 mg, 100 mg and 150 mg every 2 weeks (Q2W), and 200 mg and 300 mg every 4 weeks (Q4W) for the DFI11565 study and 150 mg Q2W, 150 mg, 200 mg, and 300 mg Q4W for the R727-CL-1003 study). DFI11565 was conducted in hypercholesterolemic patients with elevated LDL-C (≥100 mg/dL or 2.59 mmol/L) despite stable atorvastatin therapy. R727-CL-1003 study was conducted in patients with heterozygous familial hypercholesterolemia (heFH) and with elevated LDLC (≥100 mg/dL or 2.59 mmol/L) despite their current lipid lowering therapy (statin ± ezetimibe).

- The third Phase 2 study (DFI11566) aimed to evaluate in patients with hypercholesterolemia the efficacy and safety of the co-administration of alirocumab 150 mg every 2 weeks and a high daily dose of atorvastatin (80 mg) in comparison to the co-administration of placebo and this high daily dose of atorvastatin (80 mg), in patients previously receiving a stable dose of atorvastatin 10 mg. This treatment scheme is anticipated to be used when a rapid decrease in LDLC level is needed, eg after an acute coronary syndrome.

Overall, a total of 274 patients were exposed to at least one dose of alirocumab in these three Phases 2 studies.

Efficacy results:

In both dose finding studies, statistically significant decreases in percent change from baseline in LDL-C at 12 weeks were observed in all alirocumab groups compared to the placebo group. In the DFI11565 study for the Q2W dose regimen, the greatest decrease was seen in the 150 mg Q2W group (-72.4%) compared with a small decrease in the placebo group (-5.1%) (LS mean difference versus placebo of -67.3%; $p<0.0001$). The decreases observed with the doses administered Q2W were maintained from the first injection throughout the study and more particularly throughout the interval period between the injections. A similar pattern with the dose of 150 mg Q2W was seen in the R727-CL-1003 study with a significant decrease from baseline of -67.9% versus -10.7% in the placebo group (LS mean difference versus. placebo of -57.3%; $p<0.0001$). Large decreases in LDL-C from baseline to 12 weeks were also observed with doses administered Q4W; however, the treatment effect was not fully maintained over a 4-week period (ie, the time interval between the two injections).

The same magnitude of effect was shown for the dose of 150 mg Q2W in the DFI11566 study, with a statistically significant decrease in LDL-C at 8 weeks in the alirocumab 150 mg + atorvastatin 80 mg group (median reduction of – 70.6 %) compared with the placebo + atorvastatin 80 mg group (median reduction of – 26.9 %).

In all three studies, consistent results were seen for total-cholesterol (TC), ApoB, non-HDL-C and ApoB/ApoA-1 ratio. A favorable trend was also observed for high-density lipoprotein cholesterol (HDL-C), apolipoprotein A-1 (ApoA-1), triglycerides (TG) and lipoprotein a (Lp (a)).

Safety results

Alirocumab was well tolerated in all completed Phase 2 studies throughout the treatment period and for all treatment groups. Injection sites reactions were reported in patients including placebo-treated patients; the reporting of these events was greatest in the R727-CL-1003 study (40.3% in alirocumab-treated patients versus 12.6% and 3.3% in DFI11565 and DFI 11566, respectively); however these events were generally transient with no dose relationship. Rare cases of hypersensitivity reactions were reported. Among all SAEs reported for all alirocumab studies, only one case, leucocytoclastic vasculitis (angiitis), was reported as being related to alirocumab (DFI11565 study). The patient developed one episode of diarrhea followed on the same evening by rash on arms, legs and abdomen, 9-days after the first administration of alirocumab 300 mg Q4W. The diagnosis was confirmed by skin biopsy. The patient was discontinued from study drug

but completed the study. The patient fully recovered from the rash after a course of tapering steroid administration. A positive antidrug antibody (ADA) status was reported with a low titer of 30 (corresponding to the minimum titer detected by the assay), only observed at the Week 20 assessment (ie, between 2.5 and 3 months after the event) with a negative retest after 6 months. Additional tests also obtained 6 months after the event were unremarkable and included normal immunoglobulin levels, a negative antinuclear antibody test, and only a mild elevation of CRP. No particular signal was noted for TEAEs related to musculoskeletal or connective tissue disorders as well as there were no LFT elevations. Given the limited published data on the safety of LDL-C level <25 mg/dL, a prespecified statistical analysis was conducted in patients reaching LDL-C value <25mg/dL in all the Phase 2 studies with no specific safety signal identified over the study duration. In the two dose finding studies (DFI11565 and R727-CL-1003), the proportion of patients reaching an LDL-C <25 mg/dL in the 150 mg Q2W group was from 31.3% to 44.8%. In DFI11566, with atorvastatin 80mg the proportion in the 150 mg Q2W group was approximately 50%.

For detailed information, please refer to the CIB (1).

Dose and regimen selection

Based on the results of the above studies, the Q2W dosing regimen was selected as the most appropriate to maintain constant LDL-C lowering throughout the interdosing interval. Since the magnitude of effect observed with 150 mg Q2W may not be needed to achieve the LDL-C goal in all patients, a lower dose of 75 mg was selected as a starting dose. This selection is also based on the LDL-C reduction needed to provide the best benefit in terms of CVD reduction, and potential safety considerations regarding low LDL-C values.

The current and most relevant evidence around the effects of achieved low LDL-C levels comes from examinations of large statin trials (12) (13) (14) as presented above, and patients with PCSK9 loss-of-function mutations (30). The patients achieving the lower levels of LDL-C had the lower CV event rates. To date, there is no evidence that very low LDL-C levels result in significant adverse health effects based on these sources of information, though this conclusion is based on a relatively low number of patients with very low LDL-C who have been studied.

Rationale for protocol design:

The objective of the present study is to evaluate the ability of alirocumab to reduce CV events in patients who recently experienced an ACS event and despite intensive statin therapy or at maximally tolerated dose don't reach the goal as defined in the guidelines for these very high risk patients.

For this randomized, double-blind, placebo-controlled study it is estimated that approximately 18,600 patients will be enrolled, of which about 18,000 will either have died or have had a minimum follow-up of approximately 24 months, supplemented by an additional subset of patients from China (~600) possibly followed for less than 24 months. Total study duration will be approximately 5 years. Randomization will occur within 52 weeks of the index ACS event and patients will enter a run-in period during which (if not already receiving such treatment before V1) they will have to be stabilized on an LMT that includes intensive statin therapy (defined as

atorvastatin 40 or 80 mg or rosuvastatin 20 or 40 mg) or maximally tolerated dose of either of these 2 agents in case of tolerability issues, and is optimized for long-term chronic use with non-statin LMT (at Investigator's discretion). Only patients not reaching goal, ie, LDL-C ≥70 mg/d L (≥1.81 mmol/L) or ApoB ≥80 mg/dL (≥ 0.8 g/L) or non HDL-C ≥100 mg/dL (≥2.59 mmol/L) under such treatment, will be randomized to either background LMT therapy + alirocumab or background LMT therapy + placebo. The choice to select eligible patients on two other lipid parameters, in addition to the traditional LDL-C target lipid parameter, is based on the acceptance that ApoB and non HDL-C can be considered to be equal to LDL-C in risk prediction (10) (11). Some adjustment in the lipid-modifying background therapy can occur during the run-in period, e.g., in case of poor tolerance to intensive statin therapy.

The proposed primary efficacy endpoint is the effect of alirocumab compared to placebo on top of best evidence background therapy on the occurrence of the following composite endpoint: coronary heart disease (CHD) death, non-fatal myocardial infarction, non-fatal and fatal ischaemic stroke, and unstable angina requiring hospitalization with stringent criteria for the definition of this later endpoint. Based on other contemporary studies (31) (32), the primary endpoint event rate in the placebo group is assumed to be 11.4% at 48 months (3.8% at 12 months, 6.4% at 24 months, 9.0% at 36 months).

In this trial, all patients will be initially treated with 75 mg Q2W, and only those patients whose LDL-C levels remain equal or higher than 50 mg/dL (1.29 mmol/L) after 1 month of treatment will be up-titrated to 150 mg Q2W (at Month 2).

With this treatment scheme, most patients can be expected to achieve their target LDL-C, as recommended by international guidelines committees (10) (11). Furthermore, the up-titration threshold set at 50 mg/dL (1.29 mmol/L), supported by findings from post-hoc analyses of the PROVE-IT, TNT and JUPITER trials, will promote the achievement of an LDL-C level within the 'physiologic ideal' zone.

Available data do not point to a lower limit of safe and effective cholesterol lowering (12) (13) (14). However, this conclusion is based on a relatively low number of patients with very low LDL-C who have been studied. In this trial, with the use of 75 mg as starting dose and a target-based up-titration scheme, it is anticipated that few patients will reach a LDL-C level below 25 mg/dL (0.65 mmol/L). For patients titrated-up to 150 mg Q2W who reach a LDL-C level below 25 mg/dL (0.65 mmol/L), a down-titration from 150 mg to 75 mg Q2W will be performed. For patients on 75 mg Q2W, two different rules will be applied depending on the level of LDL-C. In case of an LDL-C level below 25 mg/dL (0.65 mmol/L) but greater than or equal to 15 mg/dL (0.39 mmol/L), additional monitoring will be implemented to further confirm the safety of low LDL-C levels. Due to lack of available information at a LDL-C level below 15 mg/dL (0.39 mmol/L) (except in subjects with rare genetic mutations), patients reaching such low levels on 2 consecutive occasions will have their treatment discontinued.

Addition to alirocumab in patients not yet at goal should derive to further benefits in terms of reductions in LDL-C. However a greater treatment effect in patients with higher LDL-C levels at baseline cannot be ruled out. For this reason, the distribution of LDL-C levels at baseline will be monitored to ensure that the initial assumption of a mean baseline LDL-C of 90-100 mg: dL (2.33-2.59 mmol/L) is fulfilled. In case it is observed that the distribution is shifted to lower

baseline levels of LDL-C, a capping of the number of patients with a baseline LDL-C between 70-80 mg/dL may be considered.

Conclusion on the benefit risk assessment with alirocumab

Based on the clinical data available to date, treatment with alirocumab has demonstrated a significant LDL-C lowering effect and was generally well tolerated in a population of patients with non-familial hypercholesterolemia or with heterozygous familial hypercholesterolemia. The efficacy on LDL-C was associated with consistent results in total cholesterol, ApoB, non-HDL-C and ApoB/ApoA-1 ratio and a positive trend for HDL-C, TG and Lp (a). There was no evidence that alirocumab adversely affects other cardiovascular risk factors, eg, body weight, blood pressure, glucose, or CRP.

In terms of identified or potential risks with alirocumab, local injection site reactions were reported as well as rare cases of hypersensitivity reactions. Local injection site reactions were reported in both alirocumab and placebo treatment groups with no evidence of dose relationship. These AEs will be monitored in the Phase 3 program including this study. A substantial proportion of patients reached low LDL-C levels (<25 mg/dl [0.65 mmol/L]) with no safety signal identified to date. However, further monitoring for potential AEs associated with low LDL-C levels will be implemented. Although no particular signal related to CPK elevation and associated AEs (e.g., myalgia, rhabdomyolysis) was detected with the co-administration of alirocumab and statins over a maximum duration of 12 weeks, monitoring for such adverse events will continue for all the Phase 3 studies, including this study. An independent Data Monitoring Committee (DMC), dedicated to the EFC11570 study and identified as CV DMC, will meet periodically to review unblinded safety data. This CV DMC will have a close connection with the other independent DMC implemented for all Phase 3 studies evaluating the efficacy and safety of alirocumab on LDL-C (identified as Phase 3a DMC).

This CV outcome study is undertaken to demonstrate in patients who recently experienced an ACS event and who are not at their LDL-C goal despite an intensive lipid-lowering therapy that alirocumab 75mg Q2W or 75 mg Q2W / 150 mg Q2W provides an additional benefit with the reduction of CV events.

5 STUDY OBJECTIVES

5.1 PRIMARY

The primary objective of this study is to compare the effect of alirocumab with placebo on the occurrence of cardiovascular events (composite endpoint of coronary heart disease (CHD) death, non-fatal myocardial infarction (MI), fatal and non-fatal ischemic stroke, unstable angina requiring hospitalization) in patients who have experienced an acute coronary syndrome (ACS) event 4 to 52 weeks prior to randomization and are treated with an LMT regimen that is statin-intensive (defined as atorvastatin 40 or 80 mg, or rosuvastatin 20 or 40 mg) or at maximally tolerated dose of these given statins, and optimized for long-term chronic use with other non-statin LMT(s) at Investigator's discretion.

5.2 SECONDARY

The secondary objectives are:

- To compare the efficacy of alirocumab versus placebo on secondary endpoints (any CHD event, major CHD event, any CV event, composite of all-cause mortality/non-fatal MI/non-fatal ischemic stroke, all-cause mortality)

A Clinical Events Committee (CEC) will be established to adjudicate, in a blinded fashion, events corresponding to the primary and secondary cardiovascular endpoints as well as all causes of death.

- To evaluate the safety and tolerability of alirocumab throughout the study
- To evaluate the development of anti-alirocumab antibodies
- To evaluate the effect of alirocumab on low-density lipoprotein cholesterol (LDL-C) apolipoprotein B (ApoB), and non-high-density lipoprotein cholesterol (non-HDL-C)

6 STUDY DESIGN

This is a double-blind, randomized, placebo-controlled, balanced (1:1, alirocumab: placebo), parallel-group, multi-national, multicenter study. Randomization will take place between 4 weeks (28 days) and 52 weeks (+5 days) after the qualifying index ACS event and will be stratified according to country.

Prior to this randomization, eligible patients will enter a run-in period of at least 2 weeks (14 days) but no more than 16 weeks (+ 5 days), during which Investigator ensures that patient has received an LMT regimen that is:

- statin-intensive (defined as atorvastatin 40 or 80 mg or rosuvastatin 20 or 40 mg) or maximal tolerated dose of one of these 2 statins, and
- optimized for long-term chronic use (with other non-statin LMT(s) at Investigator's discretion), and
- well tolerated after at least 2 weeks of stable dose prior to V2.

Following this run-in period, only patients not reaching goal, ie, LDL-C ≥70 mg/dL (≥1.81 mmol/L) or ApoB ≥ 80 mg/dL (≥ 0.8 g/L) or non-HDL-C ≥ 100 mg/dL (≥ 2.59 mmol/L) after ≥ 2 weeks of such treatment, will be randomized to either background LMT + alirocumab, or background LMT + placebo. All patients randomized to alirocumab will initially receive alirocumab 75 mg Q2W. Patients on alirocumab not reaching the target LDL-C level (< 50 mg/dL) at Month 1 will have their dose up-titrated to 150 mg Q2W at Month 2 in a blinded fashion.

The double-blind treatment period will continue for 24 months after the closing of randomization ex-China (last date of randomization in all countries except China) or until the target number of events (1613) is reached whichever comes last.

- *Closing of randomization ex-China* will occur shortly after a total of 18,000 patients have been randomized (these may or may not include some patients randomized in China).
- *Closing of randomization in China* will occur shortly after a total of 600 patients have been randomized in China or at the common study end date (see Section 6.2.2), whichever comes first.

NOTE 1: *Throughout this document, 'China' refers to mainland China, excluding Hong Kong.*

NOTE 2: *Continued enrolment of patients in China after the initial target of 18,000 randomized globally has been reached, and leading to an increase in sample size to about 18,600 patients, will be implemented only after appropriate local authorizations in China have been obtained.*

The corresponding estimated study duration is 64 months. All patients, even if they have achieved an endpoint or those who have prematurely discontinued the study treatment, will be asked to remain in the study until the common study end date (so that all suspected efficacy endpoints are collected until the end of study).

6.1 DESCRIPTION OF THE PROTOCOL

The study will comprise 2 periods:

- A run-in period (~ 2 to 16 weeks) during which the background lipid-modifying therapy (LMT) will be adjusted as needed, to ascertain the patient is receiving the required intensive statin treatment (defined as atorvastatin 40 or 80 mg, or rosuvastatin 20 or 40 mg) or the maximally tolerated doses of these given statins, or other non-statin LMTs prior to randomization, and to stabilize this treatment.
- A double-blind treatment period (~ 2 to 5 years) during which the following should be emphasized and reinforced:
  - *compliance with study visits and assessments*: all randomized patients (including those who permanently discontinued treatment early) must remain in the study and be followed until the end of the study; sites should maintain a contact with the patient every 2 to 3 months (as per study assessments) throughout the study and contact information (for patient, family, GP/cardiologist) should be periodically updated as necessary; in addition, it is important to continuously remind patients (and their family) throughout the study that, in case of hospitalization, patient (or patient's family member) should inform site (Investigator, Coordinator) as soon as possible and not wait until the next visit.
  - *compliance with blinded study treatment (IMP):* patients should be treated with blinded study treatment for as long as possible, unless safety concerns arise (in case of temporary interruption, blinded study treatment should be restarted, as best as possible, unless there are safety concerns; to be assessed by Investigator)
  - *compliance with required background LMT regimen* (as determined from run-in period see Section 6.1.1): intensive statin therapy (atorvastatin 40 or 80 mg or rosuvastatin 20 or 40 mg) or maximal tolerated dose of one these 2 statins, optimized with addition of non-statin LMTs (at Investigator's discretion) should be continued for as long as this regimen remains well tolerated. If tolerability concerns arise, LMT can be modified, based on clinical tolerability only (see Figure 2, Section 8.8.1)
  - *compliance with requirement to not check cholesterol levels:* every effort should be made to refrain from checking cholesterol levels during the entire duration of the study (to preserve double-blind nature of the study); Investigators are encouraged to communicate and explain this aspect to patient, patient's family and patient's family doctor/cardiologist at the time of informed consent and run-in period, and throughout the study (along with rationale that patient receives best possible LMT with intensive or maximal tolerated statin therapy with addition of non-statin LMTs, at Investigator' s discretion).

Patients should be on stable diet (NCEP-ATPIII TLC diet or equivalent) throughout the entire study duration from screening to the end of the study.

6.1.1 Run-in period

6.1.1.1 Overview of run-in period

The Run-in period starts with a screening visit (V1), continues with a qualifying visit (V2), and ends with a randomization visit (V3). V1 and V2 visits can be separate visits or, in some circumstances (described below), can be combined as one visit (V1/V2)

The main goals of the run-in period are to ensure that:

- the patient has received prior to the qualifying visit (V2), a required LMT regimen that is:
  - statin-intensive (defined as atorvastatin 40 or 80 mg or rosuvastatin 20 or 40 mg) or maximal tolerated dose of one these 2 statins, and
  - optimized for long-term chronic use with addition of non-statin LMTs (at Investigator's discretion), and
  - well tolerated after at least 2 weeks of stable dose
- lipid criteria outlined in the inclusion criteria are met at V2
- patient (and his/her family) has been adequately informed and agrees to participate in a long-term study (up to ~ 5 years) with an injection every 2 weeks
- patient has been trained on at least 2 occasions to self-administer study drug injections
  - at least 2 training injections are required on 2 different occasions. These can take place at V1, V2, Combined V1/V2, or V3 at the discretion of the study site. If the second training injection is done at V3, the randomization study drug injection may be used as the second training injection
- there are no exclusion criteria

The run-in period should be planned carefully, keeping in mind 3 elements:

- The visit and time interval requirements with respect to:
  - Index ACS event
  - V1 (start of run-in period)
  - V2/V2b (collection of lipid qualifying labs)
  - V3 (randomization)
- The required background lipid-modifying therapy (LMT)
- The coronary revascularization strategy

6.1.1.2 Visit and Time Intervals during Run-In Period

6.1.1.2.1 From qualifying index ACS event to Start of Run-In Period (V1)

Interval between index ACS event and V1 is flexible. V1 can be performed:

- as early as on the day of the index ACS event
- but no later than 50 weeks after the index ACS event if V1 and V2 are separate visits (or 50 weeks + 5 days after ACS event, if combined V1/V2)

NOTE: *In case of several ACS before V1, the last ACS event fulfilling the inclusion criteria before V1 should be used as the index ACS event. In case of rescreening, see* Section 6.1.3.2.

Prior to V1, relevant information should be provided to the patient and his/her family about the study, before obtaining informed consent. Investigators are encouraged to assess and explain the following aspects to the patient and his/her family:

- Willingness to participate in a long-term study (up to ~ 5 years) in which patient will receive an injection every 2 weeks
- Willingness to come back periodically for study visits for several years (even if study treatment was discontinued early), and to remain in contact with Investigator/Coordinator during entire duration of the study, including in case of hospitalizations outside of enrolling site

It is also advisable that the Investigator communicates with the patient's general practitioner/family doctor/cardiologist about main aspects of the study requirements (e.g. background LMT during run-in, and requirement for blinding of lipid levels during the entire study).

6.1.1.2.2 Run-In Period (from V1 to V3)

The run-in period includes 2 time interval requirements (and both should be met):

- Time from V1 to V3: this is the duration of overall run-in period. It should be between 2 weeks (14 days) and 16 weeks (+5days)
- Time from index ACS event to randomization (V3): this includes the run-in period plus time between index ACS event and V1. Randomization (V3) should occur no earlier than 4 weeks (28days) and no later than 52 weeks (+ 5 days) after the index ACS event

The run-in period can be conducted in one of 2 ways, depending on whether the required LMT regimen prior to V2 lipid qualifying labs (see below Section 6.1.1.3) was already administered for at least 2 weeks (and found well tolerated) prior to V1 or not.

If required LMT regimen was not already administered for at least 2 weeks prior to V1, then V1 and V2 visits should be separate visits with an interval of at least 2 weeks:

- Investigator will administer required LMT regimen at or after V1
- V2 should occur after at least 2 weeks of treatment with the required LMT regimen (at stable doses), and no further LMT increase is planned (i.e. no addition of LMT treatment and/or no increase in doses of statin or non-statin is planned)
- V3 (randomization) can occur as soon as the qualifying lipid lab results from V2 are obtained from the central lab (typically results are available within 2-5 days of collection) and it is determined that the patient meets the lipid eligibility criteria and all other eligibility criteria have been confirmed

If it is documented that the required LMT regimen was already administered for at least 2 weeks prior to V1 (and found well tolerated), then V1 and V2 can be combined as one visit (combined V1/V2); this scenario can occur under the following circumstances:

- patient has been on stable, well tolerated dose of atorvastatin 40/80 mg or rosuvastatin 20/40 mg for at least 2 weeks prior to V1
- patient has documented intolerance to the required high doses of atorvastatin or rosuvastatin, but has been on a stable well tolerated low/moderate dose of atorvastatin or rosuvastatin for at least 2 weeks prior to V1
- patient has documented intolerance to statin therapy (i.e. intolerance to 2 or more statins) and has been on at least 2 weeks of non-statin LMT prior to V1
- patient has documented intolerance to statin therapy (i.e. intolerance to 2 or more statins), and Investigator has determined (after discussion with patient, his/her family and patient's GP/cardiologist) that best option for the long-term is to not administer any chronic LMT (statin or non-statin) to the patient

NOTE*: Prior to conducting a combined V1/V2, prior LMT treatments (and, if applicable, intolerance to statin) must be documented in a source document such as a discharge summary, history and physical, clinic note or consultation report to confirm treatment.*

In case of combined V1/V2 visit, after qualifying lipid labs are collected and if patient is eligible, V3 (randomization) should occur at least 2 weeks (14 days) after the combined V1/V2 visit.

6.1.1.2.3 Optional V2b Visit

An optional additional V2 visit with repeat central laboratory lipid assessments (V2b) may be scheduled in the following circumstance:

- V2 labs indicate that lipid inclusion criteria are not met: Investigator has the option to keep patient in the study and continue the run-in period while monitoring tolerability of statin-intensive LMT regimen. If patient subsequently develops intolerance to statin-intensive LMT leading to lowering the statin dose (or to using the other statin or, if documented intolerance to 2 or more statins, to using no statin), Investigator can repeat V2 labs after the new lower (and well tolerated) statin dose has been administered for at least

2 weeks (and ideally 4 weeks, in order for the V2b lipid labs to fully reflect the effect of the new lower dose rather than the previous higher statin dose)

Below are 2 other scenarios, one in which V2b must be performed (i.e. not optional) and one in which V2b cannot be performed:

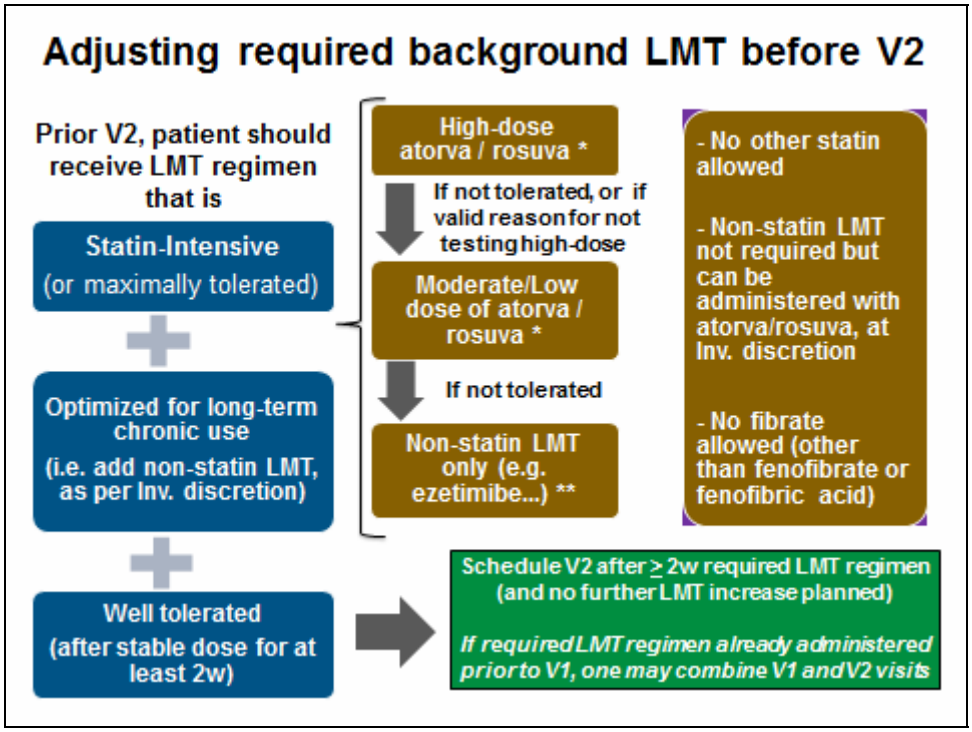
- If V2 lipid labs inclusion criteria are met however statin dose (or non-statin LMT regimen) was subsequently increased after V2, then a V2b visit (i.e. with repeat central laboratory lipid qualifying assessments) must be performed to check if patient still qualifies with this higher dose.
- If V2 lipid labs inclusion criteria were not met with a given statin regimen, a V2b visit (ie, with repeat central laboratory lipid qualifying assessments) cannot be performed when using the same statin regimen (ie, no 'second chance' regarding lipid inclusion critera is allowed, using same statin regimen).

6.1.1.3 Required background LMT during the run-in period

Since the study aims to evaluate whether alirocumab is beneficial in patients who do not meet desired lipid levels with high-dose statins, one of the main objectives of the run-in period is that the Investigator has identified prior to V2 (or combined V1/V2), a background LMT regimen that meets all following criteria:

- statin-intensive (defined as atorvastatin 40 or 80 mg, or rosuvastatin 20 or 40 mg), or with maximally tolerated dose of these given statins
- optimized for long-term chronic use (i.e. with the intent of administering such treatment, on a chronic basis, for several years)
- well tolerated (after stable dose for at least 2 weeks)

Figure 1 - Overview Adjustment Required Background LMT during Run-In Period



* Atorvastatin high-dose (80, 40 mg daily), moderate/low dose (20, 10 mg daily)
Rosuvastatin high-dose (40, 20 mg daily), moderate/low dose (10, 5 mg daily)

** In statin-intolerant patients (2 or more statins), after careful assessment (incl. after review of latest evidence and after discussion with the patient, his/her family and patient's primary GP/cardiologist), Investigator may determine that no background chronic LMT is appropriate for the patient.

6.1.1.3.1 Statin-intensive treatment

Statin-intensive treatment is defined as high-dose atorvastatin (40 or 80 mg daily) or high-dose rosuvastatin (20 or 40 mg daily); these should be administered to all patients, including:

- statin-naive patients (i.e. patients not receiving any LMT, or patients on non-statin LMT)
- patients previously treated with other statins (statins other than atorvastatin or rosuvastatin are not allowed during the run-in period, and should be discontinued at V1)
- patients treated with and tolerating moderate or low doses of atorvastatin or rosuvastatin

High-dose atorvastatin/rosuvastatin:

- may have been administered prior to V1, and should then be continued at V1 and beyond, or
- can be initiated at V1, or
- can be reached progressively during the interval between V1 and V2, starting with lower doses at V1 (such as in patients with known prior statin tolerability issues, or with advanced age, or low body mass index or other concerns)

If high doses of atorvastatin/rosuvastatin are administered but not tolerated, then Investigator should administer the maximal tolerated dose of atorvastatin 10 or 20 mg, or rosuvastatin 5 or 10 mg.

In infrequent instances, when there is a valid reason as per Investigator's best judgment (including but not limited to prior statin tolerability issues, advanced age, low body mass index or other concerns), it is acceptable to use during the run-in period, only a low or moderate dose of atorvastatin (10 or 20 mg) or rosuvastatin (5 or 10 mg), and not use high doses, as described above. In such instances however, the reasons for not treating the patient with high dose statin should be documented in source notes.

Statin-intolerant patients:

In statin-intolerant patients (defined as intolerance to at least 2 statins), LMT can be optimized with non-statins LMT only (e.g. ezetimibe, or other non-statin LMT). After careful assessment (and ideally after discussion with patient's primary GP/cardiologist), Investigator may alternatively elect to not to administer any LMT at all (i.e. use of non-statin LMT is not mandatory in statin-intolerant patients – see Section 6.1.1.3.2 below).

6.1.1.3.2 Optimized for long-term chronic use

Prior to V2, LMT should be also optimized for long-term chronic use, as per Investigator's discretion.

This means that, in addition to being statin-intensive, Investigator may choose to administer (before V2) non-statin LMT that he/she deems beneficial for the patient for long-term chronic administration. Addition of non-statin LMT to chronic administration of atorvastatin or rosuvastatin however is not required, and should be determined by the Investigator, and after discussion with patient's GP/cardiologist, and on the basis of available clinical evidence and clinical judgment to support such a strategy.

During the run-in period, fibrates (other than fenofibrate or fenofibric acid) are prohibited, and should be discontinued at V1, if patient was receiving such treatments.

6.1.1.3.3 Well tolerated LMT

Well tolerated LMT is defined as an LMT that is well tolerated after at least 2 weeks of stable LMT doses (statin and/or non-statin LMT) prior to V2(or V2b).

6.1.2 Coronary revascularization strategy

When indicated for the treatment of the qualifying index ACS event, a coronary revascularization (PCI, CABG) may have taken place before V1, but may also occur during the run-in period.

If a PCI and/or CABG occurs during the run-in period, randomization should be scheduled to allow for a minimum 2 week interval between the last coronary procedure and the randomization visit V3 (see exclusion criterion E18).

6.1.3 Screen failures and Rescreening

6.1.3.1 Screen failure

Screen failure may occur in (but is not limited to) the following circumstances:

- Lipid inclusion criteria are not met on the V2/V2b qualifying labs
- Presence of exclusionary non-lipid laboratory abnormalities (including on repeat labs) during run-in
- New ACS event or coronary intervention occurring within 2 weeks prior to last possible randomization day (52 weeks + 5 days) after original index ACS event, in a patient who had not yet been randomized (See exclusion criteria)
- Duration of run-in period has exceeded 16 weeks (+5 days)

6.1.3.2 Rescreening

A patient who failed screening and left the study may undergo rescreening and re-enter the study (only once) under the following scenarios:

- If lipid inclusion criteria at V2/V2b (LDL-C, non-HDL-C, Apo B) were met during a (first initial) screening with a given statin dose and patient failed screening for a reason not related to these lipid inclusion criteria, then patient can be rescreened using the same statin at same dose or, if documented intolerance, with same statin at lower dose or other authorized statin or no statin (later option only if documented intolerance to 2 or more statins). Reasons include but are not limited to: correction of exclusionary labs other than lipid inclusion criteria (ie, other than LDL-C, non-HDL-C, Apo B) , patient and/or family changed their mind regarding trial participation
- However, if lipid inclusion criteria at V2/V2b (LDL-C, non-HDL-C, Apo B) were not met during a (first) screening with a given statin dose, patient cannot be rescreened using the same statin at same dose (i.e. no ‘second chance’ regarding lipid inclusion critera is allowed, using same statin regimen). Such patient can only be rescreened if statin intolerance has developed subsequently (to be documented in source notes) leading to using same statin at lower dose, or using other authorized statin or no statin (later option only if documented intolerance to 2 or more statins).

In such cases, the first screening will be referred to as ‘Screening 1’, and the rescreening as ‘Screening 2’.

For the index ACS event relative to the rescreening, one should:

- Use the original index ACS event (ie, from Screening 1) as the index ACS event for Screening 2, if the run-in period can be restarted and completed within 52 weeks (+5 days) of the original index ACS event
- Otherwise, use a new (subsequent) qualifying ACS event as the index event

6.1.4 Double-blind treatment period

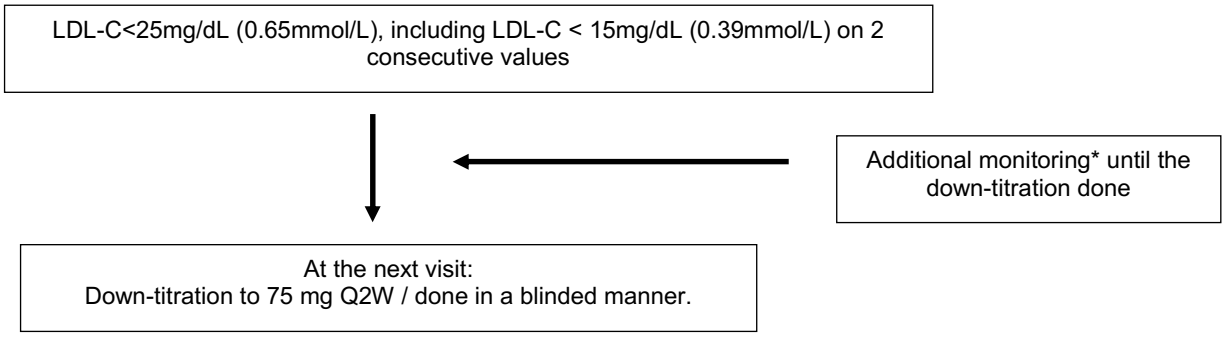
The double-blind treatment period will continue until 24 months after the closing of randomization ex-China (ie, last date of randomization in all countries except China) or until the target number of events (1613) is reached, whichever comes last (see beginning of Section 6). The corresponding estimated study duration is 64 months (as described in the sample size considerations – Section 11.1).

During this double-blind treatment period, the dosing of alirocumab is intended to achieve LDL-C levels of 30-50 mg/dL (0.78-1.29 mmol/L) which is considered as the physiologic ideal level and to avoid levels of LDL-C that are clearly below the physiologic range (ie, <15 mg/dL). To achieve this goal the following up-titration or down-titration scheme (including discontinuation if needed) will be applied:

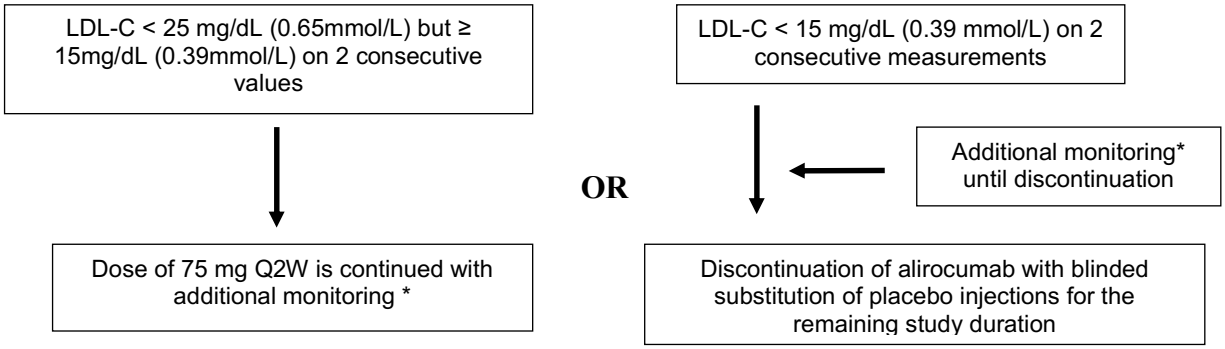
- At randomization Visit (V3), the starting dose of alirocumab will be 75 mg every 2 weeks (Q2W). At Month 2 (V5), patients randomized to alirocumab will, in a blinded manner, either:
  - Continue alirocumab 75 mg Q2W, if the Month 1 (V4) LDL-C is <50 mg/dL (1.29 mmol/L) **OR**
  - Be titrated-up to alirocumab 150 mg Q2W, if the Month 1 (V4) LDL-C is ≥50 mg/dL (1.29 mmol/L)

NOTE: *In case Month 1 (V4) LDL-C is not available or not valid (e.g. issue with blood sample) for potential up-titration at Month 2 (V5), the next available LDL-C sample at Month 2 (V5) will be used for potential up-titration at Month 4 (V6).*

- At subsequent visits, for patients on alirocumab, the following adjustments may be applied:
  - For patients receiving 150 mg Q2W:



- For patients receiving 75 mg Q2W:



* NOTE: *Additional monitoring includes*:

- *Patient level listing for surveillance and review for patients who are managed by IVRS/IWRS (i.e with planned automatic down-titration from 150mg to 75mg, or switch from 75mg to placebo)*
- *Individual patient profile monitoring for potential site alerts for patients on alirocumab 75 mg and not managed by IVRS/IWRS (i.e. with no planned automatic down-titration or switch to placebo by IVRS/IWRS)*

Further details are provided in Appendix A.

As lipid values will not be communicated to investigators after randomization to maintain the blind, the continuation of the 75 mg dose, the up-titration to the 150 mg dose, the down-titration from 150 to 75 mg, or discontinuation will occur automatically, without site or patient awareness. Moreover, blinded dose adjustment will avoid the need for dummy titrations in the placebo group.

Patients who achieve 2 consecutive LDL-C levels <25 mg/dL (0.65 mmol/L) during the study will be monitored and managed as per Appendix A . An independent external physician will be notified by the central laboratory of 2 consecutive LDL-C <25 mg/dL (0.65 mmol/L). The independent physician will review the unmasked LDL-C values and patient safety data, in close collaboration with the dedicated member of the Phase 3a DMC implemented for all Phase 3 studies evaluating the efficacy and safety of alirocumab on LDL-C (called Phase 3a studies). This dedicated Phase 3a DMC member will then transmit any information as necessary to the common member involved in both DMCs (Phase 3a DMC and CV DMC).

Atorvastatin or rosuvastatin daily dose as well as dose of other non-statin LMT (if applicable) should be stable from randomization up to the common study end date, unless safety reasons prompt dose reduction or discontinuation (see also Section 8.8.1 and Section 10.3).

NOTE*: all randomized patients, even those who have achieved an endpoint or prematurely discontinued the study treatment should be followed during the entire duration of the study (ie, from randomization until the common study end date visit V30) for collection of suspected efficacy endpoints (please refer to Section 10.3 for further details on handling of patients who discontinued treatment early).*

6.2 DURATION OF STUDY PARTICIPATION.

6.2.1 Duration of study participation for each patient

The duration of the run-in period (V1 to V3) must be between 2 weeks (14 days) and 16 weeks (+5 days). Randomization must occur no earlier than 4 weeks (28 days) and no later than 52 weeks (+ 5 days) after the index ACS event.

The double-blind treatment period will continue (for about 2 to 5 years) until 24 months after the closing of randomization ex-China (ie, after last date of randomization in all countries except China) or until the target number of events (1613) is reached, whichever comes last (see beginning of Section 6).

The corresponding estimated study duration is 64 months (as described in the sample size considerations).

6.2.2 Determination of end of clinical trial (all patients) - Common Study End Date

All randomized patients will be followed up until the Common Study End Date (CSED) visit, which is the final study visit (and a clinic visit) to be scheduled for each patient within 30 days of the CSED (see Section 10.1.5.4).

The CSED is defined as the date corresponding to 24 months after the closing of randomization ex-China (last date of randomization in all countries except China) or date when the target number of events (1613) is reached, whichever comes last.

- *Closing of randomization ex-China* will occur shortly after a total of 18,000 patients have been randomized (these may or may not include some patients randomized in China).

Closing of randomization in China will occur shortly after a total of 600 patients have been randomized in China or at the common study end date (see Section 6.2.2), whichever comes first.

Therefore, at the end of the double-blind treatment period, the overall randomized population will include about 18,000 patients who have either died or been followed for a minimum of 24 months, supplemented with an additional subset of patients from China (~600) who may be followed for less than 24 months.

NOTE: Common study end date is not dependent on the situation in China, and therefore will apply, regardless of Clinical Trial Authorization status and randomization status in China.

6.3 INTERIM ANALYSIS

Patients will be followed until 1,613 patients experience at least one primary endpoint event or for approximately 24 months after the last date of randomization ex-China, whichever comes last.

Interim analyses for futility will be performed, under the supervision of the CV DMC, when 50% and 75% of events have occurred.

An interim analysis for efficacy will be performed when 75% of events have occurred. Control of the type I and type II error will be ensured using gamma (-5) spending function for Type II error (futility) and Gamma (-22) for Type I error (efficacy). Stopping rules details are further described in Section 11.5.

6.4 STUDY COMMITTEES

Executive Steering Committee:

The Executive Steering Committee is composed of university-based scientists (experts in cardiology field, and lipids) with clinical and methodological expertise, working in collaboration with Sponsor based scientists. The Steering Committee provides scientific and strategic direction for the trial and will have overall responsibility for its execution. The committee provides guidance on producing and conducting a scientifically sound design and ensuring accurate reporting of the study. In that capacity, the Steering Committee must address and resolve scientific issues encountered during the study.

Among its responsibilities, the Steering Committee will receive blinded (aggregate) study status reports from the Sponsor. The Steering Committee will also review the recommendations from the Data Monitoring Committee throughout the study. The Steering Committee members and Sponsor based scientists will participate in face-to-face meetings at regular intervals throughout the study and in regularly scheduled teleconferences.

Detailed activities and responsibilities of the Steering Committee are described in the Steering Committee charter.

Data Monitoring Committee:

An independent Data Monitoring Committee (DMC), composed of members independent from the Sponsor and the study Investigators, is implemented in order to monitor patient safety by conducting formal reviews of accumulated safety data that will be unblinded. This DMC exclusively dedicated to this study will be identified as CV DMC. The chairman of the DMC dedicated to the Phase 3a studies supporting the LDL-C reduction indication (Phase 3a DMC) will be also a member of this CV DMC and will serve as a liaison between the two DMCs. Safety data review will include the cardiovascular outcomes adjudicated or not at the time of this review. The CV DMC will also supervise the two interim analyses for futility and efficacy conducted when 50% and 75% of events occur (see Section 6.3). The CV DMC will provide the Sponsor and the Steering Committee with appropriate recommendations on the conduct of the clinical trial to ensure the protection and safety of the patients enrolled in the study. In addition, the CV DMC will also institute any measures that may be required for ensuring the integrity of the study results during the study execution.

Additionally, the CV DMC will thoroughly analyze the aggregate data for patients who achieve LDL-C <25 mg/dL during their periodic reviews throughout the study and more particularly, will review adverse events potentially associated with LDL-C <25 mg/dL (0.65 mmol/L) (see Section 10.6.3 and Appendix A).

All activities and responsibilities of this CV DMC are described in the DMC charter.

Clinical Events Committee:

The Clinical Events Committee (CEC), managed by the Duke Clinical Research Institute (DCRI), is composed of experts in the field of cardiovascular diseases, independent from the Sponsor and the Investigators. This committee will be responsible for defining, validating and classifying, in a blinded fashion, all components of the primary and secondary endpoints related to cardiovascular outcomes as well as validating the classification of the cause of all deaths.

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

7 SELECTION OF PATIENTS

NOTE: *Qualifying visit (V2) as mentioned below in some inclusion / exclusion criteria refers to the latest visit where lipid labs are collected (before V3), and may correspond to a combined V1/V2, V2 or V2b visit.*

7.1 INCLUSION CRITERIA

I 01. (A6) Patients hospitalized for ACS (ST-elevation MI, non-ST-elevation MI or high-risk unstable angina) defined by:

- Ischemic symptoms with unstable pattern, occurring at rest or minimal exertion within 72 hrs of an unscheduled hospital admission, due to presumed or proven obstructive coronary disease **AND at least one of the following (A and/or B):**

A) Elevated cardiac biomarkers (troponin I or T or CK-MB with at least one determination >99th percentile or upper limit of normal for the laboratory).

OR

B) Resting ECG changes consistent with ischemia or infarction (B1) **AND** additional evidence of obstructive coronary disease, based upon the following criteria (B2):

B1. Resting ECG changes consistent with ischemia or infarction requires at least one of the following:

a) new or presumed new ST depression

b) new or presumed new ST elevation

c) new or presumed new T wave inversion

B2. Additional evidence of obstructive coronary disease requires at least one of the following:

a) new or presumed new evidence of myocardial ischemia or infarction by perfusion imaging

b) new or presumed new regional wall motion abnormality

c) current evidence of at least one epicardial coronary artery stenosis ≥ 70% by coronary angiography

a) need for revascularization (PCI or CABG) related to index ACS event

NOTE: *Latest ACS event occurring prior to V1 and meeting the ACS criteria as defined above will be the qualifying index ACS event. In case of rescreening, see* Section 6.1.3.2

I 02. (A6) Patient lipid levels not adequately controlled at V2 (qualifying visit) despite evidence-based lipid lowering therapy (including intensive atorvastatin/rosuvastatin therapy or maximally tolerated dose of either of these 2 statins) or other non-statin LMTs. Inadequate lipid control means that patient must meet at least one of the following criteria at V2 to qualify:

- LDL-C ≥ 70 mg/dL [≥1.81 mmol/L], or
- ApoB ≥ 80 mg/dL [≥ 0.8 g/L], or
- non-HDL-C ≥100 mg/dL [≥2.59 mmol/L]

I 03. Signed written informed consent.

7.2 EXCLUSION CRITERIA

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

7.2.1 Exclusion criteria related to study methodology

E 01. Age < 40 years.

E 02. (A6) Uncontrolled hypertension (multiple readings with SBP > 180 mmHg or DBP > 110 mmHg) at V3.

E 03. History of New York Heart Association (NYHA) class III or IV congestive heart failure persisting despite treatment or, if measured, LVEF < 25% at the most recent measurement.

E 04. Known history of hemorrhagic stroke.

E 05. History of cancer within the past 5 years, except for adequately treated basal cell skin cancer, squamous cell skin cancer, or in situ cervical cancer.

E 06. (A6) Recent diagnosis of hypothyroidism for which treatment was initiated within 1 month prior to qualifying visit (V2).

E 07. Patient who has been previously treated with at least one dose of alirocumab or any other anti-PCSK9 monoclonal antibody in other clinical trials.

E 08. Patient who has taken other investigational drugs within 1 month or 5 half-lives, whichever is longer.

E 09. (A6) Laboratory findings measured during screening and before randomization visit:

- Positive test for hepatitis B surface antigen
- Positive hepatitis C antibody confirmed with positive RNA testing (indicative of active hepatitis C infection)

- Triglycerides (TG) > 400mg/dL (>4.52 mmol/L) (1 repeat lab allowed)
- Positive serum or urine pregnancy test in females of childbearing potential
- eGFR <30 mL/min/1.73 m² according to 4-variable MDRD Study equation (calculated by central lab)
- ALT or AST >3 x ULN on most recent determination prior to randomization (1 repeat lab is allowed)
- CPK >3 x ULN on most recent determination prior to randomization (1 repeat lab is allowed)

E 10. Conditions/situations such as:

- Any clinically significant abnormality identified at the time of screening that in the judgment of the Investigator or any sub-Investigator would preclude safe completion of the study or constrain endpoints assessment such as major systemic diseases, patients with short life expectancy.
- Patients considered by the Investigator or any sub-Investigator as inappropriate for this study for any reason, eg:
  - 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 conditions (eg, geographic, social….) actual or anticipated, that the Investigator feels would restrict or limit the patient's participation for the duration of the study

For the entry into the double-blind treatment period (randomization):

E 11. (A6) All of the 3 following criteria are concomitantly present at the qualifying visit (V2):

- LDL-C <70 mg/dL (<1.81 mmol/L), and
- ApoB <80 mg/dL (<0.8 g/L), and
- non-HDL-C <100 mg/dL (<2.59 mmol/L)

NOTE: *If not all 3 but only 1 or 2 criteria are present then the patient may qualify*

E 12. (A6) Patients in whom the qualifying index ACS event occurred less than 4 weeks (28 days) or more than 52 weeks (+ 5 days) prior to randomization visit (V3).

E 13. (A6) Not on stable LMT doses (statin and/or non-statin LMT) for at least 2 weeks prior to qualifying visit (V2).

E 14. (A6) Use of fibrates, other than fenofibrate or fenofibric acid, during the run-in period.

E 15. (A6) In patients who meet lipid eligibility criteria at qualifying visit (V2), any increase in dose of atorvastatin, rosuvastatin or non-statin LMT after V2 without subsequent requalification for lipid laboratory parameters.

E 16. (A6) Use of red yeast rice products during the run-in period up to randomization Visit (V3).

E 17. (A6) New ACS within 2 weeks prior to the randomization Visit (V3).

E 18. (A6) Coronary revascularization (PCI or CABG) planned after randomization and/or performed within 2 weeks prior to the randomization Visit (V3).

E 19. Patient who withdraws consent during the screening period (patient who is not willing to continue or fails to return).

7.2.2 Exclusion criteria related to the background therapy

E 20. All contraindications to atorvastatin, rosuvastatin or other LMTs or warning/precaution of use (when appropriate) as displayed in the respective National Product Labeling for these treatments.

7.2.3 Exclusion criteria related to the current knowledge of alirocumab

E 21. (A6) Known hypersensitivity to monoclonal antibody or any component of the drug product.

E 22. Pregnant or breast-feeding women.

E 23. Women of childbearing potential not protected by highly effective method(s) of birth control (as defined in the informed consent form and/or in a local protocol addendum) and/or who are unwilling or unable to be tested for pregnancy.

NOTE: Women of childbearing potential must have a confirmed negative pregnancy test at screening and randomization visits. They must use a highly effective contraceptive method throughout the entire duration of the study while receiving blinded study treatment (IMP), and for 10 weeks following the last injection of blinded study treatment (IMP) and agree to repeat urine pregnancy test at designated visits. The applied methods of contraception have to meet the criteria for a highly effective method of birth control according to the 'Note for guidance on non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals (CPMP/ICH/286/95)' (33). Postmenopausal women must be amenorrheic for at least 12 months.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

Sterile alirocumab drug product will be supplied at a concentration of 75 mg/mL and 150 mg/mL both as 1 mL volume in an autoinjector.

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

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

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

OR

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

Should this occur, the alternative investigational medicinal product (IMP) will be maintained until the end of the study.

8.1.1 Route and method of administration

A manual for IMP administration (injection instruction manual) will be provided to patients containing detailed instructions on use. Also, an administration package containing gauze, alcohol swabs, band aids, etc will be provided to the patients.

The IMP could be administered by self-injection or by another designated person (such as a spouse, relative, nurse etc…). The used autoinjector will be discarded in a sharps container which will be provided to patients. It is recommended that the IMP injections be rotated within an anatomical area (eg, right thigh then left thigh or right abdomen then left abdomen). Patients also have the option to inject in a different anatomical area (eg, thigh then abdomen) during the study. It should be noted that if patients have problems activating the auto-injector by pressing the

needle cover against their belly (e.g. soft tissue), it is recommended to inject into the thigh, where the skin is firmer than the belly. If another concomitant drug is being injected at the same site planned for the IMP injection, then the patient should be advised to use an alternate location for administration of the IMP.

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

Instructions as outlined above should be provided to the patient (or to another designated person [such as spouse, relative, nurse etc...] who will administer the injections) during the run-in period (training injections) and as needed during the course of the study. Close supervision and feedback should be given at the training visit, randomization visit, and other visits as needed.

8.1.2 Timing of administration

During the run-in period, at least 2 training injections are required on 2 different occasions. These can take place at V1, V2, Combined V1/V2, or V3 at the discretion of the study site. First training injection (with placebo) must be done before V3. The initial IMP double-blind injection (active or placebo) performed at V3 may serve as second training injection. If needed, additional training injections (with placebo) are available.

During the double-blind treatment period, alirocumab or placebo will be administered subcutaneously every 2 weeks, starting at randomization Visit (V3, Day 1, Month 0) continuing up to the common study end date.

Further training with the scheduled double-blind IMP can be done at any time during the study as necessary.

Double-blind IMP will start as soon as possible after the call for randomization using the treatment kit number provided by the IVRS. The first injection after randomization will be done at the investigational site by the patient or another designated person (such as spouse, relative, etc…) under direct site staff supervision. Patients will be monitored at the investigational site for at least 30 minutes after this first double-blind injection.

IMP should ideally be administered every 2 weeks subcutaneously at approximately the same time of the day; however it is acceptable to have a window period of ± 3 days. The time of the day is based on patient's preference.

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

8.2 NON-INVESTIGATIONAL MEDICINAL PRODUCT(S)

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

- Statins (during run-in period: only atorvastatin or rosuvastatin are allowed; after randomization: every effort should be made to continue atorvastatin / rosuvastatin until end of study; alternative, including other statin, allowed in case intolerance to lowest dose of atorvastatin/rosuvastatin has developed post-randomization – see Figure 2, Section 8.8.2)
- Cholesterol absorption inhibitors (ezetimibe)
- Bile acid-binding sequestrants (such as cholestyramine, colestipol, colesevelam)
- Nicotinic acid (niacin)
- Fenofibrate, fenofibric acid
- Omega-3 fatty acids

Please see Section 8.8 for further information.

8.3 BLINDING PROCEDURES

8.3.1 Methods of blinding

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

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

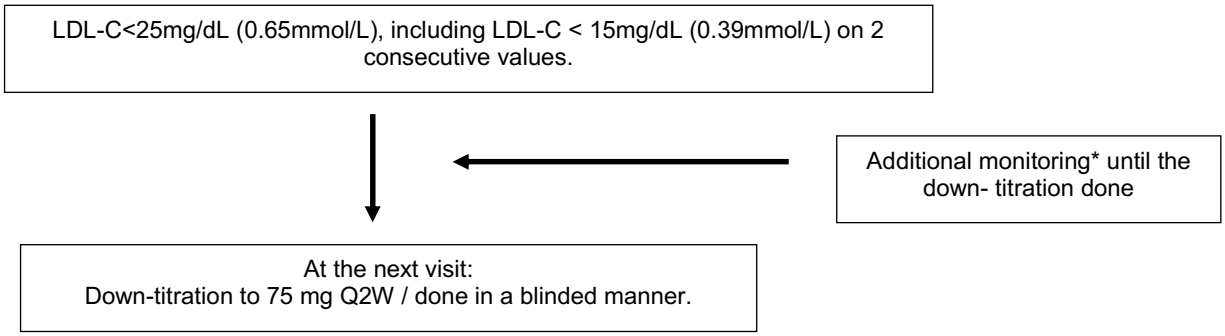
In accordance with the double-blind design, study patients, Investigators and study site personnel will remain blinded to study treatment and will not have access to the randomization (treatment codes) except under circumstances described in Section 8.3.6.

8.3.2 Lipid parameters

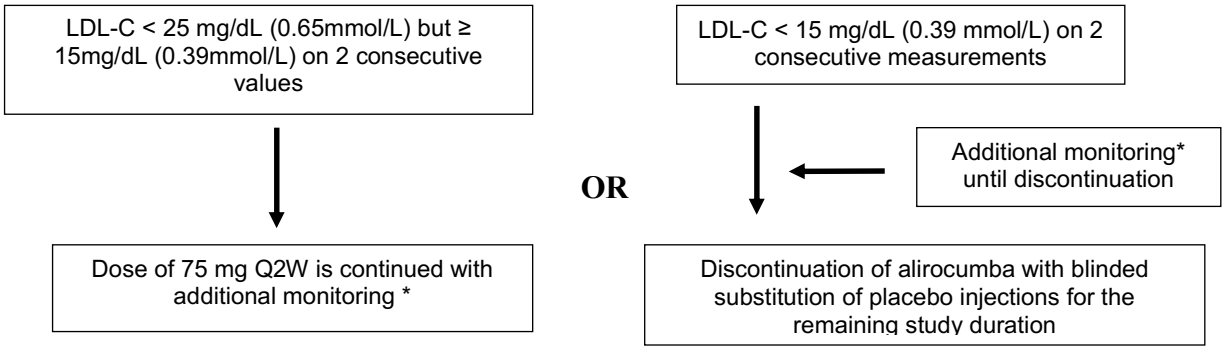
Lipid parameter values from blood samples obtained after the randomization visit, run by the central lab, will not be communicated to the sites so that they cannot deduce the treatment group of their patients based on LDL-C level attained. The sponsor's operational team will not have access to lipid parameters after randomization and until after the final database lock has occurred.

For patients who achieve 2 consecutive LDL-C <25 mg/dL (0.65mmol/L) on alirocumab and depending on the dose received, the following will be applied:

- If the dose is 150 mg Q2W:



- If the dose is 75 mg Q2W:



* NOTE: *Additional monitoring includes:*

- *Patient level listing for surveillance and review for patients who are managed by IVRS/IWRS (i.e with planned automatic down-titration from 150 mg to 75 mg, or switch from 75mg to placebo)*
- *Individual patient profile monitoring for potential site alerts for patients on alirocumab 75 mg and not managed by IVRS/IWRS (i.e. with no planned automatic down-titration or switch to placebo by IVRS/IWRS)*

Further details are provided in Appendix A.

As described above, in case of LDL-C <25 mg/dL (0.65 mmol/L) on 2 consecutive values and until specific actions are undertaken, patients will be monitored according to process outlined in Section 10.6.3 and Appendix A. In order to maintain the integrity of the blind as much as possible with this monitoring process, the following points will be undertaken:

- Specific steps will be in place to ensure that the work which will be carried out by the central lab group and the communication with the independent external physician(s) (also known as independent physician), who is responsible for closely monitoring patients with these 2 consecutive LDL-C levels, will be in strict confidence.

- The independent physician(s) and the dedicated member of the Phase 3a DMC (implemented for all Phase 3 studies evaluating the efficacy and safety of alirocumab on LDL-C) will work in close collaboration and independently from the clinical team and the sites. This dedicated Phase 3a DMC member will then transmit any information as necessary to the common member involved in both DMCs (CV DMC and Phase 3a DMC)
- The actual LDL-C levels will not be reported to the sites
- Monitoring will be discontinued when specific actions are undertaken as described above, unless patients still display a LDL-C <25 mg/dL

8.3.3 Anti-alirocumab antibodies

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

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

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

Patients who have titers at or above 240 for anti- alirocumab antibodies at the common study end date will have an additional antibody sample between 6 to 12 months after this date.

In patients who permanently discontinued treatment early, blood sample for anti- alirocumab antibodies should be drawn at the early end-of-treatment visit (V70) and when the patient returns for an on-site clinic visit where this assessment was planned, i.e. annually (see also Section 10.3.4).

8.3.4 Committees

The independent Clinical Events Committee (CEC) will review and adjudicate events in a blinded manner.

The Data Monitoring Committee will receive blinded by treatment group or unblinded (if necessary) confidential reports from an independent statistician for review (Section 6.4).

8.3.5 Data Analysis

Regular DMC safety analyses and both Interim Analyses will be performed by the external independent CV DMC Statistician and will be reviewed under the supervision of the CV DMC.

8.3.6 Randomization code breaking during the study

In case of an Adverse Event (AE), the code must be broken by the site only in exceptional circumstances when knowledge of the IMP is essential for treating the patient. If possible, a contact should be initiated with the Monitoring Team/Medical Monitor before breaking the code. All calls will be documented by the Monitoring Team as appropriate to include date and time of the call, name of the person contacted within the Monitoring Team, patient ID, documentation of the request, and decision for unblinding or not.

Code breaking can be performed at any time by using the proper module of the centralized treatment allocation system and/or by calling any other phone number provided by the Sponsor for that purpose. However, it is preferable to contact the Medical Monitor to discuss the case before unblinding the case. If the blind is broken, the Investigator should document the date, time of day, and reason for code breaking, and report this information (or "relevant information as required by") on the appropriate page of the electronic case report from (eCRF).

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

The code-breaking can also be performed by contacting the "24 hour alert system"; but this system should be used in very exceptional cases only (ie, unavailability of a centralized treatment allocation system or inability to contact Investigator and/or site staff). However, the preferred option is to unblind using a centralized treatment allocation system. The Investigators will be informed by the clinical monitoring team about the availability of the local code-breaking details (through an emergency centralized 24 hour telephone system for use with e-SMS). A patient card, including the relevant "24 hour alert system" telephone number will be provided to every patient who will participate in the study.

Unblinding may also be performed by the Sponsor for some Serious Adverse Events that are both related and unexpected in order to conform to regulatory reporting requirements.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

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

The Project Demand manager will provide the randomized list of treatment kit numbers and the Study Biostatistician will provide the randomization scheme to the centralized treatment allocation system provider. Then, this centralized treatment allocation system provider will generate the patient randomization list according to which it will allocate the treatment kits to the patients.

Patients will be randomized to receive either placebo or alirocumab during the double-blind study treatment period using a ratio 1:1, with permuted-block randomization. Randomization will be stratified according to country.

The treatment kit numbers will be allocated using the centralized treatment allocation system on randomization visit (Day 1, Month 0), Month 2, Month 4, every 4 months up to Month 24, and then every 6 months up to Month 64.

For patients in the alirocumab treatment arm, the treatment kit allocated at Month 2 (V5) will be based on their Month 1 (V4) LDL-C level following the up-titration rules (see Section 6.1.4). Regular transfer of data will be planned between the central laboratory and the centralized treatment allocation system provider in order to proceed in a blinded manner for study sites and sponsor.

Before randomizing a patient, the Investigator or designee will have to contact the centralized treatment allocation system.

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

Two types of centralized treatment allocation system will be used, the Interactive Voice Response System (IVRS) and the Interactive Web Response System (IWRS) depending on the choice of the site.

8.5 PACKAGING AND LABELING

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

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

In addition to the double-blind treatment kits, a training kit containing 1 placebo autoinjector each will be prepared for the purpose of instructing patients on injection administration which is to be performed prior to randomization. These training injections should be performed on site at screening Visit (V1, Week-16 to Week-4) and qualifying Visit (V2, Week-2), respectively. A third training injection can be performed at an additional visit such as the optional visit V2b.

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

8.6 STORAGE CONDITIONS AND SHELF LIFE

The IMP (alirocumab or placebo) will be stored in a refrigerator between +2°C and +8°C (36°- 46° F) by the site. The temperature of the site refrigerator should be checked every working day and recorded on a log sheet.

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

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

NOTE: *Exceptionally, after discussion between site and sponsor (eg, patient unable to attend a clinic visit due to special circumstances) some IMP kits could be supplied, when feasible, directly from site to patient via a sponsor-approved courier company. This process (which requires maintenance of the cold chain) would be implemented only at selected sites/countries (where certain conditions would be fulfilled, and where permitted locally) and for selected patients (who could handle and would consent to such a process). This direct-to-patient process will be described in detail in a separate document and would be implemented after appropriate training of monitoring teams and investigational sites.*

8.7 RESPONSIBILITIES

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

All IMP shall be dispensed after IVRS contact in accordance with the Clinical Trial Protocol and it is the Investigator's responsibility to ensure that an accurate record of IMP issued and returned is maintained.

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

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

Under no circumstances will the Investigator supply IMP to a third party, allows 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

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

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

- The Investigator or designee will obtain via IVRS/IWRS the treatment kit number(s) and he/she will dispense the treatment kit(s) to the patient.
- The accountability is to be performed at IMP kit re-supply visits only (see Section 10.1.5). The used and unused kit(s) should be brought back to such visits for accountability purposes.
- The Investigator or designee will complete the corresponding treatment log form from patient's diary.

  NOTES:

  At every opportunity (clinic visit or phone call), Investigator should remind patient to complete the diary and to bring the diary at the next clinic visit.

  If patient forgets to bring the diary at a clinic visit, site should come up with an alternative solution to obtain as soon as possible information contained in the diary in order to be able to complete IMP information in eCRF in a timely manner.

  If patient dies, site should make every possible effort to obtain patient diary from the family (in addition to collecting detailed information about the circumstances of patient death).
- The Investigator/study coordinator will enter data in the appropriate eCRF pages, according to data recorded in the treatment log form.
- The monitor will check the data consistency between eCRF pages, treatment log forms using patient's diary, and returned unused IMPs of a corresponding kit.

8.7.2 Return and/or destruction of treatments

Destruction of IMP kits (i.e., used, unused or expired) can be performed during the course of the study in addition to the end of the study.

Destruction at site is strongly encouraged and can be performed provided that the following requirements are met:

- Site has the appropriate facilities to destroy IMP and
- Site has procedures to allow traceability of the batches and quantities destroyed and delivers the corresponding destruction documentation/certificate,
- Sanofi provides the appropriate authorization.

In case the above requirements are not satisfied and the site cannot safely destroy IMP, the treatments will be returned to the local depot for destruction. A detailed treatment log of the returned IMP will be established with the Investigator or designee and countersigned by the Investigator and the Monitoring Team.

8.8 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient concomitantly to the study (until the common study end date).

8.8.1 Background Lipid-Modifying Therapy

During the run-in period, all LMTs are authorized with the exception of fibrates (other than fenofibrate and fenofibric acid), and statins other than atorvastatin, and rosuvastatin.

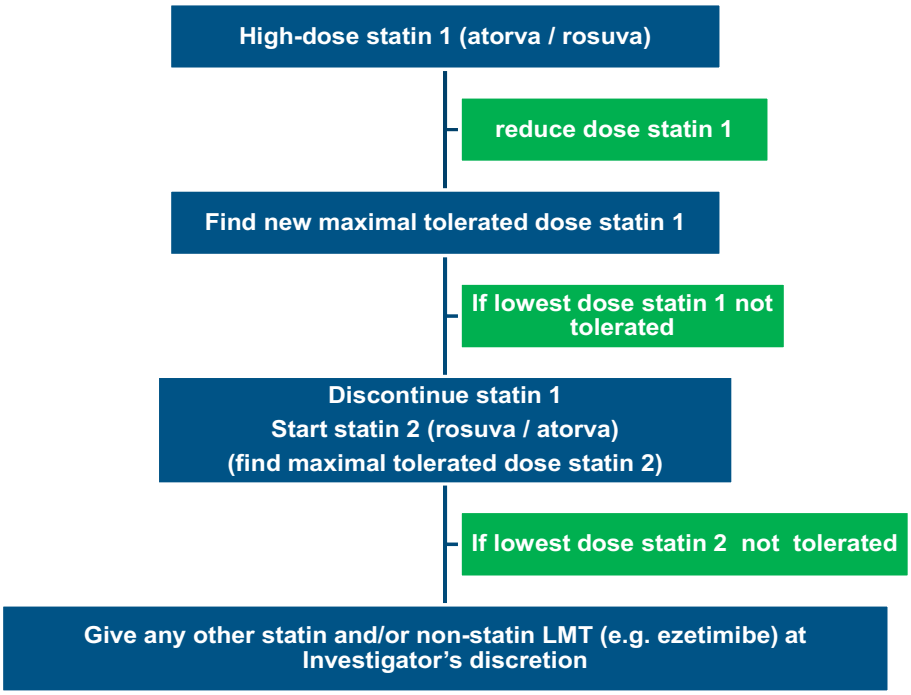
These include but are not limited to:

- Statins (atorvastatin, rosuvastatin only; other statins are not allowed during run-in period)
- Cholesterol absorption inhibitors (ezetimibe)
- Bile acid-binding sequestrants (such as cholestyramine, colestipol, colesevelam)
- Nicotinic acid (niacin)
- Fenofibrate, fenofibric acid
- Omega-3 fatty acids

After randomization, the required background LMT regimen, as determined from the run-in period, with intensive statin therapy (atorvastatin 40 or 80 mg or rosuvastatin 20 or 40 mg) or maximal tolerated dose of one these 2 statins, and optimized with addition of non-statin LMTs (at the Investigator's discretion) should be continued, for as long as this regimen remains well tolerated.

If, during the course of the study, significant tolerability concerns arise and patient is found intolerant to any dose of atorvastatin or rosuvastatin, other statins (i.e. other than atorvastatin or rosuvastatin) as well as non-statin LMTs are authorized. A proposed algorithm for modification of LMT post-randomization is provided in Figure 2.

Figure 2 - Proposed algorithm for adjusting LMT post-randomization, in case tolerability concerns arise (e.g. myalgia)



NOTE: *If statin 1 is atorvastatin, statin 2 is rosuvastatin; if statin 1 is rosuvastatin, statin 2 is atorvastatin.*

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

LMT (whether administered as prescription drugs or over the counter) will be recorded in the CRF and source data. However, detailed use of nutraceutical products (such as plant stanols found in Benecol, flax seed oil, psyllium or LMT found in multivitamins) will not be collected in the CRF but should be maintained in source documents.

8.8.2 Other Concomitant Medications

All other concomitant medication(s) are allowed.

All patients should receive contemporary evidence-based treatment for ACS and chronic CHD as described in regional professional guidelines, including, but not limited to anti-platelet agents, beta blockers, angiotensin-converting-enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs), and treatments for diabetes, hypertension, and smoking.

Concomitant medications (from a prescription or over-the-counter) that are administered chronically, as well as those that are administered during hospitalizations and considered relevant (i.e. pertaining to the patient's background or current medical history, or related to an AE/AESI/SAE, and as determined by Investigator's best judgment) are allowed and will be

recorded in the e–CRF and source data. Use of some medications related to efficacy may be collected only in (cardiovascular) efficacy endpoint eCRF pages (e.g. use of diuretics for CHF).

Other medications administered during hospitalizations and considered not relevant [including but not limited to: PRN (i.e. as needed) medications, anesthetic agents, medications given related to the performance of a procedure, IV fluids] as well use of multivitamins or nutraceuticals will not be recorded in the eCRF, however should be maintained in the source documents.

8.9 MITIGATION PLAN IN CASE OF IMP ISSUE

In the exceptional case of a major IMP issue, the following mitigation plan may be implemented in order to achieve the dual goal of optimizing IMP inventory at all sites, while maintaining patient treatment continuity with IMP:

From M24 (V16) and at all subsequent clinic visits (M30, M36, M42, M48, M54, and M60), a reduced number of IMP autoinjectors would be dispensed (12 instead of 18) covering 24 weeks of treatment. As a consequence, subsequent clinic visits would need to be scheduled in a more tightly manner and at a slightly shorter interval, ie, every 22 to 24 weeks (161d ±7d), instead of every 26w ±14d.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 EFFICACY ENDPOINTS

Any suspected cardiovascular event suggestive of an endpoint as well as all deaths will be submitted to the Clinical Events Committee (CEC). The CEC will review the data of the reported cases in a blinded manner for adjudication purpose and will validate if the event should be considered as an endpoint. The cardiovascular events adjudicated and validated by the CEC will be used for the analyses.

Events that the CEC could not classify as well as suspected event according to investigator but not confirmed by the CEC will not be part of the outcomes.

9.1.1 Primary efficacy endpoint

The primary efficacy endpoint is the time from randomization to first occurrence of one of the following clinical events, as determined by the CEC:

- CHD death (including "undetermined causes of death" as per the CEC)
- Any non-fatal MI
- Fatal and non-fatal ischemic stroke (including "stroke not otherwise specified" as per the CEC)
- Unstable angina requiring hospitalization

If none of these events is observed at the time of the analysis cut-off date (final or interim, depending of the analysis, see Section 11.4.2.1 for details), the patient will be censored at the date of last contact, at the date of death, or at the date of cut-off, whichever comes first.

Of note, suspected event according to the investigator but not confirmed by the CEC will not be part of the primary efficacy outcome; their description will be provided separately.

9.1.2 Secondary efficacy endpoints

Time-to-event secondary endpoints will be censored using the same methodology as for the primary efficacy endpoint.

9.1.3 Main Secondary Efficacy Endpoint(s):

- Time from randomization to first occurrence of any CHD event (major CHD event, unstable angina requiring hospitalization, ischemia-driven coronary revascularization procedure)
- Time from randomization to first occurrence of any major CHD event (CHD death, non-fatal MI)

- Time from randomization to first occurrence of any CV event defined as follows: any non-fatal CHD event, any CV death, and non-fatal ischemic stroke
- Time from randomization to first occurrence of all-cause mortality, non-fatal MI, non-fatal ischemic stroke
- Time from randomization to death (all-cause mortality)

9.1.4 Other Secondary Efficacy Endpoint(s):

- Component of the primary endpoint considered individually:
  - Time from randomization to CHD death
  - Time from randomization to first occurrence of any non-fatal MI
  - Time from randomization to first occurrence of fatal or any non-fatal ischemic stroke
  - Time from randomization to first occurrence of any unstable angina requiring hospitalization
- Time from randomization to first occurrence of any ischemia-driven coronary revascularization procedure
- Time from randomization to first occurrence of any congestive heart failure requiring hospitalization

9.1.5 Efficacy assessment methods

Definitions of the primary and secondary efficacy endpoints related to CV events and death are based on FDA/CDISC *Standardized Definitions for End Point Events in Cardiovascular Trials,* and on the Thygesen Universal Definition for the definition of myocardial infarction (34) (35) (36).

9.1.6 Definitions of components of the composite primary efficacy endpoint

9.1.6.1 Coronary Heart Disease (CHD) Death

Coronary Heart Disease Death is defined as the subset of Cardiovascular deaths for which there is a clear relationship to underlying coronary heart disease, including death secondary to acute MI, sudden death, heart failure, complication of a coronary revascularization procedure performed for symptoms, coronary disease progression, or new myocardial ischemia where the cause of death is clearly related to the procedure, unobserved and unexpected death, and other death that cannot definitely be attributed to a nonvascular cause (see Section 9.1.7.1 for the different definitions).

9.1.6.1.1 Death due to acute myocardial infarction

Death by any mechanism (arrhythmia, heart failure, low output) within 30 days after a myocardial infarction (MI) related to the immediate consequences of the myocardial infarction, such as progressive congestive heart failure (CHF), inadequate cardiac output, or refractory arrhythmia. If these events occur after a “break” (eg, a CHF and arrhythmia free period of at least a week), they

should be designated by the immediate cause, even though the MI may have increased the risk of that event (eg, late arrhythmic death becomes more likely after an acute myocardial infarction (AMI)). The acute myocardial infarction should be verified to the extent possible by the diagnostic criteria outlined for acute myocardial infarction or by autopsy findings showing recent myocardial infarction or recent coronary thrombus.

Sudden cardiac death, if accompanied by symptoms suggestive of myocardial ischemia, new ST elevation, new LBBB, or evidence of fresh thrombus by coronary angiography and/or at autopsy should be considered death resulting from an acute myocardial infarction, even if death occurs before blood samples or 12-lead electrocardiogram (ECG) could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.

Death resulting from a procedure to treat a myocardial infarction such as percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG), or to treat a complication resulting from myocardial infarction, should also be considered death due to acute MI.

Death resulting from an elective coronary procedure to treat myocardial ischemia (ie, chronic stable angina) or death due to a MI that occurs as a direct consequence of a CV investigation/procedure/operation should be considered as a death due to a CV procedure.

9.1.6.1.2 Sudden cardiac death

Death that occurs unexpectedly, not following an acute MI, and includes the following deaths:

a) Death witnessed and occurring without new or worsening symptoms

b) Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless documented (ie by ECG or other objective) to be due to acute myocardial infarction

c) Death witnessed and attributed to an identified arrhythmia (eg, captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review)

d) Death after unsuccessful resuscitation from cardiac arrest

e) Death after successful resuscitation from cardiac arrest and without identification of a non-cardiac etiology

f) Unwitnessed death without other cause of death (information regarding the patient's clinical status preceding death should be provided, if available)

<u>General considerations</u>

A subject seen alive and clinically stable 24 hours prior to being found dead without any evidence or information of a specific cause of death should be classified as "sudden cardiac death."

Typical scenarios include:

- Subject well the previous day but found dead in bed the next day
- Subject found dead at home on the couch with the television on

Deaths for which there is no information beyond 'Patient found dead at home' may be classified as 'Death due to other cardiovascular causes'.

9.1.6.2 Non-fatal myocardial infarction (MI)

Definition for myocardial infarction is based on the most recent Thygesen Universal Definition (37):

9.1.6.2.1 Acute myocardial infarction

The term acute myocardial infarction (MI) refers to evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis for MI:

a) Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the upper reference limit (URL) and with at least one of the following:
    - Symptoms of ischemia
    - New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB).
    - Development of pathological Q waves in the ECG
    - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
    - Identification of an intracoronary thrombus by angiography or autopsy
b) Cardiac death with symptoms suggestive of myocardial ischaemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.
c) Percutaneous coronary intervention (PCI) related MI is defined by elevation of cTn values (>5 x URL) occurring within 48h of the procedure in patients with normal baseline values (≤URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, at least one of the following is required:
    - Symptoms suggestive of myocardial ischemia
    - New ischemic ECG changes
    - Angiographic findings consistent with a procedural complication
    - Imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality

d) Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of evidence of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the URL.

e) Coronary artery bypass grafting (CABG) related MI is defined by elevation of troponin values (>10 x URL) occurring within 48h of the procedure in patients with normal baseline cTn values (≤URL). In addition at least one of the following is required:

- New pathological Q waves or new LBBB
- Angiographic documented new graft or new native coronary artery occlusion
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

Cardiac troponin is the preferred biomarker for diagnosis of MI. In absence of troponin, CK-MB will be used.

9.1.6.2.2 Silent myocardial infarction

Silent MI is not considered part of the primary endpoint.

Asymptomatic patients who develop new pathologic Q wave criteria for MI detected during routine ECG follow-up, or reveal evidence of MI by cardiac imaging, that cannot be directly attributed to a coronary revascularization procedure, are termed ‘silent MI”. Any one of the following criteria meets the diagnosis:

- Pathological Q waves with or without symptoms in the absence of non-ischemic causes
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause
- Pathological findings of a prior MI

9.1.6.2.3 Classification according to Universal MI definition subtypes

All MI events will be classified by Universal MI definition subtypes as follows:

- Type 1

Spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe coronary artery disease (CAD) but on occasion non-obstructive or no CAD.

- Type 2

In instances of myocardial injury with necrosis where a condition other than CAD contributes to an imbalance between myocardial oxygen supply and/or demand, eg, coronary endothelial dysfunction, coronary artery spasm, coronary embolism, tachy/brady-arrhythmias, anemia,

respiratory failure, hypotension, and hypertension with or without left ventricular hypertrophy (LVH).

- Type 3

Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases cardiac biomarkers were not collected.

- Type 4a

Myocardial infarction associated with PCI.

- Type 4b

Myocardial infarction associated with stent thrombosis.

- Type 4c

Myocardial infarction associated with restenosis (restenosis is the only angiographic explanation)

- Type 5

Myocardial infarction associated with CABG.

9.1.6.2.4 Sub-classifications

a) Sub-classifications into STEMI versus NSTEMI

All MI events will be sub-classified into STEMI versus NSTEMI as follows:

- STEMI: new ST elevation at the J point in two contiguous leads with the cut-points: ≥0.1 mV in all leads other than leads V2–V3 where the following cut points apply: ≥0.2 mV in men ≥40 years; ≥0.25 mV in men <40 years, or ≥0.15 mV in women.
- NSTEMI: if ECG does not meet STEMI criteria will be classified as NSTEMI
- If ECGs are unavailable or uninterpretable the MI will be classified as unknown

b) Sub-classifications into Q wave versus Non Q wave MI

MI events will be sub-classified into Q wave vs. Non Q wave MI as follows:

Criteria for abnormal Q-waves are any one of:

- Any Q wave in leadsV2–V3 ≥0.02 sec or QS complex in leads V2 and V3
- Q wave ≥0.03 sec and ≥0.1 mV deep or QS complex in leads I, II, aVL, aVF or V4–V6 in any two leads of a contiguous lead grouping (I, aVL; V1–V6; II, III, aVF)[a]

  [a] *The same criteria are used for supplemental leads V7-V9.*

- R wave ≥0.04 sec in V1–V2 and R/S ≥1 with a concordant positive T wave in absence of conduction defect

- If Q-waves criteria are not met, MI is classified as non-Q-wave MI
- If ECGs are unavailable or uninterpretable the MI will be classified as unknown

9.1.6.3 Fatal and Non-fatal stroke

Stroke is defined as an acute episode of focal or global neurological dysfunction caused by central nervous system (CNS) vascular injury as a result of hemorrhage or infarction. CNS includes brain, spinal cord and retina.

Classification:

a) Ischemic Stroke

Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by CNS infarction. Evidence of infarction is defined as:

- Pathological, imaging, or other objective evidence of acute cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; or
- In the absence of the above (i.e. imaging or autopsy unavailable), clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury is based on symptoms persisting ≥24 hours or until death, and other etiologies excluded

NOTE: *Hemorrhagic infarction, defined as parenchymal hemorrhage after CNS infarction, is considered an ischemic stroke (i.e. hemorrhagic conversion of infarction) and is part of the primary endpoint.*

Ischemic strokes may be further classified according to most likely etiology (example large artery atherosclerosis, cardio-embolic, etc.)

b) Cerebral Hemorrhage

Hemorrhages in the CNS are classified as stroke if they are nontraumatic, caused by a vascular event, and result in injury to the CNS. In contrast, traumatic hemorrhages will not be characterized as stroke. Subdural hematoma will not be classified as a stroke.

The diagnoses included in this section are intracerebral hemorrhage (intraparenchymal and intraventricular) and subarachnoid hemorrhage (both aneurysmal and nonaneurysmal).

Diagnoses included in this section are not part of the primary endpoint.

- Stroke caused by intracerebral hemorrhage

  Rapidly developing clinical signs of neurological dysfunction (focal or global) attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma.

- Stroke caused by subarachnoid hemorrhage

  Rapidly developing signs of neurological dysfunction (focal or global) and/or headache because of bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord), which is not caused by trauma.

  Hemorrhages may be further classified according to location (example, supratentorial, subtentorial, intraparenchymal etc.)

c) Stroke not otherwise specified

   An episode of acute neurological dysfunction presumed to be caused by ischemia or hemorrhage, persisting ≥24 hours or until death, but without sufficient evidence to be classified as one of the above.

   Strokes not otherwise specified are part of the primary endpoint.

A functional disability assessment will be performed for strokes after 3 to 6 months following the start date of the event (see Appendix I).

Fatal stroke

Death due to Stroke refers to death after a stroke that is either a direct consequence of the stroke or a complication of the stroke. Acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke.

9.1.6.4 Unstable angina requiring hospitalization

A diagnosis of unstable angina (new ACS event without elevations in cardiac biomarkers) that meets the primary endpoint requires the following:

- Admission to hospital or emergency room (until at least next calendar day) with symptoms presumed to be caused by myocardial ischemia with an accelerating tempo in the prior 48 hrs and/or prolonged (at least 20 min) rest chest discomfort

AND

- New high-risk ECG findings consistent with ischemia or infarction (or presumed new if no prior ECG available) as defined below:
  - New or presumed new ST depression >0.5mm in 2 contiguous leads or T wave inversion >1mm in leads with prominent R wave or R/S >1 in 2 contiguous leads, OR
  - New or presumed new ST elevation at the J point in > 2 contiguous leads >0.2mV in V2 or V3 in men or >0.15 mV in women in V2 or V3 or >0.1mV in other leads.
  - LBBB (new or presumed new)

AND

- Definite contemporary evidence (defined below) of angiographically significant coronary disease as demonstrated by:
  - Need for coronary revascularization procedure (PCI or CABG) excluding those performed to treat only restenosis lesion(s) at previous PCI site(s) **OR**
  - Angiographic evidence of at least one significant (≥ 70%) epicardial coronary stenosis not due to restenosis at previous PCI site

The coronary revascularization procedure or the diagnostic angiography must have been performed during the hospitalization for that event.

9.1.7 Definitions of the secondary efficacy endpoints

9.1.7.1 Death

All deaths will be categorized as Cardiovascular, non-Cardiovascular or Undetermined based on the definitions below. In addition, all deaths will also be categorized as Coronary Heart Disease Death and further sub-typed based on the specific Cardiovascular and non-Cardiovascular categories defined below.

9.1.7.1.1 Definition of Cardiovascular Death

Cardiovascular Death is defined as death resulting from an acute myocardial infarction, sudden cardiac death, death due to heart failure, death due to stroke, death due to cardiovascular (CV) procedures, death due to CV hemorrhage, and death due to other cardiovascular causes.

9.1.7.1.1.1 Coronary Heart Disease (CHD) Death

Definition of CHD death is described in Section 9.1.6.1.

9.1.7.1.1.2 Other Cardiovascular Deaths

Death due to Heart Failure or Cardiogenic Shock:

Death due to Congestive Heart Failure refers to a death in association with clinically worsening symptoms and/or signs of heart failure not following an acute MI. Deaths due to heart failure can have various etiologies, including single or recurrent myocardial infarctions, ischemic or non-ischemic cardiomyopathy, hypertension, or valvular disease.

Cardiogenic shock **not** occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure.
Cardiogenic shock is defined as systolic blood pressure (SBP) <90 mm Hg for greater than 1 hour, not responsive to fluid resuscitation and/or heart rate correction, and felt to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypoperfusion:

- Cool, clammy skin or
- Oliguria (urine output <30 mL/hour) or
- Altered sensorium or
- Cardiac index <2.2 L/min/m²

Cardiogenic shock can also be defined if SBP <90 mm Hg and increases to ≥90 mm Hg in less than 1 hour with positive inotropic or vasopressor agents alone and/or with mechanical support.

Death due to Stroke (see Section 9.1.6.3 for the definition of fatal stroke).

Death due to Cardiovascular Procedures

Death due to Cardiovascular Procedures refers to death caused by the immediate complications of a cardiac procedure and excludes death resulting from procedures to treat an acute MI or the complications resulting from an acute MI.

Death due to Cardiovascular Hemorrhage

Death due to Cardiovascular Hemorrhage refers to death related to hemorrhage such as a non-stroke intracranial hemorrhage, non-procedural or non-traumatic vascular rupture (eg, aortic aneurysm), or hemorrhage causing cardiac tamponade.

Death due to Other Cardiovascular Causes:

Death due to Other Cardiovascular Causes refers to a cardiovascular death not included in the above categories (e.g., pulmonary embolism or peripheral arterial disease).

9.1.7.1.2 Definition of Non-Cardiovascular Death

Non-cardiovascular death is defined as any death that is not thought to be due to a cardiovascular (CV) cause. The following categories may be collected.

9.1.7.1.2.1 Non-Malignant Causes

- Pulmonary
- Renal
- Gastrointestinal
- Hepatobiliary
- Pancreatic
- Infection (includes sepsis)
- Non-infectious (eg, systemic inflammatory response syndrome [SIRS])
- Hemorrhage* excluding hemorrhagic strokes and bleeding in the setting of coronary revascularization

- Non-cardiovascular procedure or surgery
- Accidental (e.g. physical accidents or drug overdose) or Trauma
- Suicide
- Prescription drug error (e.g. prescribed drug overdose, use of inappropriate drug, or drug-drug interaction)
- Neurological process that is not a stroke or hemorrhage
- Other non-cardiovascular, specify: _____

*Examples:
Death due to GI bleeding is not considered a CV death. Death due to retroperitoneal hematoma following PCI is considered CV death. Death due to intracerebral hemorrhage is considered CV death.

9.1.7.1.2.2 Malignant Causes

- Death results directly from the cancer; **OR**
- Death results from a complication of the cancer (e.g., infection, complication of surgery / chemotherapy / radiotherapy); **OR**
- Death results from withdrawal of other therapies because of concerns relating to the poor prognosis associated with the cancer

Cancer deaths may arise from cancers that were present prior to randomization or which developed subsequently. Those cancer deaths should be further classified (worsening prior malignancy; new malignancy).

9.1.7.1.3 Definition of Undetermined Cause of Death

Undetermined cause of death refers to a death not attributable to one of the above categories of cardiovascular death or to a non-cardiovascular cause, due to absence of any information (eg, the only available information is “patient died”). The use of this category of death is discouraged and should apply to a minimal number of cases when no information at all on the circumstances of death is available (ie, found on obituary of local newspaper). In all circumstances the reviewer will use all available information to attribute to one of the categories based on best clinical judgment.

9.1.7.2 Ischemia-driven coronary revascularization procedure

‘Ischemia-driven coronary revascularization’ includes all coronary revascularization procedures (PCI/CABG) performed during the study, and driven by new or presumed new myocardial ischemia since randomization (categories 1 and 2 described below), and excluding procedures performed only to treat restenosis lesion(s) at prior PCI site(s).

Reasons for the PCI/CABG will be collected in the CRF as follows:

1. driven by acute ischemia (ACS).
2. driven by new/progressive (i.e. not present at randomization or with indication of progression since randomization), chronic (ie not in context of ACS) ischemia, evidenced by new/progressive symptoms (angina or equivalent) or new/progressive functional testing abnormalities (e.g. stress test, imaging).
3. other (i.e. not driven by ACS event, or by new/progressive chronic ischemia).

PCI involves a catheter-based tool (eg, balloon catheters, cutting balloons, atherectomy devices, lasers, bare metal stents, and drug-eluting stents) that improves myocardial blood flow by increasing the luminal area at a site of an obstructive coronary lesion. Coronary artery bypass grafting (CABG) is an open surgical procedure designed to improve myocardial blood flow by providing a conduit (arterial, venous, or synthetic) for blood flow distal to an obstructive coronary lesion. Insertion of a guidewire through a coronary guide catheter into a coronary vessel or aortocoronary bypass graft for the purpose of percutaneous coronary intervention (PCI) is considered as a PCI (since there is an intention to perform a PCI). However, insertion of a guidewire in order to assess the severity of intermediate lesions with the use of intravascular ultrasound, Doppler flow velocity, or fractional flow reserve, will NOT be considered PCI.

9.1.7.3 Congestive Heart Failure requiring hospitalization.

Congestive Heart Failure (CHF) requiring hospitalization is defined as an event that meets ALL of the following criteria:

1) The patient is admitted to the hospital or emergency room (until at least next calendar day) with a primary diagnosis of CHF
2) The patient exhibits documented new or worsening symptoms due to CHF on presentation, including at least ONE of the following:
   a) Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea)
   b) Decreased exercise tolerance
   c) Fatigue
   d) Other symptoms of worsened end-organ perfusion or volume overload
3) The patient has objective evidence of new or worsening CHF, consisting of at least TWO physical examination findings OR one physical examination finding and at least ONE laboratory/imaging/hemodynamic criterion), including:
   a) Physical examination findings considered to be due to heart failure, including new or worsened:
      - Peripheral edema.
      - Increasing abdominal distension or ascites (in the absence of primary hepatic disease)

- Pulmonary rales/crackles/crepitations
- Increased jugular venous pressure and/or hepatojugular reflux
- S3 gallop
- Clinically significant or rapid weight gain thought to be related to fluid retention

b) Laboratory, imaging or hemodynamic evidence of new or worsening CHF, including:

- Increased B-type natriuretic peptide (BNP)/ N-terminal pro-BNP (NT-proBNP) concentrations consistent with decompensation of heart failure. In patients with chronically elevated natriuretic peptides, a significant increase should be noted above baseline
- Radiological evidence of pulmonary congestion
- Hemodynamic evidence from right-heart catheterization (e.g. elevated pulmonary capillary wedge pressure, elevated central venous pressure, or low cardiac index) or from left heart catheterization (elevated left ventricular end-diastolic pressure)

4) The patient receives initiation or intensification of treatment specifically for HF, including at least ONE of the following:

a) Significant augmentation in oral diuretic therapy

b) Intravenous diuretic, inotrope, or vasodilator therapy

c) Mechanical or surgical intervention, including:

- Mechanical circulatory support (eg, intra-aortic balloon pump, ventricular assist device)
- Mechanical fluid removal (eg, ultrafiltration, hemofiltration, dialysis)

9.2 SAFETY ENDPOINT(S):

Observation period

The observation of safety data will be as follows:

- PRE-TREATMENT period: The PRE-TREATMENT observation period is defined from the signed informed consent up to the first dose of double-blind IMP injection
- Treatment Emergent Adverse Event (TEAE) period: The TEAE observation period is defined as the time from the first dose of double-blind IMP injection to the last dose of IMP injection + 70 days (10 weeks) as residual effect of treatment is expected until 10 weeks after the stop of double-blind IMP
- POST-TREATMENT period: The POST-TREATMENT observation period is defined as the time starting the day after the end of the TEAE period up to the end of the study

Rationale for TEAE period definition is detailed in Section 4.

9.2.1 Adverse event

All adverse events diagnosed by the Investigator, irrespective of the result of the adjudication for cardiovascular events, will be reported and described.

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

AEs of special interest include, but are not limited to, the following:

- Allergic events (using special eCRF pages, see Section 10.6.2)
- Local injection site reactions (using special eCRF pages, see Section 10.6.1)
- Hemolytic anemia (using special eCRF pages, see Section 10.4.7.1)

Adverse event observation period

The AE observations are per the observation periods defined above.

Death observation period

The death observations are per the observation periods defined above.

9.2.2 Safety laboratory

The clinical laboratory data consist of hematology (red blood cell count, reticulocyte count, hemoglobin, hematocrit, platelets, white blood cell count [WBC] with differential blood count), standard chemistry (glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, uric acid, LDH, total protein, albumin, γ Glutamyl Transferase [γGT]), Hepatitis C antibody, liver panel (ALT, AST, alkaline phosphatase [ALP], and total bilirubin), and CPK.

Some additional safety laboratory parameters may be reflexively measured, based on actual data (please refer to Section 10.4.7).

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

9.2.3 Vital signs measurement

Vital signs include: weight, heart rate, systolic and diastolic blood pressure in sitting position.

9.2.4 Electrocardiogram measurement

Electrocardiogram (ECG) assessments will be described as normal or abnormal.

9.3 OTHER ENDPOINT(S):

9.3.1 Anti-alirocumab antibody assessments

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

9.3.1.1 Sampling time

Serum samples for anti-alirocumab antibody determination will be drawn periodically throughout the study as per schedule noted in the study flowchart – Section 1.2. The first scheduled sample at randomization visit will be obtained before IMP injection (pre-dose).

Patients who have titers at or above 240 for anti-alirocumab antibodies at the common study end date will have an additional antibody sample between 6 to 12 months after this date.

In patients who permanently discontinued blinded study treatment early, anti-alirocumab antibody assessments will be performed at the early end-of-treatment visit (V70) and at every subsequent clinic visit, where this assessment was planned.

9.3.1.2 Sampling procedure

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

9.3.1.3 Bioanalytical method

All anti-alirocumab antibody samples will be analyzed by the Regeneron Sample Analysis group.

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

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

9.3.2 Lipid parameters

9.3.2.1 Endpoints

The percent changes from baseline to Month 4, to Month 24, and to the final analysis cutoff date for the following parameters:

- Calculated LDL-C
- ApoB
- Non-HDL-C

All measurements (scheduled or unscheduled, fasting or not fasting) may be used to provide a value for the endpoint considered, even if assessed after patient's discontinuation to the study treatment (Intent-To-Treat [ITT] approach). The analysis windows used to allocate a time point to a measurement will be defined in the Statistical Analysis Plan (SAP).

9.3.2.2 Assessment method

LDL-C will be calculated using the Friedewald formula (38). In case of calculated LDL-C <15 mg/dL (0.39 mmol/L), LDL-C value will be confirmed with direct measurement. If the TG values exceed 400 mg/dL (4.52 mmol/L), the central lab will reflexively measure the LDL-C rather than calculating it. Direct LDL-C measurement will be done via the beta quantification method. Apo B will be directly measured by the Central Laboratory. Non-HDL-C will be calculated by subtracting HDL-C from the total-C. Detailed procedures of sample preparation, storage and shipment will be described in the specific laboratory manual which will be provided to sites. Lipids parameters will be assessed from screening to common study end date.

9.3.3 hs-CRP

The percent change in hs-CRP from baseline up to the common study end date.

9.3.4 HbA_{1c}

The absolute change in HbA_{1c} (%) from baseline up to the common study end date.

9.3.5 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, 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 Appendix G*)*. 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 change of index score from baseline Week (39).

This questionnaire will only be administered in patients receiving the double-blind treatment. Patients who will prematurely discontinue will be asked to fill in this questionnaire until the early end of treatment visit (V70) to be performed at the time of discontinuation.

9.3.6 Pharmacogenomic Samples

An optional pharmacogenomic sub-study will be conducted to identify genetic associations with clinical or biomarker response to PCSK9 inhibition, hyperlipidemia, or cardiovascular disease. If needed, samples may also be used to identify markers associated with toxicity.

Randomized patients who agree to participate in the genomics sub-study will be required to sign a separate genomics sub-study informed consent form (ICF) prior to collection of the DNA sample. Blood for DNA extraction should be collected before IMP injection (pre-dose) on randomization visit; however, it could be collected at any time during the study. Patients who choose not to enroll in the genomics sub-study are still eligible to enroll in the primary study.

Special procedures for storage and shipping of pharmacogenomic samples are summarized below (Table 1) and are described in detail in Appendix B.

Table 1 - Summary of handling procedures for DNA storage samples

Sample Type(s)	Pharmacogenetics
Blood Sample Volume	6 mL
Tube Type	6 mL Becton Dickinson K2 EDTA VACUTAINER™ Plus tubes with HEMOGARD™ closure (PN367863/4) sterile tubes
Anticoagulant	K2 EDTA
Blood Handling Procedures	Keep blood on ice or frozen at -20°C (or colder) within 30 min of sampling time. DO NOT CENTRIFUGE.
Storage Conditions	In collection tube at approximately -20°C (or colder)

The Sponsor has included safeguards for protecting patient confidentiality. The blood sample and DNA that is extracted from it will be assigned a second number, a Genetic ID (de-identification code) that is different from the Subject ID. This “double coding” is performed to separate a patient’s medical information and DNA data. The clinical study data (coded by Subject ID) will be stored in a distinct database at a different location from the database containing the pharmacogenomic data (coded by Genetic ID). The key linking Subject ID and Genetic ID will be maintained by a third party, under appropriate access control. The matching of clinical data and pharmacogenomic data, for the purpose of data analysis, will be possible only by using this key,

which will be under strict access control. All data will be reported only in coded form in order to maintain confidentiality.

DNA may be stored and used for analyses for up to 15 years from the completion of the Clinical Study Report (CSR). Analyses may include sequence determination or single nucleotide polymorphisms (SNP) from candidate genes. Candidate genes may include (but are not limited to) PCSK9, Apo B and LDL-R. Genome-wide studies, including (but not limited to) SNP analyses and/or genomic sequencing may also be performed.

9.3.7 Cardiovascular events of interest (other than efficacy endpoints)

Clinically significant complications or procedures (not planned at the time of randomization) related to peripheral arterial disease (such as critical limb ischemia, amputation, peripheral revascularization) as well as venous thromboembolic events (deep vein thrombosis, pulmonary embolism) will be collected on the case report form.

10 STUDY PROCEDURES

The study consists of a run-in period of at least 2 weeks with randomization no earlier than 4 weeks (28 days) and no later than 52 weeks (+ 5 days) after the index ACS event. The double-blind, placebo-controlled treatment period will continue for 24 months after the closing of randomization ex-China or until the target number of events (1613) is reached whichever comes last (see beginning of Section 6). The corresponding estimated study duration is approximately 64 months. All randomized patients (whether they are still receving IMP at the end of the study, or had earlier permanent treatment discontinuation) should have a final visit (CSED visit) between the CSED and CSED + 30 days.

For all visits after Day 1/Month 0 (randomization visit), a timeframe of a certain number of days will be allowed. The window period for visits at Months 1 and 2 are ± 7 days, and for all other subsequent visits it is ± 14 days during the double-blind treatment period (NOTE: in case of major IMP issue, please refer to Section 8.9).

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

Ideally all the visits should take place in the morning approximately at the same time. However after randomization in case there is no other possibility for the patient, visits can be arranged later in the day.

For the phone calls/contacts via internet to be performed in between on-site/clinic visits, they should be scheduled with the goal of maintaining a contact with the patient about every 2 months during first 24 months, and about every 3 months thereafter. Having no phone or email contact with a patient for a prolonged period (>4 months) should be avoided as much as possible.

Blood samplings:

The blood sampling for determination of lipid parameters (eg, LDL-C, Apo B, and non-HDL-C) should be preferably performed in the morning, in fasting condition (ie overnight, at least 8 hours fast) for all site visits throughout the study.

Laboratory tests:

The laboratory data are collected in accordance with the study schedule in Section 1.2 and forwarded to the central laboratory:

- Hematology

  NOTE: *At selected sites with a longer transit time to Central Lab, a duplicate hematology sample will be collected for local assessment of reticulocyte count,*

- Chemistry

- Liver panel: in case of total bilirubin values above the normal range, differentiation into conjugated and non-conjugated bilirubin will occur automatically
- Lipids
- Creatine Phosphokinase (CPK).
- Hepatitis B surface antigen
- Hepatitis C antibody

  NOTE: *In case of positive hepatitis C antibody test, a blood sample will be collected at a subsequent visit and sent to Covance Central Lab for further confirmatory testing*
- Serum pregnancy test

Central Laboratory results will be provided to sites (with the exception of lipid levels collected post-randomization in order to maintain the double-blind nature of the study). An alert will be provided by the Central Laboratory to sites in case of 2 consecutive significant elevations of triglyceride levels. Table 2 summarizes the management of selected blood samples during the study.

Table 2 - Overview of selected blood samples during study

Blood samples	Collection	Results	Comment
Blood samples described above (other than lipids)	Collected periodically at study visits during run-in and post-randomization and sent to Central Laboratory	Results provided to sites	During run-in period, results used for qualification
Blood sample for lipids	Collected at study visits during run-in period and sent to Central Laboratory	Results provided to sites	Results at V2/V2b used for qualification (run-in period)
	Collected post-randomization periodically at study visits throughout the study and sent to Central Laboratory	Results not provided to sites (in order to maintain the blind)	- Results will be analyzed at the end of the trial - Alert provided to sites by Central Laboratory for significant elevation of triglycerides (2 consecutive values) - Low cholesterol values (and associated clinical safety) reviewed in unblinded manner by Independent Physician with oversight by DMC members (who may determine upon individual circumstances that a site should be alerted) - No alert provided for high or elevation of cholesterol levels (see below)
	Additional lipid level assessments (at a local laboratory) should not be performed during entire study		- Rationale is that patient is already treated with maximal LMT regimen (statin-intensive and optimized for long-term chronic use) since study start - Compliance to required background LMT regimen should be emphasized throughout study; LMT may be modified based on clinical tolerability considerations only – see Section

Blood samples	Collection	Results	Comment
			8.8.1 - Investigator should periodically remind and educate GP/cardiologist of study requirements (i.e. during entire study, GP/cardiologist should refrain from checking lipid levels at a local laboratory, and should not modify LMT regimen without discussing with Investigator)
Cardiac biomarkers	To be collected and analyzed locally, as needed(for assessment of suspected cardiac events), with results provided to sites		Results used for efficacy endpoints

Urine samplings:

- Urinalysis will be performed periodically (yearly) throughout the study in about 750 randomized patients, at selected sites. A urine sample will be sent to Covance Central Labs for macroscopic analysis (presence of blood, protein, glucose, ketones, nitrates, leukocyte esterase, uro-bilinogen and bilirubin). In case of abnormalities, Covance Central Lab will perform a microscopic analysis.
- Urine pregnancy test – dipstick will be performed on site.

NOTE*: Any clinically relevant abnormal laboratory value should be immediately rechecked (whenever possible using the central laboratory) for confirmation before making any decision for the concerned patient. It should be documented as an AE/SAE as applicable. Please also refer to Section 10.4.4 and Section 10.4.7*.

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

Other endpoints assessment methods

All other blood parameters will also be measured by a Central Laboratory during the study (as per the schedule in Section 1.2, on blood samples taken preferably in the morning in fasting condition (at least 8 hours fast).

- Glycemic parameters (HbA_{1c}) and serum glucose will be measured by a Central laboratory, periodically throughout the study as per the schedule in Section 1.2.
- The blood sampling for inflammatory parameter, hs-CRP will be collected periodically throughout the study as per the schedule in Section 1.2.

NOTE: *In case of high HbA_{1c} values at screening, the Investigator is responsible for the optimization of the patient's treatment to achieve HbA_{1c} targets as defined by local guidelines or the Standards of Medical Care in Diabetes-2012 by the American Diabetes Association (40).*

Library samples

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

Library samples will be coded to maintain patient confidentiality and may be stored for up to 10 years or as permitted by local regulatory policies, whichever is shorter, for exploratory research of PCSK9 levels, PCSK9 function, effect(s) of PCSK9 inhibition with a monoclonal antibody, lipoprotein sub-fraction, inflammation, and cardiovascular risk markers (eg, lipoprotein–associated phospholipase A2). If needed, samples may also be used to identify markers associated with toxicity. The library samples will never be used for genomic analysis.

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

- Plasma samples: 8.5 mL blood volume to be collected as specified in the specific laboratory manual
- Serum samples: 2.5 mL blood volume to be collected as specified in the specific laboratory manual

Physical examination:

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

Blood pressure (BP)/heart rate:

BP should be measured in sitting position under standardized conditions.

Heart rate will be measured at the time of the measurement of blood pressure.

NOTE: *In case of high BP values at screening the Investigator is responsible for the optimization of the patient's treatment to achieve BP targets as defined by local guidelines or the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (41).*

ECG:

The ECGs will be interpreted locally by the Investigator. Any clinically significant abnormality should be documented as an AE/SAE as applicable (see Section 10.4.4). All ECG traces will be kept as source data.

Body weight and height

Body weight should be obtained with the patient wearing undergarments or very light clothing and no shoes, and with an empty bladder.

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

10.1 VISIT SCHEDULE

10.1.1 Screening visit - Visit 1 (at least 2 weeks prior to randomization visit) and entry in the run-in period

Visit 1 (V1) and Visit 2 (V2) can be separate visits or can be combined (see Section 6.1.1. - Run-in period.

- If V1 and V2 are separate visits, V1 should be scheduled between 0 and 50 weeks post index ACS event
- If V1 and V2 are combined, the combined V1/V2 visit should be scheduled between 0 and 50 weeks + 5 days post index ACS event

The patient will receive verbal information concerning the aims and methods of the study, its constraints and risks and the study duration. A written summary in the form of an information leaflet will be given to the patient. The written informed consent must be signed by the patient and the Investigator prior to any investigations. Only patients who meet the inclusion criteria as noted in Section 7 may be screened. Women of childbearing potential will be requested to use a medically approved contraceptive method during the entire study. If it is planned to have another designated person administer the injections to the patient during the study, then this person should be present for the first injection-training done at this visit V1.

This visit will include:

- Complete informed consent
- Assessment of inclusion and exclusion criteria
- Demographic (age, gender, race, ethnicity)
- Collect contact information (address, e mail, home and cell phone number) for patient, patient's family and patient's GP/cardiologist
- Patient's medical and surgical history (including menopausal status and cardiovascular history, and relevant family history e.g. allergy), alcohol habits, and smoking habits
- Patient's cardiovascular history
- Index ACS event: type of event and date of onset
- Record of previous LMT medications (related to statins, and non-statin LMTs) from prescription or over-the-counter within 1 month prior to screening; use of chronic statin treatment or not prior to index ACS event

- Record of concomitant medications, especially lipid-modifying treatments (statins and non-statin LMTs from prescription or over-the counter therapies as above), and cardiovascular medications
- Body weight and height measurements
- Physical examination including vital signs: sitting systolic and diastolic blood pressure (SBP and DBP), heart rate
- Collection of adverse events from this point onward:

All adverse events and serious adverse events will be collected from the time of informed consent signature and throughout the study until the common study end-date visit (V30).

- IVRS/IWRS contact for notification of screening and entry in the run-in period:
  - Patients meeting the inclusion/exclusion criteria for eligibility at screening will enter the run-in period of the study. IVRS/IWRS is to be contacted for notification of screening and for patient number allocation (please note that it is important to have the IVRS/IWRS contact before any blood sample is drawn because the patient number is given by IVRS/IWRS and it must be reported on the requisition forms). This patient number is composed of a 9-digit number containing the 3-digit country code, the 3-digit center code and the 3-digit patient chronological number (the 3-digit patient chronological number is 001 for the first patient screened in a center, 002 for the second patient screened in the same center...).
  - Allocation of a batch number for training kit
- Fasting blood sample for:
  - Lipids: TC, LDL-C, HDL-C, TG, non-HDL-C, ApoB
  - Hematology: blood cell count including hematocrit, hemoglobin, red blood cell count, white blood cell count with differential count and platelets
  - Chemistry: glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, uric acid, LDH, total protein, albumin, and γGT
  - Liver panel (ALT, AST, ALP, and total bilirubin).
  - HbA_{1c}
  - CPK
  - Hepatitis B surface antigen and hepatitis C antibody tests

    NOTE: *In case of positive hepatitis C antibody test, a blood sample will be collected at a subsequent visit and sent to Covance Central Lab for further confirmatory testing*
  - Serum pregnancy test (females of childbearing potential only)

- First potential injection-training on site (see also Section 8.1.2):
  - Injection-training should be provided as outlined in Section 8.1.2
  - The placebo should be administered by the patient or another designated person (such as spouse, relative, etc...) at the study site under supervision of site staff with appropriate feedback
  - Record batch number allocated in eCRF
- An appointment will be given for the next visit V2 after required LMT regimen (statin-intensive, and optimized for long-term chronic use with addition of non-statin LMT, at Investigator's discretion) has been administered for at least two weeks, was found well tolerated and no further increase in LMT regimen is planned.

If necessary one additional visit (V2b) and central laboratory assessments may occur during the run-in period (see Section 6.1.1.2.3)

The patient should be seen for the next visit in the morning and preferably in fasting condition (ie, overnight, at least 8 hours fast).

10.1.2 Qualifying visit - Visit 2

V2 should be scheduled after required LMT regimen was administered at stable dose for at least 2 weeks and found well tolerated (see Section 6.1.1.3).

- If V1 and V2 are separate visits, the interval between V1 and V2 should be at least 2 weeks (14 days)
- Alternatively, V1 and V2 may be combined in one visit (see Section 10.1.3)

This visit will include:

- Update contact information (address, e mail, home and cell phone number) for patient, patient's family and patient's GP/cardiologist
- Assessment of inclusion and exclusion criteria
- Record of concomitant medication (including but not limited to LMT regimen used during the 2 weeks prior to V2)

  NOTE: In case of rescreening, reason for potential different statin dose/regimen used during the 2 weeks prior to V2/Screening 2 (as compared to the 2 weeks prior to V2/Screening 1) will be recorded
- Vital signs: SBP and DBP, heart rate
- Collection of adverse events
- Check of the compliance and stability of the dose of the LMT (atorvastatin, rosuvastatin, ± other LMT)
- Fasting blood sample for qualifying lipid labs:
  - Lipids: TC, LDL-C, HDL-C, TG, non-HDL-C, ApoB

- Potential injection-training on site:
  - IVRS/IWRS contact for allocation of a batch number for training kit
  - Injection-training should be provided as outlined in Section 8.1.2
  - The placebo should be administered by the patient or another designated person (such as spouse, relative, etc...) at the study site under supervision of site staff with appropriate feedback
  - Record batch number allocated in eCRF
- An appointment will be given for the next visit (V3 randomization) in 2 to 5 days, after results of V2 labs are obtained
  - Remind patient to be in fasting conditions (ie, overnight, at least 8 hours fast) for next visit
  - The patient will be instructed to continue the LMT at the same dose

10.1.3 Combined V1/V2 Visit

If required LMT regimen (see Section 6.1.1.3) was already administered at stable dose prior to V1 for $\geq$ 2 weeks and found well tolerated, V1 and V2 visits can be combined as one visit (combined V1/V2 visit), with all assessments of V1 and V2 visits to be performed at this combined visit.

NOTE: *Prior to conducting a combined V1/V2 visit, prior LMT (and, if applicable, intolerance to statin) must be adequately documented in a source document such as a discharge summary, history and physical, clinic note or consultation report to confirm treatment.*

10.1.4 Optional qualifying visit - Visit 2b

See Section 6.1.1.2.3 for circumstances in which this visit should be performed.

This visit is similar to the Visit V2, and a training injection can be performed.

- Third (potential) training injection as necessary
  - IVRS/IWRS contact for allocation of a batch number for training kit
  - Injection-training should be provided as outlined in Section 8.1.2
  - The placebo should be administered by the patient or another designated person (such as spouse, relative, etc...) at the study site under supervision of site staff with appropriate feedback
  - Record batch number allocated in eCRF
- An appointment will be given for the next visit V3 (randomization) – See Section 10.1.5.1.1
  - Remind patient to be in fasting conditions (ie overnight, at least 8 hours fast) for next visit

10.1.5 Double-blind treatment period

10.1.5.1 Study site visits from Visit 3 (Month 0, D1) to Visit 30 (Month 64)

10.1.5.1.1 Baseline (randomization) visit - Visit 3 (Month 0, D1)

V3 should be scheduled as follows:

- If V1 and V2 are separate visits (≥ 2 weeks between V1 and V2): V3 (randomization) can occur as soon as the qualifying lipid lab results from V2 are obtained from the central lab (typically final results are available within 2-5 days of collection)
- In case of combined V1/V2 visit, after qualifying lipid labs are collected and if patient is eligible, V3 (randomization) should occur at least 2 weeks (14 days) after the combined V1/V2 visit
- In all cases, V3 (randomization) should occur no earlier than 4 weeks (28 days) and no later than 52 weeks (+ 5 days) post index ACS event
- Also, there should be no new ACS event or coronary intervention within 2 weeks prior to V3.

This visit will include:

- Update contact information (address, e mail, home and cell phone number) for patient, patient's family and patient's GP/cardiologist
- Assessment of inclusion and exclusion Criteria
- Record of concomitant medication
- Body weight measurement
- Physical examination including vital signs: SBP and DBP, heart rate
- Collection of adverse events
- Check of the compliance and stability of the dose of the LMT (atorvastatin, rosuvastatin, ± other LMT)
- Informed consent form proposal for the optional genomic sub-study, and if patient agrees to participate then obtain written consent
  - If patient declines participation in the genomic sub-study then this has no consequences for participation in the study otherwise

If the patient is confirmed eligible, the Investigator will start the next study procedures:

- IVRS/IWRS contact for randomization and allocation of a 7-digit treatment kit number according to the randomization list. Investigators should never allocate a treatment kit number to a patient without contacting IVRS/IWRS
- 12-lead ECG
- Urinalysis (at selected sites), with urine sample sent to Central Lab

- Urine pregnancy test (females of childbearing potential only)
- Blood sample for:
  - Lipids: TC, LDL-C, HDL-C, TG, non-HDL-C, ApoB, ApoA-1, ratio ApoB/ApoA-1, and Lp (a)
  - Hematology: blood cell count including hematocrit, hemoglobin, red blood cell count, reticulocyte count, white blood cell count with differential count and platelets

    NOTE: *At selected sites with a longer transit time to Central Lab, a second hematology sample will be collected for local assessment of reticulocyte count*
  - Chemistry: glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, uric acid, LDH, total protein, albumin, and γGT
  - Liver panel (ALT, AST, ALP, and total bilirubin)
  - HbA_{1c}
  - CPK
  - hs-CRP
  - Hepatitis C antibody test

    NOTE: *In case of positive hepatitis C antibody test, a blood sample will be collected at a subsequent visit and sent to Covance Central Lab for further confirmatory testing*
  - Library samples
  - Anti- alirocumab antibodies
  - Genomic specimen collection (for specifically consented patients only)

NOTE: *Collection of all blood and urine samples at V3 should be performed before first double-blind IMP injection.*

- EQ-5D patient questionnaire: to be completed by the patient on site and data will be reported onto the eCRF by site staff.
- Double-blind IMP kit dispensation as per treatment kit number provided by IVRS along with schedule reminder. The patient injection instruction manual and treatment administration package should be provided. The patient diary should be given and instructions on its completion should be reviewed.
- The first double-blind IMP injection will take place at the study site, but only after the collection of the fasting blood samples and after the assessment of all evaluations planned at that visit. Close supervision, feedback and further training to be provided for IMP administration. The patient should be stay in observation for at least 30 minutes after the injection.

  NOTE*: This first injection of double-blind IMP injection can serve as second training injection.*
- Provide ODYSSEY Outcomes card (or equivalent) to patient (and family) mentioning patient participation in the study and site contact information.

- Reminders:
  - An appointment will be given for the next study site visit
  - Remind patient to be in fasting conditions (ie overnight, at least 8 hours fast) for next study site visit, if applicable
  - Remind patient to bring 3 items at the next study visit:
    - the diary,
    - used and unused IMP kits,
    - the ODYSSEY Outcomes card (or equivalent) containing site contact information.
  - Remind patient (and family) that, in case patient is hospitalized, they should contact the site (Investigator, Research Coordinator) as soon as possible, and not wait until the next visit.

10.1.5.1.2 Visit 4 (Month 1, ± 7 days)

This visit will include:

- Update contact information (address, e mail, home and cell phone number) for patient, patient's family and patient's GP/cardiologist
- ODYSSEY Outcomes card (or equivalent) mentioning patient participation in the study and site contact information:
  - Verify that patient has the card; if unsure, provide new cards to patient (and family).
  - Verify that site contact information (Investigator, Study Coordinator) provided to the patient is correct (update as necessary).
- Record of concomitant medication
- Vital signs: SBP and DBP, heart rate
- Collection of information on suspected efficacy endpoints
- Collection of cardiovascular events of interest other than efficacy endpoints (peripheral arterial disease, venous thromboembolic events)
- Collection of adverse events
- Data collection on IMP administration and IMP compliance checked by review of diary

  NOTE: *In case patient forgets to bring back diary at the visit, site should come up with an alternative solution to obtain as soon as possible information contained in patient diary in order to be able to complete IMP information in eCRF in a timely manner.*
- Check of the compliance and stability of the dose of the LMT (atorvastatin, rosuvastatin, ± other LMT)

- Blood sample for:
  - Lipids: TC, LDL-C, HDL-C, TG, non-HDL-C
  - Liver panel (ALT, AST, ALP, and total bilirubin)
  - CPK
- The patient diary should be given and instructions on its completion should be reviewed.
- Reminders:
  - An appointment will be given for the next study site visit.
  - Remind patient to be in fasting conditions (ie overnight, at least 8 hours fast) for next study site visit, if applicable.
  - Remind patient to bring 3 items at the next study visit:
    - the diary,
    - used and unused IMP kits,
    - the ODYSSEY Outcomes card (or equivalent) containing site contact information.
  - Remind patient (and family) that, in case patient is hospitalized, they should contact the site (Investigator, Research Coordinator) as soon as possible, and not wait until the next visit.

10.1.5.1.3 Visit 5 (Month 2, ± 7 days)

This visit will include:

- Update contact information (address, e mail, home and cell phone number) for patient, patient's family and patient's GP/cardiologist
- ODYSSEY Outcomes card (or equivalent) mentioning patient participation in the study and site contact information:
  - Verify that patient has the card; if unsure, provide new cards to patient (and family).
  - Verify that site contact information (Investigator, Study Coordinator) provided to the patient is correct (update as necessary).
- Record of concomitant medication
- Vital signs: SBP and DBP, heart rate
- Collection of information on suspected efficacy endpoints
- Collection of cardiovascular events of interest other than efficacy endpoints (peripheral arterial disease, venous thromboembolic events)
- Collection of adverse events

- Data collection on IMP administration and IMP compliance check by review of diary and treatment kit accountability (used and unused kits)

  NOTE: *In case patient forgets to bring back diary at the visit, site should come up with an alternative solution to obtain as soon as possible information contained in patient diary in order to be able to complete IMP information in eCRF in a timely manner.*
- Check of the compliance and stability of the dose of the LMT (atorvastatin, rosuvastatin, ± other LMT)
- Blood sample for:
  - Lipids: TC, LDL-C, HDL-C, TG, non-HDL-C
  - Anti-alirocumab antibodies.
- EQ-5D patient questionnaire
- Double blind IMP kit dispensation as per treatment kit number provided by IVRS along with schedule reminder and the treatment administration package should be provided. The patient injection instruction manual and diary may be given, as needed
- Reminders:
  - An appointment will be given for the next study site visit
  - Remind patient to be in fasting conditions (ie overnight, at least 8 hours fast) for next study site visit, if applicable
  - Remind patient to bring 3 items at the next study visit:
    - the diary,
    - used and unused IMP kits,
    - the ODYSSEY Outcomes card (or equivalent) containing site contact information.
  - Remind patient (and family) that, in case patient is hospitalized, they should contact the site (Investigator, Research Coordinator) as soon as possible, and not wait until the next visit.

10.1.5.1.4 Visit 6 (Month 4, ± 14 days)

This visit will include:

- Update contact information (address, e mail, home and cell phone number) for patient, patient's family and patient's GP/cardiologist
- ODYSSEY Outcomes card (or equivalent) mentioning patient participation in the study and site contact information:
  - Verify that patient has the card; if unsure, provide new cards to patient (and family).
  - Verify that site contact information (Investigator, Study Coordinator) provided to the patient is correct (update as necessary).
- Record of concomitant medication
- Body weight measurement

- Vital signs: SBP and DBP, heart rate
- Collection of information on suspected efficacy endpoints
- Collection of cardiovascular events of interest other than efficacy endpoints (peripheral arterial disease, venous thromboembolic events)
- Collection of adverse events
- Data collection on IMP administration and IMP compliance check by review of diary and treatment kit accountability (used and unused kits)

  NOTE: *In case patient forgets to bring back diary at the visit, site should come up with an alternative solution to obtain as soon as possible information contained in patient diary in order to be able to complete IMP information in eCRF in a timely manner.*
- Check of the compliance and stability of the dose of the LMT (atorvastatin, rosuvastatin, ± other LMT)
- Urine pregnancy test (females of childbearing potential only)
- Blood sample for:
  - Lipids: TC, LDL-C, HDL-C, TG, non-HDL-C, ApoB, ApoA-1, ratio ApoB/ApoA-1, and Lp (a)
  - Liver panel (ALT, AST, ALP, and total bilirubin)
  - CPK
  - hs-CRP
  - Library samples
  - Anti- alirocumab antibodies
- EQ-5D patient questionnaire
- Double blind IMP kit dispensation as per treatment kit number provided by IVRS along with schedule reminder and the treatment administration package should be provided. The patient injection instruction manual and diary may be given, as needed
- Reminders:
  - An appointment will be given for the next study site visit
  - Remind patient to be in fasting conditions (ie, overnight, at least 8 hours fast) for next study site visit, if applicable
  - Remind patient to bring 3 items at the next study visit:
    - the diary,
    - used and unused IMP kits,
    - the ODYSSEY Outcomes card (or equivalent) containing site contact information.
  - Remind patient (and family) that, in case patient is hospitalized, they should contact the site (Investigator, Research Coordinator) as soon as possible, and not wait until the next visit.

10.1.5.1.5 Visit 8 (Month 8, ± 14 days)

This visit will include:

- Update contact information (address, e mail, home and cell phone number) for patient, patient's family and patient's GP/cardiologist
- ODYSSEY Outcomes card (or equivalent) mentioning patient participation in the study and site contact information:
  - Verify that patient has the card; if unsure, provide new cards to patient (and family).
  - Verify that site contact information (Investigator, Study Coordinator) provided to the patient is correct (update as necessary).
- Record of concomitant medication
- Body weight measurement
- Vital signs: SBP and DBP, heart rate
- Collection of information on suspected efficacy endpoints
- Collection of cardiovascular events of interest other than efficacy endpoints (peripheral arterial disease, venous thromboembolic events)
- Collection of adverse events
- Data collection on IMP administration and IMP compliance check by review of diary and treatment kit accountability (used and unused kits)

  NOTE: *In case patient forgets to bring back diary at the visit, site should come up with an alternative solution to obtain as soon as possible information contained in patient diary in order to be able to complete IMP information in eCRF in a timely manner.*
- Check of the compliance and stability of the dose of the LMT (atorvastatin, rosuvastatin, ± other LMT)
- Urine pregnancy test (females of child-bearing potential only)
- Blood sample for:
  - Lipids: TC, LDL-C, HDL-C, TG, non-HDL-C
- EQ-5D patient questionnaire
- Double blind IMP kit dispensation as per treatment kit number provided by IVRS along with schedule reminder and the treatment administration package should be provided. The patient injection instruction manual and diary may be given, as needed
- Reminders:
  - An appointment will be given for the next study site visit
  - Remind patient to be in fasting conditions (ie, overnight, at least 8 hours fast) for next study site visit, if applicable

- Remind patient to bring 3 items at the next study visit:
    - the diary,
    - used and unused IMP kits,
    - the ODYSSEY Outcomes card (or equivalent) containing site contact information.
- Remind patient (and family) that, in case patient is hospitalized, they should contact the site (Investigator, Research Coordinator) as soon as possible, and not wait until the next visit.

10.1.5.1.6 Visit 10 (Month 12, ± 14 days)

This visit will include:

- Update contact information (address, e mail, home and cell phone number) for patient, patient's family and patient's GP/cardiologist
- ODYSSEY Outcomes card (or equivalent) mentioning patient participation in the study and site contact information:
    - Verify that patient has the card; if unsure, provide new cards to patient (and family).
    - Verify that site contact information (Investigator, Study Coordinator) provided to the patient is correct (update as necessary).
- Record of concomitant medication
- Body weight measurement
- Physical examination including vital signs: SBP and DBP, heart rate
- Collection of information on suspected efficacy endpoints
- Collection of cardiovascular events of interest other than efficacy endpoints (peripheral arterial disease, venous thromboembolic events)
- Collection of adverse events
- Data collection on IMP administration and IMP compliance check by review of diary and treatment kit accountability (used and unused kits)

  NOTE: *In case patient forgets to bring back diary at the visit, site should come up with an alternative solution to obtain as soon as possible information contained in patient diary in order to be able to complete IMP information in eCRF in a timely manner.*
- Check of the compliance and stability of the dose of the LMT (atorvastatin, rosuvastatin, ± other LMT)
- Urinalysis (at selected sites), with urine sample sent to Central Lab
- Urine pregnancy test (females of childbearing potential only)

- Blood sample for:
  - Lipids: TC, LDL-C, HDL-C, TG, non-HDL-C, ApoB, ApoA-1, ratio ApoB/ApoA-1, and Lp (a)
  - Hematology: blood cell count including hematocrit, hemoglobin, red blood cell count, reticulocyte count, white blood cell count with differential count and platelets

    NOTE: *At selected sites with a longer transit time to Central Lab, a duplicate hematology sample will be collected for local assessment of reticulocyte count*
  - Chemistry: glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, uric acid, LDH, total protein, albumin, and γGT
  - Liver panel (ALT, AST, ALP, and total bilirubin)
  - HbA_{1c}
  - CPK
  - hs-CRP
  - Library samples
  - Anti- alirocumab antibodies
- EQ-5D patient questionnaire
- Double-blind IMP kit dispensation as per treatment kit number provided by IVRS along with schedule reminder. The patient injection instruction manual and treatment administration package should be provided. The patient diary should be given and instructions on its completion should be reviewed
- Reminders:
  - An appointment will be given for the next study site visit
  - Remind patient to be in fasting conditions (ie, overnight, at least 8 hours fast) for next study site visit, if applicable
  - Remind patient to bring 3 items at the next study visit:
    - the diary,
    - used and unused IMP kits,
    - the ODYSSEY Outcomes card (or equivalent) containing site contact information.
  - Remind patient (and family) that, in case patient is hospitalized, they should contact the site (Investigator, Research Coordinator) as soon as possible, and not wait until the next visit.

10.1.5.1.7 Visit 12 (Month 16)/ Visit 14 (Month 20)/ Visit 18 (Month 30)/ Visit 22 (Month 42)/ Visit 26 (Month 54) (± 14 days)

These visits will include:

- Update contact information (address, e mail, home and cell phone number) for patient, patient's family and patient's GP/cardiologist
- ODYSSEY Outcomes card (or equivalent) mentioning patient participation in the study and site contact information:
  - Verify that patient has the card; if unsure, provide new cards to patient (and family).
  - Verify that site contact information (Investigator, Study Coordinator) provided to the patient is correct (update as necessary).
- Record of concomitant medication
- Body weight measurement
- Vital signs: SBP and DBP, heart rate
- Collection of information on suspected efficacy endpoints
- Collection of cardiovascular events of interest other than efficacy endpoints (peripheral arterial disease, venous thromboembolic events)
- Collection of adverse events
- Data collection on IMP administration and IMP compliance check by review of diary and treatment kit accountability (used and unused kits)

  NOTE: *In case patient forgets to bring back diary at the visit, site should come up with an alternative solution to obtain as soon as possible information contained in patient diary in order to be able to complete IMP information in eCRF in a timely manner.*
- Check of the compliance and stability of the dose of the LMT (atorvastatin, rosuvastatin, ± other LMT)
- Urine pregnancy test (females of childbearing potential only)
- Blood sample for:
  - Lipids: TC, LDL-C, HDL-C, TG, non-HDL-C
  - Liver panel (ALT, AST, ALP, and total bilirubin)
  - CPK
- EQ-5D patient questionnaire
- Double-blind IMP kit dispensation as per treatment kit number provided by IVRS along with schedule reminder. In case an extra kit for the patient is needed, it should be done by contacting the IVRS/IWRS. The patient injection instruction manual and treatment administration package should be provided. The patient diary should be given and instructions on its completion should be reviewed

- Reminders:
  - An appointment will be given for the next study site visit
  - Remind patient to be in fasting conditions (ie, overnight, at least 8 hours fast) for next study site visit, if applicable
  - Remind patient to bring 3 items at the next study visit:
    - the diary,
    - used and unused IMP kits,
    - the ODYSSEY Outcomes card (or equivalent) containing site contact information.
  - Remind patient (and family) that, in case patient is hospitalized, they should contact the site (Investigator, Research Coordinator) as soon as possible, and not wait until the next visit.

10.1.5.1.8 Visit 16 (Month 24)/ Visit 20 (Month 36)/ Visit 24 (Month 48)/ Visit 28 (Month 60) (± 14 days)

These visits will include:

- Update contact information (address, e mail, home and cell phone number) for patient, patient's family and patient's GP/cardiologist
- ODYSSEY Outcomes card (or equivalent) mentioning patient participation in the study and site contact information:
  - Verify that patient has the card; if unsure, provide new cards to patient (and family).
  - Verify that site contact information (Investigator, Study Coordinator) provided to the patient is correct (update as necessary).
- Record of concomitant medication
- Body weight measurement
- Physical examination including vital signs: SBP and DBP, heart rate
- Collection of information on suspected efficacy endpoints
- Collection of cardiovascular events of interest other than efficacy endpoints (peripheral arterial disease, venous thromboembolic events)
- Collection of adverse events
- Data collection on IMP administration and IMP compliance check by review of diary and treatment kit accountability (used and unused kits)

  NOTE: *In case patient forgets to bring back diary at the visit, site should come up with an alternative solution to obtain as soon as possible information contained in patient diary in order to be able to complete IMP information in eCRF in a timely manner.*

- Check of the compliance and stability of the dose of the LMT (atorvastatin, rosuvastatin, ± other LMT)
- Urinalysis (at selected sites), with urine sample sent to Central Lab
- Urine pregnancy test (females of childbearing potential only)
- Blood sample for:
  - Lipids: TC, LDL-C, HDL-C, TG, non-HDL-C (in addition, at Month 24 only, ApoB will be collected)
  - Hematology: blood cell count including hematocrit, hemoglobin, red blood cell count, reticulocyte count, white blood cell count with differential count and platelets

    NOTE: at selected sites with a longer transit time to Central Lab, a second hematology sample will be collected for local assessment of reticulocyte count
  - Chemistry: glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, uric acid, LDH, total protein, albumin, and γGT
  - Liver panel (ALT, AST, ALP, and total bilirubin)
  - HbA_{1c}
  - CPK
  - Anti- alirocumab antibodies
- EQ-5D patient questionnaire
- Double-blind IMP kit dispensation as per treatment kit number provided by IVRS along with schedule reminder. In case an extra kit for the patient is needed, it should be done by contacting the IVRS/IWRS. The patient injection instruction manual and treatment administration package should be provided. The patient diary should be given and instructions on its completion should be reviewed
- Reminders:
  - An appointment will be given for the next study site visit
  - Remind patient to be in fasting conditions (ie, overnight, at least 8 hours fast) for next study site visit, if applicable
  - Remind patient to bring 3 items at the next study visit:
    - the diary,
    - used and unused IMP kits,
    - the ODYSSEY Outcomes card (or equivalent) containing site contact information.
  - Remind patient (and family) that, in case patient is hospitalized, they should contact the site (Investigator, Research Coordinator) as soon as possible, and not wait until the next visit.

10.1.5.2 Contacts (phone calls, text messages or contacts via internet) from randomization

Contacts should be scheduled in between on-sites visits as follows: Visit 7 (Month 6)/ Visit 9 (Month 10)/ Visit 11 (Month 14)/ Visit 13 (Month 18)/ Visit 15 (Month 22)/ Visit 17 (Month 27)/ Visit 19 (Month 33)/ Visit 21 (Month 39)/ Visit 23 (Month 45)/ Visit 25 (Month 51)/ Visit 27 (Month 57)/ Visit 29 (Month 62).

Although flexibility is allowed in the timing of phone call in between the on-site/clinic visits, it should be scheduled with the goal of maintaining a contact with the patient about every 2 months during first 24 months, and about every 3 months thereafter. Having no phone or email contact with a patient for a prolonged period (>4 months) should be avoided as much as possible. Some additional instructions for scheduling phone call may be provided at time of interim analysis.

This contact will include:

- Update contact information (address, e mail, home and cell phone number) for patient, patient's family and patient's GP/cardiologist
- Review compliance with background LMT (including statin, ezetimibe)
- Collection of information on IMP administration (and remind patient to complete diary)
- Collection of information on suspected efficacy endpoints (and remind patient to call site in case of hospitalization and not wait until next visit)
- Reminders: as applicable for IMP administration schedule, timing of next visit, fasting conditions for next lab assessment, to bring the diary and used and unused kits at the next study site visit

In addition to the contacts detailed above, a SMS/text messaging vendor (EXCO InTouch) has been engaged to send appointment and injection reminders to any patient who wishes to and is able to receive them. This service is optional and each study site will have the opportunity to participate or refuse as per their policies.

These contacts will conform to privacy regulations at each site.

10.1.5.3 Early end of treatment visit – Visit 70

For patients who will have prematurely permanently discontinued IMP (see Section 10.3.2 for more details on when to consider that a patient has permanently discontinued treatment), an end of treatment visit called Visit 70 (early end of treatment visit) will be performed as soon as practically possible (within 1 month) after IMP discontinuation is considered permanent by the Investigator. Assessments done at this visit will be similar to those planned for the study completers at the final visit (Visit 30, Month 64) (see Section 1.2).

In addition:

- Update contact information (address, email, home and cell phone number) for patient, patient's family, and patient's GP/cardiologist
- ODYSSEY Outcomes card (or equivalent) mentioning patient participation in the study and site contact information:
  - Verify that patient has the card; if unsure, provide new cards to patient (and family).
  - Verify that site contact information (Investigator, Study Coordinator) provided to the patient is correct (update as necessary).

Then those patients must continue to remain in the study and will be strongly encouraged to complete all the remaining study visits as originally scheduled (as described in Section 1.2), until the common study end date (ie, final visit, Visit 30, Month 64). Complete usual study assessments (with the exception of IMP administration and its associated procedures) will be performed for 6 months following V70. Thereafter, study assessments are reduced (see Section 10.3.4 for more details). Patients who will not be able to attend any particular study visit will be invited to attend a subsequent visit.

Finally, the Investigator will make every effort to contact participants who are lost to follow-up. Attempts to contact such participants must be documented in the participant's records.

10.1.5.4 Common study end date visit (Final Visit) – Visit 30 (~Month 64, between CSED and CSED + 30 days)

This final CSED visit should be scheduled and be performed on or shortly after the actual occurrence of the CSED (see also Section 6.2.2). CSED is scheduled to occur at around Month 64, and will be announced by the sponsor in advance in order for sites to be able to plan this final visit.

This final CSED visit (Visit 30, Month 64):

- should be a clinic visit,
- should be performed for all randomized patients regardless of the patient status (still receiving IMP or having prematurely discontinued IMP permanently),
- however there are some differences on how to plan the visit (and last IMP injection, when applicable) and in assessments to be performed at that final visit, depending on patient status.

For patients still receiving IMP (study completers), both CSED visit and last IMP injection should be determined taking into account the following:

- CSED visit should take place between CSED and CSED + 30 days
- CSED visit should occur 14 days (±3 days) after last IMP injection
- Site has clearly communicated and agreed in advance with patient (and family) on date of last IMP injection and date of CSED visit

- In order to ensure compliance with these critical final study procedures, sites should:
  - contact patients a few days prior to the agreed-upon date of last IMP injection,
  - remind patient about the final IMP injection and final CSED visit, and
  - ask patient to return to the investigational site in the morning preferably in fasting condition (ie, overnight, at least 8 hours fast) and to bring the used and unused kits and the diary.

Assessments to be performed at the CSED visit for study completers are described in Section 10.1.5.4.1.

For patients who had previously permanently discontinued IMP:

- CSED visit should take place between CSED and CSED + 30 days.
- Site has communicated and agreed in advance with patient (and family) on date of CSED visit.
- In order to ensure compliance with these critical final study procedures, sites should:
  - contact patients a few days prior to the final CSED visit, and
  - ask patient to return to the investigational site in the morning preferably in fasting condition (ie, overnight, at least 8 hours fast).
  - If IMP permanent discontinuation occurred after the prior most recent clinic visit and/or if patient still has IMP kits at home, patient should bring the used and unused kits and the diary.

Assessments to be performed at the CSED visit for patients who had permanently discontinued IMP are described in Section 10.1.5.4.2.

10.1.5.4.1 Final Visit - Visit 30 for study completers

This visit will include:

- Record of concomitant medication
- Body weight measurement
- Physical examination including vital signs: SBP and DBP, heart rate
- Collect information on suspected efficacy endpoints
- Collection of cardiovascular events of interest other than efficacy endpoints (peripheral arterial disease, venous thromboembolic events)
- Collection of adverse events

- Data collection on IMP administration and IMP compliance check by review of diary and treatment kit accountability (used and unused kits)

  NOTE: *In case patient forgets to bring back diary at the visit, site should come up with an alternative solution to obtain as soon as possible information contained in patient diary in order to be able to complete final IMP information in eCRF.*
- Check of the compliance and stability of the dose of the LMT (atorvastatin, rosuvastatin, ± other LMT)
- 12-lead ECG
- Urinalysis (at selected sites), with urine sample sent to Central Lab
- Urine pregnancy test (females of childbearing potential only)
- Blood sample for:
  - Lipids: TC, LDL-C, HDL-C, TG, non-HDL-C, ApoB, ApoA-1, ratio ApoB/ApoA-1, and Lp (a)
  - Hematology: blood cell count including hematocrit, hemoglobin, red blood cell count, reticulocyte count, white blood cell count with differential count and platelets

    NOTE: *At selected sites with a longer transit time to Central Lab, a second hematology sample will be collected for local assessment of reticulocyte count*
  - Chemistry: glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, uric acid, LDH, total protein, albumin, and γGT
  - Liver panel (ALT, AST, ALP, and total bilirubin)
  - HbA_{1c}
  - CPK
  - hs-CRP
  - Hepatitis C antibody test

    NOTE: *In case of positive hepatitis C antibody test at V30, patient should be recontacted as soon as possible after the site has been informed by Central Lab of this positive test, and a subsequent visit should be scheduled also as soon as possible, for collection of a confirmatory blood sample to be sent to Covance Central Lab.*
  - Library samples
  - Anti-alirocumab antibodies
- EQ-5D patient questionnaire
- IVRS/IWRS contact for notification of the date of this final visit; for patients still on treatment this will also be the end of treatment visit

This will be the final study visit for the patient. New or ongoing related or serious AE (as well as new or ongoing AESI) at this CSED visit should continue to be followed until resolution, stabilization, or death (whichever comes first) and related data will be collected (see Section 6.2.1).

10.1.5.4.2 Final Visit - Visit 30 for prematurely discontinued patients

This visit will include:

- Collection of information on suspected efficacy endpoints
- Collection of cardiovascular events of interest other than efficacy endpoints (peripheral arterial disease, venous thromboembolic events)
- Collection of related and/or serious AEs
- Selected concomitant medications (statin, ezetimibe)
- Blood sample for
  - Lipids: TC, LDL-C, HDL-C, TG, non-HDL-C, ApoB
  - HbA1c
  - Anti-alirocumab antibodies
- IVRS/IWRS contact for notification of the date of this final visit

10.2 DEFINITION OF SOURCE DATA

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

- Agreement, date, and signature of informed consent mentioning the study identification
- Patient identification, last participation in a clinical trial, medical history, associated diseases, and data related to the studied pathology
- Contraception methods for women of childbearing potential
- Previous and concomitant medication (including the lipid modifying therapy)
- Study identification
- Treatment number, dates of administration
- Dates of visits and assessments including the examination report
- Vital signs, height, body weigh.
- Faxed central lab reports (dated and signed by the Principal Investigator or Sub-Investigator)
- IVRS/IWRS confirmation fax (screening, screen failure, training kit allocation, randomization, treatment reallocation, discontinuation, end of double blind treatment period, end of study, unblinding if applicable)
- ECG records signed and dated

- Adverse events and follow-up
  - In case of SAE, the site should file in the source document at least copies of the hospitalization reports and any relevant examination reports documenting the follow up of the SAE
- Date of premature study discontinuation (if any) and reason

Source documentation may be found in the following:

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

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

All randomized patients should be treated with blinded study treatment (IMP) for as long as possible.

As a general rule, any IMP treatment discontinuation should be initially considered temporary, and Investigator should make best effort to resume IMP treatment as early as practically possible, after several weeks or months (pending there are no safety concerns), and perform all study visits and assessments as usual.

Permanent IMP discontinuation should be a last resort. Any IMP discontinuation should be fully documented in the eCRF and source notes.

Pregnancy will lead to permanent treatment discontinuation in all cases.

All randomized patients should be followed-up (and suspected efficacy endpoints collected) until the end of the study (common study end date visit), even if treatment was permanently discontinued early.

10.3.1 Temporary treatment discontinuation with investigational medicinal product(s)

Temporary treatment discontinuation (also referred to as treatment interruption) may be considered by the Investigator in case of AEs/SAEs or for other reasons. In general, every effort should be made to resume treatment with blinded study drug (IMP) following a temporary interruption. In case of AEs/SAEs, resuming treatment with the IMP will be done under close and appropriate clinical and/or laboratory monitoring once the Investigator has considered according to his/her best medical judgment that the responsibility of the IMP in the occurrence of the concerned event was unlikely and patient does not meet any permanent discontinuation criteria.

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

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

10.3.2 Permanent treatment discontinuation with investigational medicinal product(s)

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

Investigator is strongly encouraged to discuss with monitoring team before considering any treatment discontinuation as permanent. A discussion with National Coordinator may occur regarding other possible options.

10.3.3 List of criteria for permanent treatment discontinuation

The patients may withdraw from treatment with the IMP if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision. All efforts should be made to document the reasons for treatment discontinuation and this should be documented in the eCRF.

Patients should discontinue the Investigational Medicinal Product (IMP) for the following reasons:

- Pregnancy, intention for pregnancy, or no longer with effective contraceptive method of birth control (females only)
- Acute injection reaction of clinical concern
- Serious adverse event (or non-serious but severe in intensity) of hypersensitivity reaction considered related to IMP
- At patient request
- If, in the Investigator's opinion, continuation with the administration of the IMP would be detrimental to the patient's safety or well-being (NOTE: please refer to Section 10.4.7, Appendix C and Appendix D, for management and follow-up of selected laboratory abnormalities, including guidance for treatment discontinuation)
- At the specific request of the Sponsor
- Any code breaking requested by the Investigator
- Patient receives double-blind treatment prior to randomization

Patient withdrawal from the study treatment or study should be avoided as much as possible. If this occurs, every attempt should be made to restart study drug if medically appropriate, whatever the duration of discontinuation. In case of permanent study treatment discontinuation, the appropriate follow-up until the common study end date visit should still be continued.

All efforts should be made to document the reasons for treatment discontinuation and this should be documented in the eCRF.

10.3.4 Handling of patients after permanent treatment discontinuation

Patients in whom IMP treatment discontinuation is considered permanent by Investigator should come for an extra visit (early end-of-treatment visit V70) as soon as practically possible (within 1 month) after IMP discontinuation is considered permanent by Investigator. V70 is similar to the common end of study visit (Visit 30, Month 64) for study treatment completers, and should include similar procedures.

Such patients must continue to remain in the study and will be strongly encouraged to complete all the remaining study visits as originally scheduled in Section 1.2, until the common study end-date visit. Therefore, a contact should be maintained with these patients every 2 to 3 months (as per study assessments), and a clinic visit performed every 4 to 6 months until the common study end-date visit (V30).

- Over the 6 months following V70, all assessments (other than IMP administration and its associated procedures) should be performed as originally planned. These include but are not limited to collection of suspected efficacy endpoints, AE/AESI/SAE, concomitant medications, hematology and chemistry labs, lipid labs and anti- alirocumab antibodies.
- From 6 months post V70 until common study end date visit (V30), assessment at visits are simplified and will include updating patient contact information (as well as patients' family and patient's GP/cardiologist) and the collection of:
  - suspected efficacy endpoints
  - cardiovascular events of interest other than efficacy endpoints (peripheral arterial disease and venous thromboembolic events)
  - related and/or serious AEs
  - selected concomitant medications (statins, ezetimibe)
  - selected labs:
    - anti alirocumab antibodies, lipid panel and HbA1c: annually (at M12, M24, M36, M48, M60) and at common study end-date
    - ApoB at month 24 and at common study end-date.

  Previously observed AEs/AESIs/SAEs that had not resolved should be followed-up until an outcome (e.g. resolution, stabilization) has been determined.
- In case of difficulty to comply with the 4 to 6-month clinic visit periodicity in patients who discontinued treatment early, every effort should be made to have an actual clinic visit at least annually (with periodic phone/internet contacts every 3 months in between) and a final visit V30. During that annual visit and at V30, selected blood samples as described above should be collected.

In rare cases of written withdrawal of consent (WOC) for follow-up visits (i.e. patient does not wish to come back even for an annual visit), and unless otherwise stated by the patient in the informed consent form, Investigators will be encouraged to get information from the general practitioner, any other physician, or other medical-care provider, in order to follow the medical status of the patients (especially when they withdraw their consent after having experienced an AE/SAE or a cardiovascular event [efficacy endpoint]). Investigators will also be expected to try as much as possible to re-contact those patients at the end of the trial, in order to obtain at least

their vital status (dead or alive), as well as their cardiovascular status if possible, and thus avoid lost to follow-up for the efficacy assessment.

If the patient exercises his right of opposition to transmission of the data to the sponsor or removal of data from the database, the investigator will inform, in writing, the clinical trial sponsor, and the sponsor will decide how to handle the subject data and samples based on local regulations and data privacy requirements.

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

10.3.5 Procedure and consequence for patient withdrawal from study

The patients may withdraw from the study, before study completion if they decide to do so, at any time and irrespective of the reason or this may be the Investigator's decision:

- All study withdrawals should be recorded by the Investigator in the appropriate screens of the eCRF and in the patient's medical records when considered as confirmed (at least date of withdrawal and reason for). IVRS/IWRS should be notified when a patient prematurely discontinues study
- The patients should be assessed using the procedure normally planned for the visit V70 which corresponds to the early end of treatment visit. (see Section 10.3.4)

However, all randomized patients should be followed-up (and suspected efficacy endpoints as well as related and/or serious AEs collected) until the end of the study (common study end date visit), even if treatment was permanently discontinued early.

In case of study treatment discontinuation (temporary or permanent) due to an adverse event, such patients will be closely monitored until the resolution or stabilization of this adverse event. This may mean that follow-up will continue after the patients have completed the study.

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

For patients considered lost to follow-up, the eCRF must be completed up to the last visit performed. The statistical analysis plan will provide the details concerning the analysis of these patients.

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

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

Please refer to Appendix E for Adverse Event (AE) reporting requirements.

10.4.1.1 Adverse event

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

10.4.1.2 Serious adverse event

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

- Results in death, or
- Is life-threatening, or
  Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect
- Is a medically important event
  Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above

  NOTE: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:
  - Intensive treatment in an emergency room or at home for:
    - Allergic bronchospasm
    - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc)
    - Convulsions (seizures, epilepsy, epileptic fit, absence, etc)
  - Development of drug dependency or drug abuse
  - ALT >3 x ULN + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN
  - Suicide attempt or any event suggestive of suicidality

- Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
- Bullous cutaneous eruptions
- Cancers diagnosed during the study or aggravated during the study
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study

10.4.2 Adverse event of special interest

Adverse Events of Special Interest (AESI) are AEs (serious or non-serious) that need to be monitored, documented, and managed in a pre-specified manner described in the protocol. Please see Section 10.4.6.2 and Appendix E for additional information.

10.4.3 Serious adverse events waived from expedited regulatory reporting to health authorities

Unlike most studies where the primary efficacy variable is the resolution or improvement of an existing condition, in this study efficacy outcomes include the occurrence of life-threatening events. Indeed, participants to this study are recruited precisely because they are at high risk for these life threatening events. They are therefore expected to have at least one cardiovascular efficacy endpoint during the course of the study.

In light of the above, (primary and secondary) suspected cardiovascular efficacy endpoints as specified in this protocol will not be considered as AEs and are waived from regulatory reporting to Health Authorities except if the Investigator according to his/her best medical judgment considers these events as unexpected in the context of the underlying disease condition. In that case, the Investigator will complete an AE/SAE form (in addition to eCRF efficacy endpoint page – see below) including causality assessment within 24 hours.

For this study, all suspected cardiovascular efficacy endpoints will be reported (within 24 hours) in the specific eCRF efficacy endpoint pages; the system will automatically send the notification to the Clinical Event Committee Coordination Center at DCRI. This automatic notification will occur after the Investigator has approved the eCRF screens or after a standard time interval has elapsed, whichever comes first.

Expedited reporting to Health Authorities for the following cardiovascular outcomes will be waived:

- CV death including CHD death
- All other causes of death
- Non-fatal MI
- Non-fatal stroke
- Unstable angina requiring hospitalization
- Ischemia-driven coronary revascularization procedure
- Congestive heart failure requiring hospitalization

10.4.4 General guidelines for reporting adverse events

- AEs are to be recorded in corresponding screen(s) included in the eCRF.
- The reporting requirement of AEs depends on patient status (study completer or patient who had premature permanent discontinuation of IMP)
  - In patients who receive IMP until the end of the study (study completer), all AEs, regardless of seriousness or relationship to IMP/NIMP, spanning from the signature of the informed consent form until the CSED visit are to be recorded in the eCRF. Patients who experience a new or ongoing related or serious AE or a new or ongoing AESI (see Section 10.4.2) at the CSED visit should be followed beyond the CSED visit until resolution, stabilization, or death (whichever comes first) and related data will be collected (see Section 10.1.5.4.1).
  - In patients who have permanent premature IMP discontinuation:
    - All AEs, regardless of seriousness or relationship to IMP/NIMP, spanning from the signature of the informed consent form until 6 months following V70 (end of treatment visit) are to be recorded in the eCRF.
    - From 6 months following V70 until the CSED visit, related and/or serious AEs should be recorded in the eCRF.

  NOTE: *Reporting requirement for suspected efficacy endpoints is the same regardless of patient status (study completers or patients who had premature permanent discontinuation of IMP); suspected efficacy endpoinsts should be reported in all randomized patients until the end of the study (CSED).*
- Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP.
- When treatment is prematurely discontinued, the patient will be maintained in the study and the patient's observations will continue until the common study end date visit (see Section 10.3.4).
- Laboratory, vital signs or ECG abnormalities are to be recorded as AEs only if:
  - Symptomatic and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to IMP discontinuation or modification of dosing (with exception of LDL-C levels which may lead to IMP dosing modification, but in a blinded manner), and/or
  - Considered as clinically relevant (such as for ECG a prolonged QTcB > 500 ms or an increase in QTcB of > 60 msec compared to baseline), and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AE of special interest with immediate notification

See Appendix E for a summary of AE and efficacy endpoint reporting guidelines.

10.4.5 Instructions for reporting serious adverse events

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

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the eCRF; the system will automatically send a notification to a representative of the pharmacovigilance team after approval of the Investigator within the eCRF or after a standard time has elapsed, whichever comes first. Transmission to the pharmacovigilance team of information related to the SAE will be done either by fax or with an electronic solution.
- SEND (preferably by fax or e-mail) a photocopy of all examinations carried out and the dates on which these examinations were performed, to a representative of the pharmacovigilance team whose name, fax number, and email address will be provided for each region in a separate document. 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 eCRF 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 a representative of the pharmacovigilance team within 24 hours of knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life threatening within a week (7 days) of the initial notification.
- A back-up plan (using a paper CRF process) is available and should be used when the eCRF system does not work.

10.4.6 Guidelines for reporting adverse events of special interest

10.4.6.1 Reporting of adverse events of special interest with immediate notification

For these AEs, the Sponsor will be informed immediately (ie within 24 hours), as per SAEs notification described in Section 10.4.5, even if not fulfilling a seriousness criterion, using the corresponding screens in the eCRF.

- ALT ≥3 ULN (if baseline ALT < ULN) Or ALT ≥2 times the baseline value (if baseline ALT ≥ ULN) (Please refer to related flowchart in Appendix C).
- Allergic events
  - Allergic drug reactions and/or local injection site reactions deemed to be allergic (or have an allergic component) that require consultation with another physician for further evaluation of hypersensitivity/allergy, as per the investigator's medical judgment or as per Section 10.6.2, should be reported as an AESI with immediate notification.
  - All allergic events, and all injection site reactions having an allergic component or deemed to be allergic, require completion of the specific eCRF screen (see Section 10.6.2), regardless of requirements for immediate reporting.

- Hemolytic anemia (see Section 10.4.7.1 and Appendix D)
  - If there is a decrease in hemoglobin and reflexive testing as per Appendix D suggesting hemolysis, then report this as an AESI with immediate notification. Special eCRF screen will need to be completed
- Pregnancy
  - *Pregnancy occurring in a female patient enrolled in the study* will be recorded as a pre-specified AE with immediate notification in all cases, and IMP should be discontinued in all cases. It will be qualified as an SAE only if it fulfills the SAE criteria. The follow-up of the pregnancy will be mandatory until the outcome of the pregnancy has been determined.
  - *Pregnancy occurring in the female partner of a male patient included in the clinical trial*: if permitted by the female partner and by local regulatory policies, it will be recorded as a pre-specified AE with immediate notification (SAE if it fulfills the SAE criteria), and pregnancy should be followed-up until the outcome has been determined.
- Symptomatic Overdose with IMP
  - An overdose (accidental or intentional) is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic injection counts) and defined as at least twice of the intended dose within the intended therapeutic interval (ie, 2 or more injections from the double-blind treatment kit are administered in <7 calendar days); to be reported using the corresponding screens in the eCRF using the Term “symptomatic OVERDOSE (accidental [or intentional])”. The patient should be monitored and appropriate symptomatic treatment instituted
  - The circumstances of the overdose should be clearly specified in the verbatim
- Neurologic and Neurocognitive Events
  - Neurologic and Neurocognitive Events that require additional examinations/procedures and/or referral to a specialist should be reported as an AESI with immediate notification (see also Appendix E for reporting requirements).

10.4.6.2 Reporting of adverse events of special interest without immediate notification

See Appendix E.

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

- Asymptomatic overdose with IMP
  - An overdose (accidental or intentional) is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic injection counts) and defined as at least twice of the intended dose within the intended therapeutic interval (ie, 2 or more injections from the double-blind treatment kit are administered in <7 calendar days); to be reported using the corresponding screens in the eCRF using

the Term “asymptomatic OVERDOSE (accidental [or intentional])” The patient should be monitored for any AEs and treated, as needed

- Local injection site reactions (see Section 10.6.1)
  - Local injection site reactions related to IMP that are considered as non-allergic events should be further characterized by evaluating the related symptoms that comprise an injection site reaction such as but not limited to redness, pain, etc (See Appendix F). Special eCRF screens will need to be completed. If such an AE was to occur, then do not report the individual components of the reaction but rather the term “local injection site reaction”, the individual components being described in the specific eCRF screen
- Allergic events not referred for consultation with another physician (see Section 10.4.6.1)
  - All allergic events will need to have allergy specific eCRF screens completed (see Section 10.6.2), regardless of requirements for immediate reporting.
- Neurologic and Neurocognitive events
  - AEs related to neurologic or neurocognitive abnormalities with the exception of those requiring additional examinations/procedures and/or referral to a specialist (as mentioned in Section 10.4.6.1) should be reported in accordance with Appendix E.

10.4.7 Guidelines for management of specific laboratory abnormalities

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

- Neutropenia
- Thrombocytopenia
- Increase in ALT
- Acute renal insufficiency
- Decrease in hemoglobin (defined as ≥1.5 g/dL decrease from pre-randomization baseline value)
- Increase in CPK (other than cardiac-related) and suspicion of rhabdomyolysis.

Investigators are strongly encouraged to follow these algorithms in Appendix C and Appendix D, especially in situations where the abnormality persists or when there is no clear explanation for the observed abnormality.

However there may be situations where these algorithms are not entirely applicable, therefore Investigator may use his/her best judgment. Also, in some situations, the Sponsor may wish to discuss with the Investigator. Examples where these algorithms may not be applicable include (but are not limited to) the following situations:

- patients with known stable low or borderline neutrophil or platelet count or impaired renal function at baseline; Investigator should attempt to have a diagnosis for the observed finding and should use his/her best judgment whether or not to enroll these patients, and if

patient is enrolled, on how to best monitor these baseline abormalities throughout the study

- patients with ALT increase or elevated CK for which the abnormality resolves following statin dose reduction or statin discontinuation
- patients with elevated CK caused by a myocardial infarction

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

10.4.7.1 Hemoglobin decrease

See Appendix D.

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

NOTE: *At selected sites with a longer transit time to Central Lab where reticulocyte count cannot be measured by Central Lab, a second hematology sample will be collected for local assessment of reticulocyte count,*

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

  The patient should be referred to a hematologist. The hematologist should obtain a peripheral blood smear and anti-erythrocyte antibodies (direct and indirect) by Coombs test. Further investigations are at the discretion of the hematologist.
- If the results are normal or the pattern of abnormality is something other than that described above, then the Investigator should exercise his/her medical judgment in the interpretation of the results, necessity for workup of the decrease in hemoglobin or referral to a hematologist

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

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, IECs/IRBs as appropriate and to the Investigators.

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

In this study, cardiovascular efficacy endpoints specified (primary and secondary efficacy endpoints) are waived from expedited reporting to Health Authorities providing an agreement has been reached with them.

Also some other AEs may be considered related to the underlying condition and thus will not be considered unexpected as given in the Investigator's Brochure.

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

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

10.6 SAFETY INSTRUCTIONS

10.6.1 Local tolerability (Local Injection Site Reactions)

In case the Investigator or the patient recognizes any signs of local intolerability, then this should be treated and followed up as per the Investigator's medical judgment. See Section 10.4.6.2 and Appendix F for further information.

10.6.2 Allergic adverse events (See Section 10.4.6.1 and Section 10.4.6.2)

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

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

Adverse events that may constitute an allergic reaction (eg, generalized itch, nasal itch, swelling at injection site, flushing, hives, swelling at lips, eyes, face, tongue, hands, feet, lump in throat, difficulty to swallow, hoarseness, change in pitch of voice, incapacity to speak, wheezing, chest tightness, stridor, etc) should be considered to be reported on the General Allergic Reaction and/or Local Injection Site Reaction Complementary Form.

Adverse events that are obviously not of allergic origin (eg, local injection site reactions related to IMP and with no allergic component) should only be recorded on the Local Injection Site

Reaction Complementary Form. However, injection site reactions which progress/expand/worsen/etc should be evaluated as recommended in Section 10.6.2.1 and General Allergic Reaction Complementary form should be completed.

The IMP should be immediately interrupted (temporarily discontinued) if there is a suspicion of an allergic event related to IMP. See Section 10.3.1 for further information on treatment interruption and Section 10.3.2 for criteria for permanent treatment discontinuation.

10.6.2.1 Allergic adverse event with cutaneous involvement

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

The investigator should evaluate the patient for possible etiologies (new medications, etc) and extra-cutaneous symptoms and signs. An unscheduled Central Laboratory assessment for hematology, chemistry, liver panel, and ADA should be obtained. If it is possible, the site will take pictures of the skin lesions in order to provide the patient with them for the dermatologist's visit. If the photos are obtained, then copies should be kept as source documents which may later be collected by the sponsor. The investigator will provide a summary of the patient's case, reason for consultation, and information being requested to the consulting dermatologist.

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

10.6.2.2 Acute allergic injection reactions (Section 10.4.6.2)

Acute allergic injection reaction (which are considered under the category of general allergic reactions) is defined as any AE that occurs during or shortly after injection of the IMP (characterized by but not limited to hypotension, bronchoconstriction, urticaria, edema, angioedema, nausea, vomiting). The investigator should ascertain that patient can be rapidly managed with emergency equipment and medication for the treatment of these potential adverse effects (eg, antihistamines, bronchodilators, IV saline, corticosteroids, acetaminophen, and epinephrine) for the injections at the training, and randomization visits.

Patients will be observed at the investigational site for at least 30 minutes following the injection that takes place at the randomization visit. Patients should be treated symptomatically if any AEs are observed. Patients are to remain on observation until any acute injection reaction is assessed as stable, per the Investigator's or emergency team's discretion. General Allergic Reaction and/or Local Injection Site Reaction Complementary Form will have to be completed.

10.6.3 Monitoring related to two consecutive LDL-C <25 mg/dL (0.65 mmol/L)

Patients who achieve 2 consecutive LDL-C levels <25 mg/dL (0.65 mmol/L) during the study will be monitored and managed as per Appendix A (any time after randomization) as the lower limit of safe and effective LDL-C lowering has not yet been established. An independent external physician(s) (also known as independent physician) will be notified by the central laboratory of 2consecutive LDL-C <25 mg/dL (0.65 mmol/L). The independent physician will review the unmasked LDL-C values and patient safety data, in close collaboration with the dedicated member of the Phase 3a DMC (implemented for all Phase 3 studies evaluating the efficacy and safety of alirocumab on LDL-C). This dedicated Phase 3a DMC member will then transmit any information as necessary to the common member involved in both DMCs (CV DMC and Phase 3a DMC).

Please see Appendix A for an outline of the process.

Then at subsequent visits, specific actions can be undertaken depending on the alirocumab dose (down-titration or discontinuation) as follows:

- On dose of 150 mg Q2W: if LDL-C <25 mg/dL (including LDL-C <15 mg/dL) on 2 consecutive values, down-titration to 75 mg Q2W will be done in a blinded manner at the next visit. The patient will remain at the down titrated dose of 75 mg Q2W for the remaining duration of the study, unless patient meets criteria below. As described above, specific monitoring consisting of review of patient level listing will be implemented.
- On dose of 75 mg Q2W:
  - If LDL-C <25 mg/dL on 2 consecutive values but there are no 2 consecutive measurements < 15 mg/dL (i.e. no measurement < 15 mg/dL or only one occasional measurement < 15 mg/dL): study treatment with 75 mg Q2W will be continued but additional monitoring with review of individual patient profiles will be implemented, to further confirm the safety of low LDL-C levels. A site alert related to 2 consecutive LDL-C < 25 mg/dL (0.65 mmol/L) may be requested by the independent physician (after consultation with dedicated phase 3a DMC member)
  - If measured LDL-C <15 mg/dL on 2 consecutive measurements: study treatment with 75 mg Q2W will be discontinued at the next visit. In order to maintain the blind there will be blinded substitution to placebo injections for the remaining duration of the study

As lipid values will not be communicated to investigators after randomization to maintain the blind, the continuation of the 75 mg dose, the up-titration to the 150 mg dose, the down-titration from 150 to 75 mg, or discontinuation will all occur automatically, without site or patient awareness. Moreover, blinded dose adjustment will avoid the need for dummy titrations in the placebo group.

10.7 ADVERSE EVENTS MONITORING

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

11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

The sample size calculations are based on the primary efficacy variable, with the following assumptions:

- Primary efficacy endpoint is the time from randomization to the date of first occurrence of one of the following Clinical Events, as determined by the CEC: CHD death, any non-fatal MI, fatal and non-fatal ischemic stroke, unstable angina requiring hospitalization. Based on PROVE-IT results (8) and considering adjustment based on the study design and endpoints definition, the following Kaplan-Meier probabilities of event in the placebo group have been considered: 3.8% at 12 months, 6.4% at 24 months, 9.0% at 36 months, 11.4% at 48 months. Probability of event at different time points are estimated using a piece-wise exponential model. The primary efficacy endpoint will be analyzed on an intent-to-treat basis (all randomized patients, including those who discontinue study medication are followed for any efficacy event until the termination of the study)
- Hazard ratio of 0.85 in test group relative to placebo (corresponding to a 15% risk reduction). Constant hazard ratio assumption is used
- A log-rank test at a 1-sided 2.5% significance level with 90% power
- Two interim analyses, according to a group sequential design, using for efficacy Gamma (-22) α-spending function, and for futility a Gamma (-5) β-spending function. Non-binding spending functions are used. See Section 11.5 for interim analysis details
- 1% lost-to-follow rate at 24 months in both arms
- Enrolment rate: sample size of about 18,600 patients enrolled in 1400 sites (these sites should be active within 12 months). The table below describes the expected enrolment rate per month; these assumptions are based on internal experience to enroll this patient population

Table 3 - Enrolment rate assumptions per month

Month	1 to 3	4	5	6	7	8	9	10	11	12 to 40
No. pts per month	32	64	80	104	160	240	320	420	520	560
Cumulative no. patients	96	160	240	344	504	744	1064	1484	2004	2564 at M12, 18000 at M40

Based on the above assumptions, 1613 events are needed for 90% power. In order to achieve the 1613 targeted events, about 18000 patients (~9000 per group) will need to be randomized over a period of about 40 months. However, taking into account the situation in China (target of about 600 randomized patients in China based on local regulatory considerations, and local delayed

study start), the total number of patients randomized will be increased to approximately 18,600 patients (~9,300 per group). At the end of the study, the overall population will include about 18,000 randomized patients who have either died or been followed for a minimum of 24 months, supplemented with an additional subset of patients from China (~600) who may be followed for less than 24 months.

NOTE: *Continued enrolment of patients in China after the initial target of 18,000 randomized globally has been reached, and leading to an increase in sample size to about 18,600 patients, will be implemented only after appropriate local authorizations in China have been obtained.*

Calculations were made using East 5.4 software.

11.2 DISPOSITION OF PATIENTS

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

Randomized patients consist of all screened patients, with a double-blind treatment kit number allocated and recorded in the IVRS/IWRS database, regardless of whether the treatment kit was used or not. Patients treated without being randomized or treated with a double-blind treatment kit before the randomization will not be considered as randomized and will not be included in any analysis population. The safety experience of these patients will be reported separately, and they will not be in the safety population.

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

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy populations

11.3.1.1 Intent–to-treat population

The primary efficacy analysis population will be the intent-to-treat (ITT) population, consisting of all randomized patients as defined above. Patients in the ITT population will be analyzed according to the treatment group allocated by randomization.

11.3.2 Safety population

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

In addition:

- Randomized patients for whom it is unclear whether they took the study medication will be included in the safety population as randomized
- For patients receiving double-blind IMP from more than 1 treatment group during the trial, the treatment group allocation for as-treated analysis will be the one to which the patient was treated with the longest duration
- In case of two consecutive LDL-C values <15 mg/dL, placebo injections will be given to patients randomized in the alirocumab group in order to maintain the blind. Those placebo injections will not be considered as double-blind IMP

11.3.3 Other analysis populations

The anti- alirocumab antibody analysis will be performed on all treated patients (safety population) with a blood sample on D1 (baseline) and at least one evaluable blood sample for antibodies post double-blind IMP injection.

Analysis populations for pharmacogenomics will be defined in a specific Statistical Analysis Plan (SAP).

11.4 STATISTICAL METHODS

11.4.1 Extent of study treatment exposure and compliance

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

In order to ensure the continuity of the investigational treatment for the patients without interruption (only in case a disruption occurs in the availability of device components or during production of the auto injectors), back-up plans may be implemented as described in Section 8.1.

In that case, exposure to initial device and back-up device, if applicable, will be summarized and impact on study results will be assessed. More details will be provided in the SAP, if applicable.

Double-blind IMP injections are those administered from randomization to discontinuation of the study treatment, that is:

- Containing placebo for the ones administered to patients randomized in the placebo group
- Containing 75 or 150 mg of alirocumab

Placebo injections given to patients randomized to alirocumab following 2 consecutive LDL-C <15 mg/dL will not be considered as double-blind IMP in the statistical analyses.

11.4.1.1 Extent of investigational medicinal product exposure

The total exposure will be assessed by:

- Duration of IMP exposure in months defined as: (last dose of double-blind IMP injection date +14 – first dose of double-blind IMP injection date)/30.4375, regardless of unplanned intermittent discontinuations
- The total number of double-blind IMP injections by patient
- Duration of observation period (months), defined as: (last contact date – first dose date+1)/30.4375. Non-integer values will be rounded to one decimal place

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

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

11.4.1.2 Compliance

Compliance will be assessed using the following parameters:

- The injection frequency will be defined for each patient as the average number of days between 2 injections, that is: (last dose date – first dose date)/(number of injections -1)
- The overall compliance will be defined for each patient as: 100-(% days with under-planned dosing + % days with above-planned dosing).Under-planned and above-planned dosing will be defined as follows, considering that injections should be performed every 2 weeks (+/- 3 days allowed time window):
  - The % days with under-planned dosing will be defined for each patient as the number of days with no injection administered within the previous 17 days divided by the duration of IMP injection exposure in days.
  - The % days with above-planned dosing will be defined for each patient as the number of days with more than one injection administered within the 11 days before/duration of IMP exposure in days.

These parameters will be summarized descriptively (N, Mean, standard deviation [SD], Median, Min and Max) at 6 months, by year, and on the overall study period.

Cases of overdose (ie, 2 or more injections from the double-blind treatment kit are administered in <7 calendar days) will be summarized by treatment group.

11.4.2 Analyses of efficacy endpoints

All efficacy analyses will be performed based on intent-to-treat (ITT) approach that included events occurring or assessments performed from randomization to the analysis cut-off date, even after the patient has discontinued the study treatment.

11.4.2.1 Analysis of primary efficacy endpoint(s)

The analysis of primary efficacy endpoint will be the comparison between the two treatments using the log-rank test procedure stratified by region (North America, South America, Western Europe, Eastern Europe, Asia, Other). As the number of events per individual country is expected to be low (about 50 countries), the analysis will be stratified according to a grouping of countries into regions.

This primary comparison is the test of the following hypotheses on the hazard ratio (HR), applying a one-sided nominal type I error of 0.0249 at the final analysis:

$$H_0: HR \geq 1 \text{ versus } H_1: HR < 1$$

The estimates of the HR and corresponding confidence interval at (1-2α) % level (α being the one-sided nominal significance level: α=0.249 at final analysis, α=0.0001 at second interim analysis) will be provided using a Cox Proportional Hazard Model stratified by region as for the log-rank test described above.

Consistency of the treatment effect across regions will be assessed.

Underlying assumptions of the Cox Proportional Hazard Model will be checked using graphical methods. If proportionality is not observed, some ad-hoc sensitivity analyses will be performed depending on the data (data-driven).

The survival curves will be estimated using Kaplan-Meier estimates: cumulative incidence of events at 6 months and by year, and appropriate confidence interval will be presented by treatment arm using Kaplan-Meier estimates. Kaplan-Meier curves will be displayed by treatment arm.

Two interim analyses will be performed See Section 11.5 for description of these analyses. The cut-off dates of final and interim analyses are expected to be:

- First interim analysis (futility): when 807 patients have been experienced at least one primary efficacy event (50% fraction information)
- Second interim analysis (futility and efficacy): when 1210 patients have been experienced at least one primary efficacy event (75% fraction information)
- Final analysis: when 1613 patients have experienced at least one primary efficacy event or 24 months after the last date of randomization ex-China, whichever comes last

Subgroup analyses

For the primary endpoint, the treatment effects across the following subgroup factors will be examined:

- Gender
- Age group (<65, ≥65)
- Race (Caucasian, Black, Asian/Oriental, and Other, as appropriate)

- Country (IVRS stratum, depending on the size of subgroups)
- Region (USA/Non-USA, and North America/South America/Eastern Europe/Western Europe/Asia/Rest of world)
- Time from ACS event to randomization (eg, 4-24 weeks, > 24 weeks)

For each parameter, a Cox proportional hazard model will be used for the overall population, including the parameter and the treatment by parameter interaction. In addition, Kaplan-Meier curves and summary statistics showing number of patients, number (%) of primary efficacy outcome events, cumulative incidence of events at 6 month and by year, and appropriate confidence interval may be provided for each treatment arm in previously selected subgroups defined by the baseline characteristic/prognostic factors.

In addition, the effect of the time from ACS event to randomization (weeks) will be assessed using a Cox proportional hazard model including the time from ACS event to randomization (continuous) as a covariate, the treatment group and the interaction.

11.4.2.2 Analyses of secondary efficacy endpoints

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

Time to events secondary endpoints will be analyzed using the same statistical methodology as for the primary endpoint.

The percent change from baseline in calculated LDL-C at Month 4, at Month 24 and at the end of the study will be analyzed in the ITT population using an analysis of covariance (ANCOVA) model with treatment group and region as fixed effects, and the baseline calculated LDL-C as covariate.

Similar analyses will be performed for ApoB and non-HDL.

Based on previous experiences and published data on these endpoints, the assumptions of normality of the residuals, homogeneity of slopes and homoscedasticity underlying these models are usually valid.

Throughout the ANCOVA models, the alirocumab group will be compared to placebo using an appropriate contrast tested at the two-sided 0.05 level, and providing the 95% confidence interval (CI) of the difference.

For patients without calculated LDL-C, ApoB, or non-HDL-C value in the time window analyzed, the percent change from baseline will not be calculated.

11.4.2.3 Multiplicity consideration

In order to handle multiple main secondary endpoints, the overall Type-I error will be controlled by the use of a sequential inferential approach. Statistical significance of the primary parameter is

required before drawing inferential conclusions about first key secondary parameter (at the 0.0001 one-sided alpha level at the second interim analysis or at the 0.0249 one-sided alpha level at the final analysis). The order of tests is detailed in Section 9.1.3. Inferential conclusions about successive main secondary parameters require statistical significance of the prior one.

This fixed hierarchical approach will ensure a strong control of the overall type-I error rate at the required one-sided level (0.0001 for the second interim analysis and 0.0249 at the final analysis).

No further adjustments will be made for other secondary endpoints or subgroup analyses for which p-values will be provided for descriptive purpose only.

11.4.3 Analyses of safety data

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

All safety analyses will be performed on the Safety population, using the last available value before first double-blind IMP injection as baseline definition.

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

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

AE definition:

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

Possible drug-induced liver injury

The liver function tests, namely ALT, AST, alkaline phosphatase and total bilirubin, are used to assess possible drug induced liver toxicity. The proportion of patients with PCSA values at any post-baseline visit by baseline status will be displayed by treatment group for each parameter.

A graph of distribution of peak values of ALT versus peak values of total bilirubin will also be presented. Note that the ALT and total bilirubin values are presented on a logarithmic scale. The

graph will be divided into 4 quadrants with a vertical line corresponding to 3 x ULN for ALT and a horizontal line corresponding to 2 x ULN for total bilirubin.

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

11.4.3.1 Adverse events

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

Adverse event incidence table will be provided by treatment group for all types of TEAEs: all TEAEs, all treatment emergent AESI (defined with a PT or a prespecified grouping), all treatment emergent SAEs and all TEAEs leading to permanent treatment discontinuation. If any clinically significant signal is detected and need further characterization or for adverse event of clinical interest (eg, injection site reaction, allergic reaction), exploration of time to onset will be performed for these selected TEAEs as described below to account for the differential exposure time in all patients.

Local injection site reaction could be further described in terms of time pattern (time to first occurrence, duration, recurrence) and intensity.

Selected TEAEs will be also analyzed using time-to-event approach (Kaplan-Meier methodology). Time from the first dose of double-blind IMP injection to the first occurrence of the event will be calculated (only the first event will be counted). Patients without any event will be censored at the end of the TEAE period. Incidence rates at 6 months and by year of exposure will be presented and Kaplan-Meier curves will be provided.

<u>LDL-C <25 mg/dL:</u>

Summaries of adverse events will be also provided on the safety subgroup population of patients with two consecutive LDL-C <25mg/dL in the alirocumab group. Only adverse events, for which it will be confirmed or unclear that they occurred, worsened or became serious after the first level of LDL-C <25mg/dL will be considered.

Death:

The following deaths summaries will be generated:

- Number (%) of patients who died by study period (TEAE, on-study) and adjudicated reasons, 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 eCRF page as reported by the Investigator) by primary SOC , HLGT, HLT and PT showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT.

11.4.3.2 Laboratory data and vital signs

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

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

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

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

Hepatitis C antibody:

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

11.4.4 Other endpoints:

11.4.4.1 Cardiovascular events of interest (other than efficacy endpoints)

Clinically significant complications or procedures (not planned at the time of randomization) related to peripheral arterial disease, and venous thromboembolic events (see Section 9.3.7) will be analyzed using a time-to-event approach (Kaplan-Meier methodology) in the ITT population. Time from randomization to the first occurrence of the event will be calculated. Patients without any event will be censored using the same methodology as for the primary efficacy endpoint.

11.4.4.2 Other endpoints

All analyses for other endpoints (not already described above) will be performed on the Safety population. The baseline value is defined as the last available value before first double-blind IMP injection.

The number and percentage of patients with calculated LDL-C <25 mg/dL (respectively, LDL-C <15 mg/dL) will be provided by treatment group and visit.

Exploratory variables defined in Section 9.3 will be summarized by time points using number of available data, mean, SD, median, minimum, and maximum for each treatment group (for hs-CRP, Q1 and Q3 will be also provided). The time profile of each parameter will be also plotted by treatment group with the corresponding standard errors. For hs-CRP, the incidence of PCSA at any time during the TEAE period will be also summarized by treatment group using descriptive statistics.

The anti-alirocumab antibody status (positive/negative) and antibody titers will be summarized by treatment group and visit using descriptive statistics. Anti- alirocumab antibody will be further described in terms of time-to-onset, persistence (transient/persistent anti- alirocumab antibodies). Correlations between antibody titers, safety and/or efficacy endpoints could be also provided by graphical methods. Further details will be provided in SAP.

11.5 INTERIM ANALYSIS

Two interim analyses (IA) are planned, when 50% and 75% of the total number of expected events have occurred:

- Interim analysis for futility will be conducted, when approximately 807 events (50% of the targeted number of primary endpoint events) have occurred.
- Interim analysis for futility and overwhelming efficacy will be conducted, when approximately 1210 events (75% of the targeted number of primary endpoint events) have occurred.

Both IA will be performed by the external independent CV DMC Statistician and will be reviewed under the supervision of the CV DMC. The CV DMC will also review secondary efficacy endpoints and safety data (AEs, laboratory data, vital signs) available at the time of the IA.

Control of the type I and type II error will be ensured using gamma (-5) spending function for Type II error (futility) and Gamma (-22) for Type I error (efficacy) at each IA (the Type I error spending function is also applied at the first IA, even if the objective of this first IA is only futility). It has to be noted that, in order to protect the global type one error in case the decision is taken to overrule the futility rule, non binding boundaries were used.

The following table shows the stopping rules at each interim analysis (using the sample size assumptions described in Section 11.1):

Table 4 - Interim Analyses stopping boundaries corresponding to Gamma (-22) type I error and Gamma (-5) type II error spending functions

Timing of analyses	Stopping boundaries (one-sided p-value and Hazard ratio)	
	Futility	**Overwhelming efficacy**
First IA : 50% of targeted events	p > 0.548 (⇔ HR > 1.008)	NA
Second IA: 75% of targeted events	p > 0.19 (⇔ HR > 0.951)	p < 0.0001* (⇔ HR < 0.802)

Calculations done using EAST 5.4

*Should the second interim analysis be triggered just before or after 1210 events have been reached, the exact nominal significance level to be used at the second IA would be re-computed based on a Gamma(-22) spending function.

The CV DMC could consider early stopping of the study for overwhelming efficacy at the second IA, if the following conditions are met:

- Stopping boundaries for overwhelming efficacy are crossed
- Positive trend observed for secondary efficacy endpoints, including all cause mortality, and no excess of non-CV mortality
- Consistency of the treatment effect on the primary efficacy endpoint across subgroups and regions

12 ETHICAL AND REGULATORY STANDARDS

12.1 ETHICAL PRINCIPLES

This clinical trial will be conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, and the International Conference on Harmonization [ICH] guidelines for good clinical practice (GCP).

In compliance with Sanofi public disclosure commitments, this clinical trial will be recorded in the public registry website clinicaltrials.gov before the enrollment of the first patient. The registry will contain basic information about the trial sufficient to inform interested patients (and their healthcare practitioners) how to enroll in the trial.

12.2 LAWS AND REGULATIONS

This clinical trial will be conducted in compliance with all international guidelines, and national laws and regulations of the country(ies) in which the clinical trial is performed, as well as any applicable guidelines. Please see Section 13.1

12.3 INFORMED CONSENT

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

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

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

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

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

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

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

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

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

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

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator(s) and delegated Investigator staff undertake(s) to perform the clinical trial in accordance with this clinical trial protocol, ICH guidelines for Good Clinical Practice and the applicable regulatory requirements.

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

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

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

13.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this clinical trial is responsible to health authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial protocol as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the e-s. 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 guidelines for Good Clinical Practice, and in accordance with the Sponsor's guidelines and policies for source document verification, the monitoring team will check the eCRF entries against the source documents. This does not include pre-identified source data directly recorded in the eCRF. 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 eCRFs (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 (eCRFS) AND ADDITIONAL REQUEST

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

Should a correction be made, the corrected information will be entered in the eCRF 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 eCRF.

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

13.5 USE OF COMPUTERIZED SYSTEMS

Computerized systems used during the different steps of the study are:

- For data management activities, Medidata RAVE version 5.6.4 (Covance)
- For statistical activities, nQuery Advisor 6.01, SAS, EAST 5.4
- For pharmacovigilance activities, AWARE , Business Objects XI
- For monitoring activities, CTMS of each involved institution (DCRI, Covance, and Sanofi, as applicable).
- For medical writing activities, DOMASYS

External data loading is planned for this clinical trial.

14 ADMINISTRATIVE EXPECTATIONS

14.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification and training of each Investigator and Subinvestigator will be signed, dated and provided to the Sponsor prior to the beginning of the clinical trial.

14.2 RECORD RETENTION IN STUDY SITES

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

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

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

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

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

14.3 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to, the clinical trial protocol, 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 Subinvestigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Subinvestigators of the confidential nature of the clinical trial.

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

Furthermore, the Investigator and the Sponsor agree to adhere to the principles of personal data confidentiality in relation to the patients, Investigator and its collaborators involved in the study.

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 mention any information or the Product in any application for a patent or for any other intellectual property rights.

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

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

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

14.5 DATA PROTECTION

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

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

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

14.6 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from maintaining their own liability insurance policy. An insurance certificate will be provided to the Ethics Committees (IECs/IRBs) or health 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 Decided by the Sponsor

Decided by the Sponsor in the following cases

- If the information on the product leads to doubt as to the benefit/risk ratio
- If 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
- In the event of breach by the Investigator of a fundamental obligation under this agreement, including but not limited to breach of the clinical trial protocol, breach of the applicable laws and regulations or breach of the ICH guidelines on Good Clinical Practice
- If the total number of patients are included earlier than expected

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

14.8.2 Decided by the Investigator

The Investigator must notify (30 days' prior notice) the Sponsor of his/her decision and give the reason in writing.

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

14.9 CLINICAL TRIAL RESULTS

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

14.10 PUBLICATIONS AND COMMUNICATIONS

During the course of the study, the Executive Steering Committee co-Chairs will form a Publications Subcommittee, which will include all ESC members, and Sponsor representatives and to which selected National Leaders may be invited. The role of the Publication Sub-Committee will be to oversee the publications from the Study, assign authorship, assure that authorship requirements are met, and that the publications which are created are of the highest scientific quality.

The Publications Subcommittee will review and approve all manuscripts of Study results prior to publication.

All study participants (Investigators and Committee members) give full authority to the ESC for primary presentation and/or primary publication of results. No other publication is allowed before the primary publication. Any subsequent presentation or publication by a study participant must be approved by this Publications Committee and/or ESC and make reference to the study and the primary publication.

As the study is being conducted at multiple sites, the Sponsor and the Publications Subcommittee agree that, consistent with scientific standards, first presentation or publication of the results of the study shall be made only as part of a publication of the results obtained by all sites performing the protocol. However, if no multicenter publication has occurred 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 to the review procedure set forth herein. The Investigator shall provide the Sponsor and the Publications Subcommittee with a copy of any such presentation or publication derived from the study 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 measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

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

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

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

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

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

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

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

16 BIBLIOGRAPHIC REFERENCES

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3. Antman EM, Hand M, Armstrong PW, Bates ER, Green LA, Halasyamani LK et al. 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Group to Review New Evidence and Update the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction). J Am Coll Cardiol 2008; 51(2): 210–47.

4. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE et al., ACC/AHA 2007 guidelines for the management of patients with unstable angina/non–ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction). J Am Coll Cardiol 2007; 50(7):e1-e157

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