AMENDED CLINICAL TRIAL PROTOCOL 01

COMPOUND: alirocumab

A Multi-Country, Multicenter, Single-Arm, Open-Label Study to Document the Safety, Tolerability and Effect of Alirocumab on atherogenic lipoproteins in High Cardio-Vascular Risk Patients With Severe Hypercholesterolemia Not Adequately Controlled With Conventional Lipid-Modifying Therapies

STUDY NUMBER: LPS14245

STUDY NAME: ODYSSEY APPRISE

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CLINICAL STUDY DIRECTOR: [redacted]

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NAMES AND ADDRESSES OF

COORDINATING INVESTIGATOR	Name: Address: Tel: Fax: E-mail:	
MONITORING TEAM'S REPRESENTATIVE	Name: Address: Tel: Fax: E-mail:	
SPONSOR	Company: Address:	
OTHER EMERGENCY TELEPHONE NUMBERS		

CLINICAL TRIAL SUMMARY

COMPOUND: alirocumab	**STUDY No: LPS14245**
TITLE	A Multi-Country, Multicenter, Single-Arm, Open-Label Study to Document the Safety, Tolerability and Effect of Alirocumab on atherogenic lipoproteins in High Cardio-Vascular Risk Patients With Severe Hypercholesterolemia Not Adequately Controlled With Conventional Lipid-Modifying Therapies.
INVESTIGATOR/TRIAL LOCATION	Europe & Canada.
PHASE OF DEVELOPMENT	Phase IIIb.
STUDY OBJECTIVE(S)	**Primary objective** • To provide patients with severe hypercholesterolemia at risk for subsequent cardiovascular (CV) events and not adequately controlled with currently available lipid modifying therapy (LMT) access to alirocumab ahead of commercial availability and to document the overall safety and tolerability of alirocumab in this patient population. **Secondary objective(s)** • To document the effect of alirocumab on low-density lipoprotein cholesterol (LDL-C) levels as well as non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (total-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) levels after 12 weeks of treatment. • To document patient's acceptability of self-injection (Self Injection Assessment Questionnaire, SIAQ).
STUDY DESIGN	This study will be conducted as a multi-country, multi-center prospective, single arm, open-label, phase IIIb clinical trial. After enrollment, patients will receive study treatment alirocumab 150 mg subcutaneous (SC) once every 2 weeks (Q2W) or 75 mg subcutaneous (SC) Q2W. During the study, the dose may be adjusted according to the investigator, based on treatment response, Alirocumab will be administered on top of stable maximally tolerated statin therapy ±other LMTs. The study consists of: • A screening period of up to 3 weeks, including an intermediate visit during which the patient or another designated person (such as spouse, relative, etc) will be trained to self-inject/inject. • An open-label treatment period with alirocumab of at least 12 weeks and until the product becomes commercially available and reimbursed. However, the open label treatment period will not exceed 30 months. • An end-of-study visit will take place at least 14 days after the last treatment injection. Patients should be on a stable diet (NCEP-ATPIII TLC diet or equivalent) throughout the entire study duration from screening to the end of the study treatment. Statin dose and dose regimen as well as dose and dose regimen of other LMTs (if applicable) should be stable throughout the whole study duration including the screening period. Nevertheless, modification of LMT is allowed under certain conditions after enrollment as described in Section 8.

STUDY POPULATION **Main selection criteria**	**Inclusion Criteria:** • Signed written informed consent. • Age ≥18 years or legal age of majority at screening visit. • Either A, B, C, D or E below and not adequately controlled with a maximally tolerated dose of statin* with or without other LMT, all at stable doses for at least 4 weeks prior to the screening visit (Week -3): • A- Patients suffering from heterozygous familial hypercholesterolemia (heFH) with LDL-C concentrations ≥160 mg/dL (4.14 mmol/L) despite treatment. • B- Patients suffering from heFH with LDL-C concentrations ≥130 mg/dL (3.36 mmol/L) despite treatment and two or more CV risk factors among this list : - LDL-C >250 mg/dL (6.46 mmol/L) at the time of the familial hypercholesterolemia (FH) diagnosis (before treatment), - Family history of premature-onset coronary heart disease (CHD) (first-degree male relative with onset before age 55 years; first-degree female relative with onset before age 65 years), - Metabolic syndrome (cf. definition), - HDL-C <40 mg/dL (1.03 mmol/L), - Hypertension (BP >140/90 mmHg or drug treatment), - Lipoprotein a [Lp(a)] ≥50 mg/dL (1.78 µmol/L), - Tendon xanthoma. • C- Patients suffering from heFH with LDL-C concentrations ≥130 mg/dL (3.36 mmol/L) despite treatment and one of the following characteristics: - Established CHD or other CVD (history of acute myocardial infarction, ischemic stroke, peripheral arterial disease, coronary or peripheral arterial revascularization, stable or unstable angina, transient ischemic attack, carotid artery stenosis ≥50%, aortic abdominal aneurysm), - Drug treated type 2 diabetes mellitus or type 1 with target organ damage, - Family history of first or second degree relative with very premature onset CHD (first or second degree male relative onset before age 45; first or second degree female relative onset before age 55). • D- Non-FH patients suffering from established CHD or other CVD (history of acute myocardial infarction (MI), ischemic stroke, peripheral arterial disease (PAD), coronary or peripheral arterial revascularization, stable or unstable angina, transient ischemic attack (TIA), carotid artery stenosis ≥50%, aortic abdominal aneurysm) and with LDL cholesterol concentrations ≥130 mg/dL (3.36 mmol/L). • E- Patients suffering from progressive cardiovascular disease [coronary artery disease, or peripheral arterial occlusive disease or cerebrovascular disease as documented clinically or by imaging techniques, with a subsequent CV event (acute MI, ischemic stroke, ischemia driven revascularization, unstable angina, TIA) occurring despite stable doses of maximally tolerated LMT] with LDL cholesterol concentrations ≥100 mg/dL (2.59 mmol/L).

	Note: * Definition of maximally tolerated dose (any of the following are acceptable): • Rosuvastatin 20 mg or 40 mg daily. • Atorvastatin 40 mg or 80 mg daily. • Simvastatin 80 mg daily (if already on this dose for >1 year). • Patients not able to be on any of the above statin doses should be treated with the dose of atorvastatin, rosuvastatin or simvastatin which is considered appropriate for the patient as per the investigator's judgment or concerns. NB: in exceptional and well documented cases described in Exclusion criteria E04, another statin regimen may be used. • Some examples of acceptable reasons for a patient taking a lower statin dose include, but are not limited to: adverse effects on higher doses, advanced age, low body mass index, concomitant medications, and co-morbid conditions such as impaired glucose tolerance /impaired fasting glucose. The reason(s) will need to be documented in the case report form. **Exclusion criteria** • Not on a stable dose of LMT (including statin) for at least 4 weeks prior to the screening visit (Week -3) and from screening to enrollment. • Use of a fibrate other than fenofibrate within 4 weeks of the screening visit (Week-3) or between screening and enrollment. • Daily doses above atorvastatin 80 mg, rosuvastatin 40 mg or simvastatin 40 mg (except for patients on simvastatin 80 mg for more than one year, who are eligible). • Use of statin other than simvastatin, atorvastatin or rosuvastatin, prior to the screening visit (Week-3) or between screening and enrolment with the exception of the cases in which there is a documented reason for intolerance to the above mentioned potent statins in which case the use of a different statin is allowed. • Fasting serum TG >400 mg/dL (>4.52 mmol/L) at the screening visit (Week-3). • Uncontrolled hypertension (>180 mm Hg systolic and/or >110 mm Hg diastolic at screening or inclusion visit). • New York Heart Association class III or IV congestive heart failure persisting despite treatment. • History of hemorrhagic stroke. • Liver transaminases >3 times upper limit of normal at screening visit. • Laboratory evidence of current hepatitis B or C infection. • Creatine kinase >3 times upper limit of normal at screening visit. • Estimated glomerular filtration rate <30 mL/min (1.73 m^2) at screening visit. • Pregnant or breastfeeding woman or with childbearing potential without appropriate contraception. • Patients eligible for enrollment into an ongoing clinical study of alirocumab conducted at same investigational site. • Hypersensitivity to alirocumab or any of the excipients. • For a full list of exclusion criteria, see Section 7.2.
Total expected number of patients	It is anticipated that approximately 1300 patients will be enrolled in this study.

STUDY TREATMENT(s)	
Investigational medicinal product(s)	Alirocumab. Prefilled pens containing alirocumab 75 mg/mL or 150mg/mL.
Formulation	Sterile alirocumab drug product supplied at a concentration of 75 mg/mL and 150 mg/mL in histidine, pH 6.0, polysorbate 20, and sucrose, both as 1 mL volume in a pre-filled pen.
Route(s) of administration	Subcutaneous (SC) injections in the abdomen, thigh or outer area of upper arm.
Dose regimen	The dose is 75 mg or 150 mg administered subcutaneously once every 2 weeks (Q2W). The dose selection should be based on individual patient characteristics and goal of therapy. The dose can be adjusted based on treatment response.
Injection for training	Placebo for alirocumab.
Formulation	Sterile solution consisting of histidine, pH 6.0, polysorbate 20, and sucrose, as 1 mL volume in a pre-filled pen.
Route of administration	Subcutaneous (SC) injections in the abdomen, thigh or outer area of upper arm.
ENDPOINT(S)	**Primary endpoint:** Safety parameters (adverse events, adverse events of special interest, laboratory data, product complaints and vital signs) assessed throughout the study. **Secondary endpoint(s):** Patients' acceptability of self-injection (Self Injection Assessment Questionnaire). Among other endpoints of interest, see Section 9.2.2: • Proportion of patients reaching calculated LDL-C <100 mg/dL (2.59mmol/L) at Week 12. • Proportion of patients reaching calculated LDL-C <70 mg/dL (1.81mmol/L) at Week 12. • Proportion of patients with LDL-C <70 mg/dL (1.81 mmol/L) and/or ≥50% reduction from baseline in LDL-C (if LDL-C ≥70 mg/dL [(1.81 mmol/L]) at Week 12. • Percent changes from baseline in LDL-C as well as non-HDL-C, total-C, HDL-C, and TG levels after 12 weeks of treatment. All endpoints will be defined in the SAP.
ASSESSMENT SCHEDULE	**Patient's assessments in the screening period:** • On-site visits: Week -3 (screening visit), Week -1 (injection training visit if needed). **Patient's assessments in the treatment period:** • On-site visits: Week 0 (inclusion visit), Week 4, Week 8, Week 12, Week 24, Week 48, then every 12 weeks until end of treatment (EOT/EOS). • Phone calls: Week 2 and Week 18. • Dispensation visits every 12 Weeks after Week 24.

STATISTICAL CONSIDERATIONS

Sample size determination:

No formal sample size calculation is performed.

The table below displays the 95% Confidence intervals (95%CI) associated to a variety of adverse event rates for a targeted sample size of 1300 patients.

Expected 95% Confidence interval for various event rates

Adverse event rates	10%	20%	30%	40%	50%
95%CI	[8.4%; 11.6%]	[17.8%; 22.2%]	[27.5%; 32.5%]	[37.3%; 42.7%]	[47.3%; 52.7%]

For a rare non observed event, by using the rule of three, it can be estimated that the upper limit of the 95% confidence interval of the event rate is approximately 0.23% (1 per 433).

Analysis population:

Safety population: all enrolled patients who actually received at least one dose or partial dose of alirocumab.

Efficacy population:

Modified Intend To Treat population (mITT): all enrolled patients who received at least one dose or partial dose of alirocumab, with a baseline LDL-C value available and with at least one on-treatment LDL-C measurement during the efficacy treatment period.

Primary analysis:

Safety analysis (adverse events, laboratory, product complaints and vital signs) will be performed on the safety population. Only descriptive summaries will be provided.

The number of adverse events (AEs) during the study will be displayed. Adverse event incidence tables will present, by system organ class (SOC) high level group term (HLGT), high level term (HLT) and preferred term (PT), the number (n) and percentage (%) of patients experiencing an AE.

Secondary analysis:

The effects of alirocumab will be documented by the proportion of patients reaching calculated LDL-C <100 mg/dL (2.59 mmol/L) at Week 12, the proportion of patients reaching calculated LDL-C < 70 mg/dL (1.81 mmol/L) at Week 12 as well as by values and percent changes from baseline in LDL-C, non-HDL-C, total-C, HDL-C, and TG levels after 12 weeks of treatment and at other time points.

A descriptive analysis of the SIAQ will be done on the safety population.

More details regarding statistical analyses will be provided in the SAP.

DURATION OF STUDY (PER PATIENT)

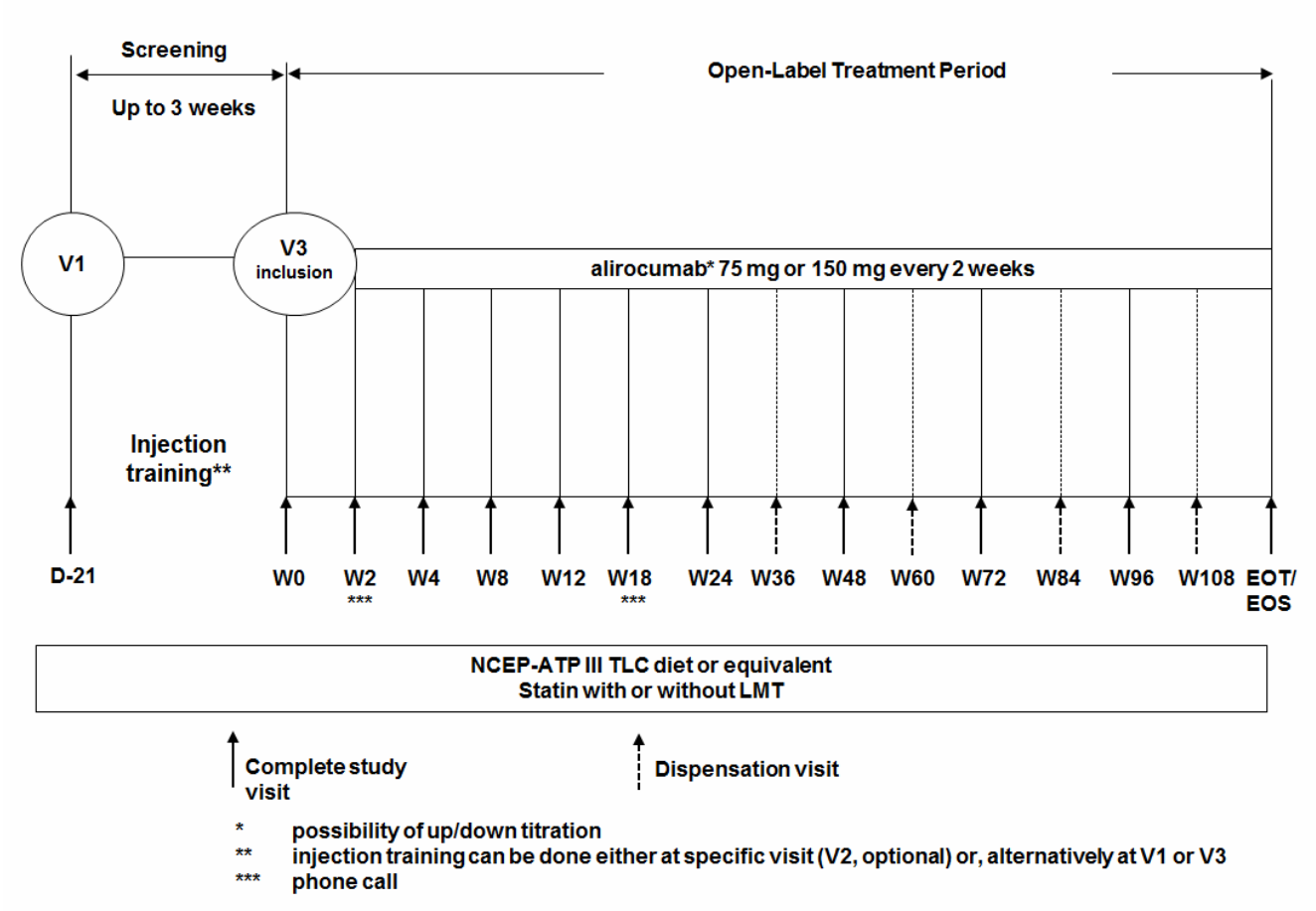
The study duration includes up to 3 weeks of screening period, a minimum of 12 weeks and up to a maximum 30 months of open label study treatment period and at least 2 weeks after the last study treatment injection.

In each country, patient recruitment will end when alirocumab becomes commercially available (ie, accessible to the patient as per each country regulation) and reimbursed. In this case, study treatment can be switched to the commercial product once the patient has completed the minimum of 12 weeks of study treatment.

STUDY COMMITTEES	**Steering Committee:** ☐ **Yes** ☒ **No** **Data Monitoring Committee:** ☐ **Yes** ☒ **No** **Adjudication Committee:** ☐ **Yes** ☒ **No**

1 FLOW CHART

1.1 GRAPHICAL STUDY DESIGN



1.2 STUDY FLOW CHART

Study time points	Screening period		Inclusion visit	Study Treatment													
	W-3 (D-21 to -8) Screening visit	W-1 D-7 Injection training visit * (optional)	W0 D1	W2 D15 ☎	W4 D29	W8 D57	W12 D85	W18 D127 ☎	W24 D169	W36 ** D253	W48 D337	W60 ** D421	W72 D505	W84 ** D589	W96 D673	W108 ** D757	EOT/EOS Week 120 *** Day 841 +2 weeks after last injection
Visit number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17
Visit windows			+3	±3	±3	±3	±3	±5	±5	±7	±7	±7	±7	±7	±7	±7	+7
Inclusion and exclusion criteria	✓		✓														
Eligibility confirmation and enrollment			✓														
Informed consent form	✓																
Demography	✓																
Medical history	✓																
Prior/Concomitant medication/LMT [a]	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Review of diet	✓				✓	✓	✓		✓		✓		✓		✓		✓
Patient diary: dispensation / review / collection			✓		✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓
Injection training	✓																
SIAQ PRE	✓																
SIAQ POST			✓		✓	✓	✓		✓		✓		✓		✓		
Physical examination [b]	✓		✓		✓	✓	✓		✓		✓		✓		✓		✓

Study time points	Screening period		Inclusion visit	Study Treatment													
	W-3 (D-21 to -8) Screening visit	W-1 D-7 Injection training visit * (optional)	W0 D1	W2 D15 ☎	W4 D29	W8 D57	W12 D85	W18 D127 ☎	W24 D169	W36 ** D253	W48 D337	W60 ** D421	W72 D505	W84 ** D589	W96 D673	W108 ** D757	EOT/EOS Week 120 *** Day 841 +2 weeks after last injection
Visit number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17
Visit windows			+3	±3	±3	±3	±3	±5	±5	±7	±7	±7	±7	±7	±7	±7	+7
Hematology and biochemistry[c] [d]	✓				✓		✓		✓		✓		✓		✓		✓[j]
HbA1c	✓						✓		✓		✓		✓		✓		✓[j]
Lipid profile [e]	✓				✓	✓	✓		✓		✓		✓		✓		✓[j]
Urinalysis	✓		✓				✓										✓
Liver panel [f]	✓				✓	✓	✓		✓		✓		✓		✓		✓[j]
Hepatitis B and C serology	✓																✓ [l]
Telephone assessment ☎				✓				✓									
Study treatment dispensation			✓		✓[k]	✓[k]	✓		✓	✓	✓	✓	✓	✓	✓	✓	
Compliance check [i]					✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓
Study treatment administration [g]			✓	←———	———	———	———	———	———	———	———	———	———	———	———	———→	
Pregnancy test (women of childbearing potential)	✓[m]		✓[n]														✓[n]
+AE/SAE recording [h]	←- - -	- - -	- - -	- - -	- - -	- - -	- - -	✓	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -	- - -→

* Injection training can also be performed during the screening or the inclusion visit.

** Dispensation visits.

*** Those patients with unresolved SAE/AESI at the EOT/EOS visit will be followed up by the investigator for as long as medically indicated, but without further recording in the eCRF

a. Prior and concomitant medications started within 4 weeks before screening visit, lipid lowering therapies, antihypertensive medications, AEs/SAEs corrective therapies.

Study time points	Screening period		Inclusion visit	Study Treatment													
	W-3 (D-21 to -8) Screening visit	W-1 D-7 Injection training visit * (optional)	W0 D1	W2 D15 ☎	W4 D29	W8 D57	W12 D85	W18 D127 ☎	W24 D169	W36 ** D253	W48 D337	W60 ** D421	W72 D505	W84 ** D589	W96 D673	W108 ** D757	EOT/EOS Week 120 *** Day 841 +2 weeks after last injection
Visit number	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17
Visit windows			+3	±3	±3	±3	±3	±5	±5	±7	±7	±7	±7	±7	±7	±7	+7

b. Physical examination and vital signs: height (only at screening), weight, HR, BP.
c. Hematology: hemoglobin, RBC, Hb, Hematocrit, platelets, WBC count with differential blood count. Recent (1 week) lab result may be used instead. In case of unexpected or aberrant value a retest must be done before inclusion.
d. Biochemistry: glucose, urea, calculated creatinine clearance, creatinine and eGFR using MDRD study equation, total CPK, sodium, potassium, chloride, bicarbonate, calcium, phosphorus, uric acid, total protein, LDH, albumin, GGT, Hepatitis C antibody (at screening, EOT/EOS and in case of transaminases elevation) to be confirmed by reflexive testing when positive, Hepatitis B antigen (screening only). Recent (1 week) lab result may be used instead. In case of unexpected or aberrant value a retest must be done before inclusion.
e. Lipid profile: Total Cholesterol, Triglycerides, Calculated LDL-C, HDL-C, non-HDL-C. Recent (1 week) lab result may be used instead. In case of unexpected or aberrant value a retest must be done before inclusion.
f. Liver panel: SGOT (AST), SGPT (ALT), alkaline phosphatase, total bilirubin. Recent (1 week) lab result may be used instead.
g. Dose regimen: alirocumab 75 mg/mL or 150 mg/mL, SC, Q2W for the entire study treatment duration. Depending on the clinical situation, alirocumab can be started at 75 mg or 150 mg administered once every 2 weeks. During the study, the dose may be adjusted according to the investigator, based on treatment response.
h. Safety evaluation: Adverse Events (AEs), product complaints, regardless of seriousness or relationship to alirocumab treatment, will be collected from the time the patient signs the informed consent form up to the EOT/EOS visit
i. Review patient diary and treatment kit +data collection on study treatment administration.
j. Repeat lab only in case of abnormality at EOT/EOS.
k. New kit dispensation only if needed as per lab results.
l. Hepatitis C only.
m. Serum pregnancy test.
n. Urine pregnancy test.

2 TABLE OF CONTENTS

3 LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
Apo	apolipoprotein
AST	aspartate aminotransferase
CABG	coronary artery bypasses graft surgery
CHD	coronary heart disease
CIB	clinical investigator's brochure
CPK	creatine phosphokinase
CT	computed tomography
CV/CVD	cardiovascular/cardiovascular disease
DNA	deoxyribonucleic acid
DRF	discrepancy resolution form
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EZE	ezetimibe
FH	familial hypercholesterolemia
GCP	good clinical practice
γGT	gamma-glutamyl transferase
HbA1c	glycated hemoglobin A1c
HDL-C	high density lipoprotein cholesterol
HLGT	high level group term
HLT	high level term
ICF	informed consent form
ICH	international conference on harmonization
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous
IVRS	interactive voice response system
IWRS	interactive web response system
LDH	lactic 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
MI	myocardial infarction
mITT	modified intent-to-treat

mmHg	millimeter of mercury
NCEP-ATP III	National Cholesterol Education Program Adult Treatment Panel III
NYHA	New York Heart Association
NIMP	non investigational medicinal product
PCI	percutaneous coronary intervention
PCSA	potentially clinically significant abnormality
PCSK9	proprotein convertase subtilisin/kexin type 9
PRO	patient reported outcomes
PT	preferred term
Q2W	Quoque 2 weeks
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
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
TSH	thyroid stimulating hormone
ULN	upper limit of normal range
WOCBP	women of childbearing potential

4 INTRODUCTION AND RATIONALE

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

Alirocumab is also referred to as "SAR236553/REGN727" in previous documents. However, in the context of the LPS14245 study protocol, it will be referred to as "alirocumab".

Background:

Hypercholesterolemia, particularly an increase in low-density lipoprotein cholesterol (LDL-C) levels, constitutes a major risk for the development of atherosclerosis and coronary heart disease (CHD) (1), the leading cause of death and disability in the Western world (2).

Low-density lipoprotein cholesterol (LDL-C) is identified as the primary target of cholesterol lowering therapy (3) and is accepted as a valid surrogate endpoint (4, 5). Numerous studies have demonstrated that reducing LDL-C levels mainly with 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG CoA) inhibitors (commonly referred to as statins), reduces the risk of CHD, with a strong direct relationship between LDL-C levels and CHD events; for each 1 mmol/L (~40 mg/dL) reduction in LDL-C, cardiovascular disease (CVD) mortality and morbidity is lowered by 22% (6).

Greater reductions in LDL-C produce greater reduction in events, and comparative data of intensive versus standard statin treatment suggest that the lower the LDL-C level, the greater the benefit in patients at high cardiovascular risk (6, 7, 8, 9). Accumulating data on the benefits of effective LDL-C lowering therapy led to the evolution of therapeutic guidelines over time, with more aggressive LDL-C goals in patients at high risk for CHD (3, 10, 11, 12).

The long-term elevations of LDL-C leading to a progressive accumulation of coronary atherosclerosis require a long-term management which includes lifestyle measures as the primary intervention. However since lifestyle measures rarely reduce plasma LDL-C by >15%, use of pharmacologic treatments are needed to adequately treat dyslipidemic patients (13). Current LDL-C lowering medications include statins, ezetimibe (EZE), bile acid sequestrants, niacin, and fibrates, of which statins are the most commonly prescribed, as they have shown a great ability to lower LDL-C and reduce CHD events.

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

PCSK9 belongs to the subtilisin family of serine proteases and is highly expressed in the liver.

PCSK9 is involved in regulating the levels of the low-density lipoprotein receptor (LDL-R) protein (14, 15). Once PCSK9 is secreted into plasma it directly binds to the LDL-R and promotes its lysosomal degradation after internalization. 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 (16, 17). 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 (18, 19). 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 (20).

Summary of clinical studies with alirocumab published to date:

Phase 2 studies:

Three Phase 2 studies (DFI11565, R727-CL-1003, DFI11566) have been conducted in patients receiving a statin (with or without ezetimibe) as background therapy: overall, a total of 274 patients were exposed to at least one dose of alirocumab in these three Phase 2 studies. In addition, a fourth Phase 2 study (DFI12361) has been conducted in Japanese patients with 75 patients exposed to at least one dose of alirocumab.

Efficacy results:

In both dose-finding studies, statistically significant decreases in percent change from baseline in LDL-C at 12 weeks were observed in all alirocumab groups compared to the placebo group. The greatest decrease was seen in the 150 mg Q2W group, with a mean decrease from baseline of up to 72.4%. (LS mean difference versus placebo of -67.3% in DFI11565, -69.1% in DFI12361, -57.2% in R727-CL-1003; all $p < 0.0001$) (21).

Decreases observed with the doses administered Q2W were maintained from the first injection throughout the study. Large decreases in LDL-C from baseline to 12 weeks were also observed with doses administered Q4W; however, the treatment effect was not fully maintained over a 4-week period (ie, the time interval between the two injections) in all these statin-treated patients. The same magnitude of effect was shown for the dose of 150 mg Q2W in the DFI11566 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 (Total-C), apolipoprotein B (ApoB), non-high density lipoprotein cholesterol (non HDL-C) and ApoB/ApoA-1 ratio. A favorable trend was also observed for HDL-C, 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 site reactions were reported in patients including placebo-treated patients; the reporting of these events was greatest in the R727-CL-1003 study (40.3% in alirocumab -treated patients versus 12.6%, 9.3% and 3.3% in DFI11565, DFI12361 and DFI 11566, respectively); however these events were generally transient with no dose relationship. Rare cases of hypersensitivity reactions were reported. Among all serious adverse

events (SAE)s reported for all alirocumab studies, only one case, leucocytoclastic vasculitis (angiitis), was reported as being related to alirocumab (DFI11565 study). The patient developed one episode of diarrhea followed on the same evening by rash in arms, legs and abdomen 9 days after the first administration of alirocumab 300 mg Q4W. The diagnosis was confirmed by skin biopsy. The patient was discontinued from study drug but completed the study. The lesions resolved after a course of tapering steroid administration. No particular signal was noted for treatment emergent adverse events (TEAEs) related to musculoskeletal or connective tissue disorders as well as no elevations in liver enzymes. For detailed information, please refer to the CIB.

Selection of the dose:

Based on the results of the dose finding studies carried out with statin as background therapy, the Q2W dosing regimen is appropriate to maintain constant LDL-C lowering throughout the interdosing interval in statin-treated patients, with the maximum efficacy at 12 weeks provided by the 150 mg Q2W dosing.

A 75 mg Q2W dose was developed for patients who may not need the magnitude of effect observed with the 150 mg Q2W to achieve the target LDL-C goal, with up-titration to 150 mg Q2W in patients not achieving their LDL-C goal.

Two dosing regimens of alirocumab administered Q2W dosing are evaluated in the on-going ODYSSEY Phase 3 program:

- Initiation with 75 mg, with up-titration to 150 mg in patients who do not reach pre-defined LDL-C goals based on their CV risk, and,
- Initiation with the 150 mg Q2W dose.

In the present study, the dose selection should be based on individual patient's characteristics and goal of therapy. The dose can be adjusted based on treatment response. Lipid levels can be analyzed after 4 weeks, when maximum LDL-C reduction is usually achieved.

Summary of Efficacy and Safety Findings of Completed Phase 3 Studies (as of 11 November 2014)

The Phase 3 program is comprised of 14 studies mainly carried out in HeFH, patients at high CV risk, and statin-intolerant patients. Most had a background of lipid modifying therapy, including statins. Efficacy and safety summaries of completed Phase 3 studies (COMBO I, OPTIONS I, OPTIONS II, MONO, ALTERNATIVE) in addition to LONG TERM and HIGH FH which are relevant to the present study are described below.

ODYSSEY COMBO I (EFC11568) is a randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of alirocumab in high cardiovascular risk patients with hypercholesterolemia not adequately controlled with their lipid modifying therapy.

The numbers of treated patients were 207 and 107 in the alirocumab and placebo group, respectively. Patients with hypercholesterolemia and CHD or CHD risk equivalents on a maximally-tolerated dose of a potent statin, with 63% receiving atorvastatin 40 to 80 mg, rosuvastatin 20 to 40 mg or simvastatin 80 mg daily, had a mean (SD) overall calculated LDL-C at baseline of 102.2 (31.6) mg/dL (2.646 [0.820] mmol/L). They were administered with alirocumab 75 mg (with possibility for up titration to 150 mg at Week 12) or placebo Q2W.

A decrease in calculated LDL-C from baseline (intent-to-treat [ITT] analysis) was observed in the alirocumab group (LS mean [standard error (SE)] versus baseline: -48.2% [1.9]), compared to the placebo group (LS Mean [SE] versus baseline: -2.3% [2.7]), with an LS mean difference for the percent change from baseline of -45.9% ([95% CI: -52.5 to -39.3]; p <0.0001) at Week 24. The LS mean calculated LDL-C in the alirocumab group was 51.4 mg/dL (1.332 mmol/L) at Week 24 as compared to 97.8 mg/dL (2.533 mmol/L) in the placebo group. Results of the on-treatment analysis at Week 24 were consistent with the ITT analysis. A calculated LDL-C reduction compared with baseline in the alirocumab group was observed from the first post-dose measurement at Week 4 and was maintained at all-time points up to Week 52. Alirocumab at the dose of 75 mg every 2 weeks (Q2W) used as initiation dose provided a statistically significant decrease in calculated LDL-C at Week 12 (LS mean difference for the percent change from baseline for the alirocumab versus placebo groups of -47.4% (95% CI: -53.6 to - 41.3; p <0.0001) (ITT analysis). At Week 24, the proportion of patients achieving a pre-defined calculated LDL-C target of <70 mg/dL [<1.81 mmol/L] was greater for alirocumab treatment (75.0%) compared with placebo (9.0%) in the ITT analysis.

In the alirocumab group, 3 patients reported serious general allergic TEAEs (Asthma in 2 patients and Interstitial Lung Disease in 1 patient). Two patients on alirocumab permanently discontinued treatment due to a general allergic TEAE (Interstitial Lung Disease and Rash Generalized). One patient in the alirocumab group reporting an SAE of Retinal Detachment and another reported Muscular Weakness considered being an SAE. Three death cases were reported in each of the alirocumab and placebo groups, but none was related to the alirocumab. Thirty-nine patients (19.5%) in the alirocumab group had 2 consecutive calculated LDL-C values <25 mg/dL (<0.65 mmol/L) including 9 patients with 2 consecutive calculated LDL-C values <15 mg/dL (<0.39 mmol/L) in this study. No particular safety concerns were observed in these patients.

ODYSSEY OPTIONS I (R727-CL-1110) is a randomized, double-blind, parallel-group study of the efficacy and safety of alirocumab added-on to atorvastatin versus ezetimibe added-on to atorvastatin versus atorvastatin dose increase versus switch to rosuvastatin in patients who are not controlled on atorvastatin. The number of patients treated with alirocumab, ezetimibe and double dose of statin were 104, 101 and 149, respectively. All patients in this study had hypercholesterolemia with a high or very high CV risk and they were on an atorvastatin treatment regimen (20 mg or 40 mg daily) at screening. They were administered with alirocumab 75 mg Q2W (with possibility for up titration to 150 mg at Week 12) or ezetimibe 10 mg daily as add-on to atorvastatin, or increasing dose of atorvastatin, or rosuvastatin 40 mg daily. The mean (SD) calculated baseline LDL-C for all patients was 105.1 (34.1) mg/dL (2.723 [0.884] mmol/L).

A statistically significant difference in the percent change from baseline in calculated LDL-C at Week 24 in the ITT analysis was observed for all prespecified comparisons between the addition of alirocumab to baseline therapy compared with other treatment choices. In the atorvastatin 20 mg baseline regimen, reductions from baseline in LS mean LDL-C at Week 24 were significantly greater in the alirocumab + atorvastatin 20 mg group (-44.1%) compared with the atorvastatin 40 mg (-5.0%; p <0.0001) and atorvastatin 20 mg + ezetimibe 10 mg (-20.5%; p =0.0004) groups. In the atorvastatin 40 mg baseline regimen, LS mean reductions from baseline in LDL-C at Week 24 were significantly greater in the alirocumab + atorvastatin 40 mg group (-54.0%) compared with the rosuvastatin 40 mg (-21.4%; p <0.0001), the atorvastatin 80 mg (-4.8%; p <0.0001), and atorvastatin 40 mg + ezetimibe 10 mg (-22.6%; p <0.0001) groups.

Two patient deaths were reported in the study; both patients were in the atorvastatin 20 mg + ezetimibe 10 mg treatment group. Treatment-emergent SAEs occurred in 4 patients (3.8%) in the pooled alirocumab treatment group, 8 patients (5.4%) in the pooled statin intensification treatment group, and 7 patients (6.9%) in the pooled ezetimibe treatment group. A total of 19 patients discontinued study treatment early due to a TEAE, specifically 7 patients (6.7%) in the pooled alirocumab treatment group, 8 patients (5.4%) in the pooled statin intensification treatment group, and 4 patients (4.0%) in the pooled ezetimibe treatment group. Nineteen patients (18.3%) in the pooled alirocumab treatment group had 2 consecutive LDL-C values <25 mg/dL (0.65 mmol/L) during the treatment period compared with 1 patient (0.7%) in the pooled statin intensification group and none in the pooled ezetimibe add-on group. None of the TEAEs occurred in these patients was serious or led to treatment discontinuations. No other safety findings were reported.

ODYSSEY OPTIONS II (R727-CL-1118) is a randomized, double-blind study of the efficacy and safety of alirocumab added-on to rosuvastatin versus ezetimibe added-on to rosuvastatin versus rosuvastatin dose increase in patients who are not controlled on rosuvastatin. The number of patients treated with alirocumab 75 mg Q2W, ezetimibe 10 mg daily and double dose of rosuvastatin were 103, 101 and 101, respectively. All patients in this study had hypercholesterolemia with high or very high CV risk on a baseline daily dose of either rosuvastatin 10 mg or rosuvastatin 20 mg. The mean (SD) calculated baseline LDL-C for all patients was 111.3 mg/dL (39.0) (2.882 mmol/L [1.009]). Patients received alirocumab 75 mg Q2W (with possibility for up titration to 150 mg at Week 12) or ezetimibe10 mg daily or increasing dose of rosuvastatin (10, 20 or 40 mg daily) as add-on therapies to baseline rosuvastatin. A statistically significant difference in the percent change in calculated LDL-C from baseline to Week 24 in the ITT analysis was observed for the rosuvastatin 10 mg baseline regimen, but not for the rosuvastatin 20 mg baseline regimen. In the rosuvastatin 10 mg baseline regimen, reductions from baseline in LS mean LDL-C at week 24 were significantly greater in the alirocumab + rosuvastatin 10 mg treatment group (-50.6%) compared with the rosuvastatin 20 mg (-16.3%; p<0.0001) and ezetimibe 10 mg + rosuvastatin 10 mg (-14.4%; p <0.0001) treatment groups. However, in the rosuvastatin 20 mg baseline regimen, LS mean reductions from baseline in LDL-C at Week 24 were numerically, but not significantly, greater in the alirocumab + rosuvastatin 20 mg treatment group (-36.3%) compared with the rosuvastatin 40 mg (-15.9%; p =0.0453) and ezetimibe 10 mg + rosuvastatin 20 mg (-11.0%; p =0.0136) treatment groups based upon the established level of significance of p <0.0125. The failure to reach statistical significance is partly due to larger variability than previously observed in the Phase 2 studies. One patient died during the course of the study. This patient, a 71 year old male receiving ezetimibe 10 mg + rosuvastatin 20 mg experienced a fatal Subdural Hematoma on study Day 56. A total of 18 patients (5.9%) discontinued treatment prematurely due to a TEAE: 5 patients (4.9%) in the alirocumab add-on group, 5 patients (5.0%) in the double-dose rosuvastatin group, and 8 patients (7.9%) in the ezetimibe add-on group. Thirteen patients (12.6%) reported 2 consecutive calculated LDL-C measurements below 25 mg/dL and all occurrences were reported in the alirocumab add-on group. None of the TEAEs occurred in these patients was serious or led to treatment discontinuations.

ODYSSEY MONO (EFC11716) is a randomized, double-blind, active-controlled, parallel-group study to evaluate the efficacy and safety of alirocumab over 24 weeks in patients with primary hypercholesterolemia. In this study, 52 patients were treated with alirocumab and 51 with ezetimibe 10 mg daily. Patients with moderate CV risk not treated with a statin nor with another lipid modifying therapy (LMT) had a mean (SD) overall baseline LDL-C of 139.7 (25.8) mg/dL (3.619 [0.668] mmol/L). They received alirocumab 75 mg Q2W (with the possibility for up titration to150 mg Q2W) or ezetimibe 10 mg daily. At the end of the 24-week treatment period, the percent change from baseline in LDL-C in the ITT population was greater in the alirocumab group (LS mean percent change from baseline: -47.2%) compared to the ezetimibe group (LS mean percent change from baseline: -15.6%), with a statistically significant LS mean difference versus ezetimibe of
-31.6% [95% CI: -40.2 to -23.0], p <0.0001). The large percent decrease observed with alirocumab was achieved from Week 4 and maintained at all further time points throughout the study. At Week 12, before possible up-titration of alirocumab to 150 mg Q2W, statistical significance was also reached in the ITT population with the 75 mg Q2W dose (LS mean percent change from baseline: -48.1% for the alirocumab group versus -19.6% for the ezetimibe group), with an LS mean difference versus ezetimibe of -28.5%, (95% CI: -35.7 to -21.2), p <0.0001. The proportion of patients reaching LDL-C <100 mg/dL (2.59 mmol/L) was 88.1% patients in the alirocumab group compared with 32.2% patients in the ezetimibe group at Week 24. The proportion of patients reaching LDL-C <70 mg/dL (1.81 mmol/L) was 59.4% patients in the alirocumab group compared with 2.4% patients in the ezetimibe group at Week 24.
Two treatment-emergent SAEs were reported, 1 Pulmonary Embolism in a patient in the Alirocumab group and 1 Bone Erosion in a patient in the ezetimibe group. Neither of the SAEs was considered to be related to the alirocumab by the Investigator. Nine patients prematurely discontinued treatment due to an adverse event (AE), 5 patients (9.6%) in the alirocumab group and 4 patients (7.8%) in the ezetimibe group. Treatment-emergent AEs leading to permanent treatment discontinuation in the Alirocumab group were Flushing (with concomitant symptoms of fatigue, nausea, and headache in 1 patient), Pulmonary Embolism, Diarrhea, Arthralgia (generalized aching), and Injection Site Reaction.

ODYSSEY ALTERNATIVE (R727-CL-1119) is a randomized, double-blind, active-controlled study to evaluate the efficacy and safety of alirocumab in patients with primary hypercholesterolemia who are intolerant to statins. The number of patients treated with alirocumab, ezetimibe and atorvastatin were 126, 124 and 63, respectively. In this study of patients with primary hypercholesterolemia who were considered statin intolerant, the majority of patients was considered “very high CV risk” and was diagnosed with non-familial hypercholesterolemia (FH). Baseline LDL-C levels were high (mean 191.3 mg/dL in all patients) and all patients had a history of prior LMT use. They received alirocumab 75 mg Q2W (with possibility for up titration to 150 mg at Week 12) or ezetimibe 10 mg daily, or atorvastatin 20 mg daily. The primary efficacy endpoint in the ITT analysis demonstrated a statistically significant reduction in percent change from baseline calculated LDL-C in alirocumab treated patients (LS mean -45.0%) when compared with ezetimibe treated patients (LS mean -14.6%), with an LS mean difference between treatment groups of -30.4% (p <0.0001). Among the 109 patients who received at least 1 alirocumab injection after Week 12, 54 patients (49.5%) received automatic dose up titration to 150 mg Q2W. The proportion of very high CV risk patents reaching calculated LDL-C <70 mg/dL (<1.81 mmol/L) or moderate or high CV risk patients reaching calculated

LDL-C <100 mg/dL (<2.59 mmol/L) and the proportion of patients reaching calculated LDL-C <70 mg/dL (<1.81 mmol/L) at Week 24 were greater in the alirocumab treatment group than in the ezetimibe treatment group. Treatment-emergent SAEs occurred in 12 patients (9.5%) in the alirocumab treatment group, 7 patients (11.1%) in the atorvastatin treatment group, and 10 (8.1%) patients in the ezetimibe treatment group. A somewhat lower percentage of patients in the alirocumab treatment group experienced TEAEs leading to discontinuation of study treatment (18.3%) when compared with the atorvastatin treatment group (25.4%) and the ezetimibe treatment group (25.0%). The most frequent TEAEs leading to study drug discontinuation were in the system-organ-class (SOC) Musculoskeletal and Connective Tissues Disorders and within this SOC, the most frequently reported preferred term (PT) leading to study drug discontinuation was Myalgia.

Summary of Efficacy and Safety Findings of ODYSSEY HIGH FH and LONG TERM (as of November 2014)

ODYSSEY HIGH FH (EFC12732) is a randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of alirocumab over 78 weeks in patients with heterozygous familial hypercholesterolemia and LDL-C higher or equal to 160 mg/dL with their lipid modifying therapy. In this study, 72 patients were treated with alirocumab 150 mg Q2W and 35 with placebo. All patients were on a maximum tolerated dose of statin ± other lipid modifying therapies. Baseline LDL-C values were 196.3 (57.9) mg/dL in the alirocumab group and 201.0 (43.4) mg/dL in the placebo group. The percent change from baseline in LDL-C in the ITT population at Week 24 (primary study endpoint) was greater in the alirocumab group (LS mean percent change from baseline: -45.7%) compared to placebo group (LS mean percent change from baseline: -6.6%), with a statistically significant LS mean difference versus placebo of -39.1 % (6.0) (p <0.0001). Fifty-seven percent of alirocumab patients compared to 11% of placebo patients achieved an LDL-C< 100 mg/dL (p <0.0001). The current safety analysis for HIGH FH included all data collected until the last patient visit at Week 52 of the study. TEAEs occurred in 61.1% (44) and 71.4% (25) in alirocumab and placebo groups respectively. Treatment emergent SAEs occurred in 11.1% (8) of alirocumab patients and 11.4% (4) of placebo patients. TEAEs leading to discontinuation occurred in 4.2% (3) of alirocumab patients and 2.9% (1) of placebo patients. There were no TEAEs leading to death in the study.

ODYSSEY LONG TERM (LTS11717) is a randomized, double-blind, placebo-controlled, parallel-group study to evaluate the long-term safety, tolerability, and efficacy of alirocumab over 78 weeks in HeFH or high cardiovascular risk hypercholesterolemia patients not adequately controlled with their lipid modifying therapy. In this study, 1553 patients were treated with alirocumab 150 mg Q2W and 788 with placebo. All patients were on a maximum tolerated dose of statin ± other lipid modifying therapies. Baseline LDL-C values were 122.7 (42.6) mg/dL in the alirocumab group and 121.9 (41.4) mg/dL in the placebo group. Just over 17% of patients in both treatment groups had HeFH. The percent change from baseline in LDL-C in the ITT population at Week 24 (primary study endpoint) was greater in the alirocumab group (LS mean percent change from baseline: -61.0%) compared to placebo group (LS mean percent change from baseline: ±0.8%), with a statistically significant LS mean difference versus placebo of -61.9% (1.3) (p <0.0001). Seventy-nine percent of alirocumab patients compared to 8% of placebo patients achieved an LDL-C< 70 mg/dL (p <0.0001).

The current safety analysis for LONG TERM included at least 52 weeks for all patients continuing treatment, including 607 patients who completed Week 78 visit. TEAEs occurred in 78.6% (1218) and 80.6% (635) in alirocumab and placebo groups respectively. Treatment emergent SAEs occurred in 16.5% (255) of alirocumab patients and 17.6% (139) of placebo patients. TEAEs leading to discontinuation occurred in 6.2% (96) of alirocumab patients and 5.5% (43) of placebo patients. TEAEs leading to death occurred in 0.5% (7) of alirocumab patients and 1.0% (8) of placebo patients.

Conclusion on the benefit risk assessment with alirocumab:

Based on the clinical data available to date, treatment with alirocumab has demonstrated a significant LDL-C lowering effect and was generally well tolerated in a population of hypercholesterolemic patients with non-FH or with heFH, including patients with a history of intolerance to statins. The efficacy on LDL-C was associated with consistent results in Total-C, ApoB, non-HDL-C and ApoB/ApoA-1 ratio. Reduction in triglycerides and lipoprotein (a) and increases in HDL-C were also observed with alirocumab treatment. There was no evidence that alirocumab adversely affects body weight, blood pressure, glucose, or high sensitivity C-reactive protein.

No safety signal has been confirmed with regard to neurologic events and neurocognitive disorders, alanine aminotransferase (ALT) increase and hepatic disorders, adjudicated CV events, diabetes mellitus or ophthalmologic events overall; however, more cataracts were noted in patients treated with alirocumab who achieved 2 consecutive LDL-C values <25 mg/dL (2.1%) compared to those treated with alirocumab who did not meet this criterion (0.6%). Injection site reactions, influenza (upper respiratory symptoms), and pruritus were identified as ADRs. Rare and sometimes serious allergic adverse reactions (eg, hypersensitivity, eczema nummular, urticaria, and hypersensitivity vasculitis) have been reported from clinical studies in patients receiving alirocumab. Alirocumab lowered LDL-C below 25 mg/dL in some patients. Safety of such low LDL-C values is still being assessed, including a potential risk of cataract with LDL-C values <25 mg/dL (0.65 mmol/L), but no safety issues have been confirmed.

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

Note: ODYSSEY program refers to the alirocumab clinical trial program.

Despite treatment with potent statins, achieving LDL-cholesterol-level goals remains a challenge in individuals who have very high baseline LDL-cholesterol levels (such as familial hypercholesterolemia), in those with very high CVD risk who require intensive therapy goals; or in patients for whom statin dosage is limited owing to potentially serious drug interactions, comorbid conditions or intolerance to high drug doses.

As a result, there is a need to provide these patients with poorly controlled LDL-C levels with more effective LDL-C lowering therapies in addition to standard of care in order to adequately reduce their LDL-C attributable CV risk.

In all clinical trials completed to date, alirocumab in combination with maximally-tolerated statins, with or without other LMTs, or as monotherapy showed significant, sustained LDL-C reductions from baseline and similar rates of adverse events versus comparators.

Alirocumab is now is approved for use in the U.S. and Europe. In the US, alirocumab is approved as adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of low-density lipoprotein cholesterol.

The European Commission approved alirocumab for the treatment of adult patients with primary hypercholesterolemia (HeFH and non-familial) or mixed dyslipidemia as an adjunct to diet: a) in combination with a statin, or statin with other lipid-lowering therapies in patients unable to reach their LDL-cholesterol goals with the maximally-tolerated statin or b) alone or in combination with other lipid-lowering therapies for patients who are statin intolerant, or for whom a statin is contraindicated. The effect of alirocumab on cardiovascular morbidity and mortality has not yet been determined. The ability of alirocumab to reduce major CV events is being investigated in the ongoing ODYSSEY OUTCOMES trial, with results anticipated in 2017.The use of a non-registered or non-yet reimbursed product within an early access program (ie, before marketing authorization and reimbursement are granted in a country) may be a treatment option for patients with an unmet medical need for which no suitable or clinically satisfactory alternative is currently available.

This study is therefore aimed at providing patients with severe hypercholesterolemia at risk for subsequent cardiovascular (CV) events and not adequately controlled with maximally tolerated doses of currently available lipid modifying therapy (LMT) with access to alirocumab ahead of commercial availability.

This study will also permit collection of data with the aim to document the overall safety and tolerability of alirocumab in this patient population, the effect of alirocumab on atherogenic lipoproteins and the patient's acceptability of self-injection.

By providing data from a close to real- life setting, this study will further extend the understanding of the efficacy, safety and tolerability profile of alirocumab in a severe hypercholesterolemic population.

Rationale for the study population

The study population of the present trial includes patients with familial or non-familial severe hypercholesterolemia, who despite maximally tolerated doses of high potent statins ±other lipid lowering therapies have LDL-Cholesterol levels far from the guideline recommended targets.

Individuals with familial hypercholesterolemias (FH) have a very high lifetime risk of coronary heart disease (CHD) and are at very high risk of premature onset CHD.

Any of the following places FH patients at higher CHD risk: clinically evident CHD or other atherosclerotic CVD, diabetes, a family history of very early CHD (in men, 45 years of age and women, 55 years of age), current smoking, two or more CHD risk factors, or high lipoprotein (a) ≥50 mg/dL using an isoform insensitive assay (22). Patients featuring these characteristics will be enrolled in the present study.

Recent guidelines recommend that in FH patients without any of the characteristics listed above, intensification of drug therapy may be considered if LDL cholesterol remains ≥160 mg/dL (22). These patients are also part of the current study.

Patients with non-familial hypercholesterolemia with CVD are at the highest priority for treatment. European guidelines on cardiovascular disease prevention (3) recommend for these patients an LDL-C goal of less than 70 mg/dL (<1.8 mmol/L) or a ≥50% LDL cholesterol reduction when the target level cannot be reached.

The ODYSSEY LTS11717 trial, the largest (2,400 patients) and longest (65 weeks – mean treatment duration) blinded study with a PCSK9 inhibitor reported so far enrolled around 20% of patients with HeFH and 68% of patients with previous CHD. More than 25% of patients enrolled in this study had an LDL-C at baseline >130 mg/dl placing these patients at the highest risk of CVD: interquartile range Q1-Q3 of LDL-C (mg/dL): 96.4-140.9 and 90.7-132.8 for calculated and measured LDL-C, respectively.

Based on these data, the current study aims to enroll this subgroup of patients who are at the highest cardiovascular risk for a subsequent event.

5 STUDY OBJECTIVES

5.1 PRIMARY

The primary objective of this study for patients with severe hypercholesterolemia at risk for subsequent cardiovascular (CV) events and not adequately controlled with currently available lipid modifying therapy (LMT) is to provide access to alirocumab ahead of commercial availability and to document the overall safety and tolerability of alirocumab in this patient population.

5.2 SECONDARY

The secondary objectives are:

- To document the effect of alirocumab on low-density lipoprotein cholesterol (LDL-C) levels as well as non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (total-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG) levels, after 12 weeks of treatment.
- To document patient acceptability of self-injection (Self Injection Assessment Questionnaire, SIAQ) throughout the study.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE PROTOCOL

This trial is to be conducted as a multi-country, multi-center prospective, single arm, open-label, phase IIIb clinical trial.

After enrollment, patients will receive study treatment alirocumab 150 mg SC once every 2 weeks (Q2W) or 75 mg SC Q2W. The dose may be adjusted according to the investigator, based on treatment response.
Alirocumab will be administered on top of stable maximally tolerated statin therapy ±other LMTs over a period of at least 12 weeks and until the product becomes commercially available and reimbursed .

The investigator will manage, based on his/her own judgment and LDL-C value, adjustment of alirocumab doses (either up-titration from 75 to 150 mg every 2 weeks or down-titration from 150 to 75 mg every 2 weeks, or maintenance of the dose, will be possible). In case a modification of the current dose is decided, the patient will be contacted by the site staff and an unscheduled visit will be planned to dispense the new treatment kit and retrieve the current one.

The study consists of:

- A screening period of up to 3 weeks, including an injection training during which the patient or another designated person (such as spouse, relative, etc) will be trained to self-inject/inject). An optional dedicated visit could be scheduled as needed.
- An open-label treatment period with alirocumab of at least 12 weeks and until the product becomes commercially available and reimbursed. However, the open label treatment period will not exceed 30 months.
- An End-of-Treatment/End-of-Study visit will take place at least 2 weeks after last study treatment injection.

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

Statin dose and dose regimen as well as dose and dose regimen of other LMTs (if applicable) should be stable throughout the whole study duration including the screening period.

Nevertheless, modification of LMT is allowed under certain conditions after enrollment as described in Section 8.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

The study duration includes up to 3 weeks of screening period, a minimum of 12 weeks and up to a maximum 30 months of open label study treatment period and at least 2 weeks after the last alirocumab injection.

In each country, patient recruitment will end when alirocumab becomes commercially available (ie, accessible to the patient as per each country regulation) and reimbursed. In this case, study treatment can be switched to the commercial product (or another LMT) once the patient has completed the minimum of 12 weeks of study treatment.

The end of the study per patient is the last protocol planned visit or the resolution/stabilization of all SAEs and adverse event of special interest (AESI), or death, whichever comes last.

6.2.2 Determination of end of clinical trial (all patients)

The end of study is defined as being the last patient last on site visit as scheduled per protocol (ie, no later than beginning 2018).

6.3 INTERIM ANALYSIS

No formal interim analysis is planned for this study. However some descriptive analyses might be performed before the end of the study in order to support the submission of a reimbursement dossier if requested by local health authorities.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

I 01. Signed written informed consent.

I 02. Age ≥18 years or legal age of majority at screening visit.

I 03. Either A, B, C, D or E below and not adequately controlled with a maximally tolerated dose of statin* with or without other lipid modifying therapy (LMT), all at stable doses for at least 4 weeks prior to the screening visit (Week -3).

A. Patients suffering from heterozygous familial hypercholesterolemia (heFH) with LDL-C concentrations ≥160 mg/dL (4.14 mmol/L) despite treatment**

B. Patients suffering from heFH with LDL-C concentrations ≥130 mg/dL (3.36 mmol/L) despite treatment and **two or more CV risk factors** among this list:

- LDL-C >250 mg/dL (6.46 mmol/L) at the time of the FH diagnosis (before treatment),
- Family history of premature-onset CHD (first-degree male relative with onset before age 55 years; first-degree female relative with onset before age 65 years),
- Metabolic syndrome (cf. definition),
- HDL-C <40 mg/dL (1.03 mmol/L),
- Hypertension (BP >140/90 mmHg or drug treatment),
- Lp(a) ≥50 mg/dL (1.78 µmol/L),
- Tendon xanthoma.

C. Patients suffering from heFH with LDL-C concentrations ≥130 mg/dL (3.36 mmol/L) despite treatment and **one of the following** characteristics:

- **established CHD or other CVD** (history of acute myocardial infarction, ischemic stroke, peripheral arterial disease, coronary or peripheral arterial revascularization, stable or unstable angina, transient ischemic attack, carotid artery stenosis ≥50%, aortic abdominal aneurysm),
- **drug treated type 2 diabetes mellitus or type 1 with target organ damage,**
- **family history of first or second degree relative with very premature onset CHD** (first or second degree male relative onset before age 45; first or second degree female relative onset before age 55).

D. Non-FH patients suffering from established CHD or other CVD (history of acute myocardial infarction, ischemic stroke, peripheral arterial disease, coronary or peripheral arterial revascularization, stable or unstable angina, transient ischemic attack, carotid artery stenosis ≥50%, aortic abdominal aneurysm) **and with LDL cholesterol concentrations ≥130 mg/dL (3.36 mmol/L).**

E. Patients suffering from progressive cardiovascular disease [coronary artery disease, or peripheral arterial occlusive disease or cerebrovascular disease as documented clinically or by imaging techniques, **with a subsequent CV event** (*acute myocardial infarction, ischemic stroke, ischemia driven revascularization, unstable angina, transient ischemic attack*) **occurring despite stable doses of maximally tolerated LMT] with LDL cholesterol concentrations ≥100 mg/dL (2.59 mmol/L).**

For HeFH diagnosis, please refer to Appendix B and Appendix C.

Metabolic syndrome is defined as follows: 3 of 5 characteristics:

- Increased waist circumference:
  Men >40" (>37" in some populations) and women >35",
- Blood pressure ≥130 mm Hg or ≥80 mm Hg or drug treatment,
- Triglycerides ≥150 mg/dL or drug treatment,
- Low HDL-C:
  Men <40 mg/dL and women <50 mg/dL,
- Elevated glucose ≥100 mg/dL or drug treatment.

Note:

* Definition of maximally tolerated dose (any of the following are acceptable):
  - Rosuvastatin 20 mg or 40 mg daily.
  - Atorvastatin 40 mg or 80 mg daily.
  - Simvastatin 80 mg daily (if already on this dose for >1 year).

Patients not able to be on any of the above statin doses should be treated with the dose of daily atorvastatin, rosuvastatin or simvastatin which is considered appropriate for the patient as per the investigator's judgment or concerns.

Some examples of acceptable reasons for a patient taking a lower statin dose include, but are not limited to: adverse effects on higher doses, advanced age, low body mass index, concomitant medications, and co-morbid conditions such as impaired glucose tolerance /impaired fasting glucose. The reason(s) will need to be documented in the case report form.

NB: in exceptional and well documented cases described in Exclusion criteria E04, another statin regimen may be used.

** Diagnosis of heFH will be documented, either by genotyping or by clinical criteria. For patients who are not genotyped, the clinical diagnosis will be based on either the Simon Broome criteria or the WHO/Dutch Lipid Network criteria and the diagnostic must be "definite" (see Simon Broome criteria for "definite" or a diagnostic scoring >8 for WHO criteria).

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. Not on a stable dose of lipid lowering therapy (statin or other LMT), for at least 4 weeks prior to the screening visit (Week-3) or from screening to enrollment.

E 02. Use of a fibrate other than fenofibrate within 4 weeks of the screening visit (Week-3) or between screening and enrollment.

E 03. Daily doses above atorvastatin 80 mg, rosuvastatin 40 mg or simvastatin 40 mg (except for patients on simvastatin 80 mg for more than one year, who are eligible).

E 04. Use of statin other than simvastatin, atorvastatin or rosuvastatin, prior to the screening visit (Week-3) or between screening and enrolment with the exception of the cases in which there is a documented reason for intolerance to the above mentioned potent statins in which case the use of a different statin is allowed.

E 05. Systolic blood pressure (BP) >180 mmHg or diastolic BP >110 mmHg at screening (Week-3) and/or enrollment (Week 0) visit.

E 06. History of New York Heart Association (NYHA) Class III or IV heart failure within the past 12 months (see Appendix D).

E 07. History of a MI, unstable angina leading to hospitalization, coronary artery bypass graft surgery (CABG), percutaneous coronary intervention (PCI), uncontrolled cardiac arrhythmia, carotid surgery or stenting, stroke, transient ischemic attack, carotid revascularization, endovascular procedure or surgical intervention for peripheral vascular disease within 1 month prior to the screening visit (Week-3).

E 08. Known history of hemorrhagic stroke.

E 09. Patients not previously instructed on a cholesterol-lowering diet prior to the screening visit (Week-3).

E 10. Presence of any clinically significant uncontrolled endocrine disease known to influence serum lipids or lipoproteins.

Note: Patients on thyroid replacement therapy can be included if the dosage of thyroxin has been stable for at least 3 months prior to screening and their sensitive-Thyroid Stimulating Hormone (s-TSH) levels is within ±10% of the normal ranges of the site laboratory.

E 11. Use of systemic corticosteroids, unless used as replacement therapy for pituitary/adrenal disease with a stable regimen for at least 6 weeks prior to screening.

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

E 12. New cancer or active progression of cancer within the past 5 years, except for adequately treated basal cell skin cancer, squamous cell skin cancer, or in situ cervical cancer.

E 13. Known history of a positive HIV test.

E 14. Patient who has taken any active investigational drugs with the exception of alirocumab within 1 month or 5 half-lives, whichever is longer.

NB: Patients who received an investigational drug before 1 month or 5 half-lives (whichever is longer) and who fulfill all the other selection criteria can be enrolled but only after the formal approval from the Sponsor.

E 15. Known history of homozygous familial hypercholesterolemia.

E 16. Use of continuous hormone replacement therapy unless the regimen has been stable in the past 6 weeks prior to the Screening visit (Week-3) and no plans to change the regimen during the study.

E 17. Patient who withdraws consent during the screening period (patient who is not willing to continue or fails to return).

E 18. 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.

E 19. 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,
- Those deemed unable to administer or tolerate long-term injections as per the patient or the investigator,
- 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.

E 20. Laboratory findings during the screening period:
- Positive test for Hepatitis B surface antigen or Hepatitis C antibody,
- Positive serum or urine pregnancy (including Week 0) test in women of childbearing potential,
- Triglycerides >400 mg/dL (>4.52 mmol/L) (1 repeat lab is allowed),
- Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m² according to 4-variable modification of diet in renal disease (MDRD) Study equation,
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x upper limit normal range (ULN [1 repeat lab is allowed]),
- Creatine phosphokinase (CPK) >3 x ULN (1 repeat lab is allowed),
- Thyroid stimulating hormone (TSH) < Lower limit of the normal range (LLN) or >ULN (for patients on thyroid replacement therapy see earlier exclusion criterion (E.10); within ±10% of the normal ranges of the site laboratory is accepted.

E 21. Patients eligible for enrollment into an ongoing clinical study of alirocumab conducted at same investigational site.

E 22. Any country-related specific regulation that would prevent the subject to entering the study. See Appendix L (country-specific requirements).

7.2.2 Exclusion criteria related to the mandatory background therapies

E 23. All contraindications to the background statins or warning/precaution of use (when appropriate as displayed in the respective National Product Labeling). However, patients with documented medical history of adverse reactions with statins (eg, rhabdomyolysis, transaminases elevations, muscle symptoms…) preventing the subsequent use of any statin at any dose may be included in this study once the formal approval is obtained from the Sponsor.

7.2.3 Exclusion criteria related to the current knowledge of Sanofi compound

E 24. Known hypersensitivity to alirocumab or any component of the excipients.

E 25. Pregnant or breast-feeding women.

E 26. Women of childbearing potential not protected by highly-effective method(s) of birth control (as defined in the informed consent form and/or in a local protocol addendum) and/or who are unwilling or unable to be tested for pregnancy.

Note: Women of childbearing potential must have a confirmed negative pregnancy test at screening and inclusion visits. They must use an effective contraceptive method throughout the entire duration of the study treatment and for at least 10 weeks after the last study treatment injection. The applied methods of contraception have to meet the criteria for a highly effective method of birth control according to the "International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. M3 (R2): Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals. ICH. 2009 Jun:1-25."

Postmenopausal women must be amenorrheic for at least 12 months.

E 27. Male participant with a female partner of childbearing potential not protected by a highly-effective method(s) of birth control. See Appendix K (country-specific requirements).

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

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

Patient (or another designated person) will have to perform during the screening period (V1 or dedicated V2) or at the latest on V3 (Day 1) a placebo self-injection training, using a pre-filled pen, before the first alirocumab administration.

Injection for training: sterile placebo for alirocumab will be prepared in the same formulation as alirocumab without the addition of protein as 1 mL volume in a pre-filled pen, for the patients to perform an injection training.

Each alirocumab administration will consist of 1mL subcutaneous injection over the abdomen, thigh, or outer area of upper arm (ie, deltoid region).

The recommended dose is 75 mg or 150 mg administered subcutaneously once every 2 weeks (Q2W).

The dose selection should be based on individual patient characteristics and goal of therapy.

The dose can be adjusted based on treatment response. Lipid levels will be analyzed from Week 4, when maximum LDL-C reduction is usually achieved.

The Investigator is free to adjust the dose (up and down-titration) throughout the study based on clinical judgment.

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.

The investigational medicinal product (IMP) could be administered by self-injection or by another designated person (such as a spouse, relative, etc). The used pre-filled pen will be discarded in a sharps container which will be provided to patients. It is recommended that the subcutaneous IMP injections be rotated within an anatomical area (eg, right thigh then left thigh or right abdomen then left abdomen). Patients also have the option to inject in a different anatomical area (eg, thigh then abdomen the outer area of upper arm) during the study.

In case a designated person is due to inject alirocumab to a patient during the study, it must be ensured that this person has been adequately trained previously.

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

8.1.2 Timing of administration

During screening period, patients will have to perform a placebo self-injection training using a pre-filled pen, before the first alirocumab injection.

At inclusion visit, the first alirocumab injection will be done at the site by the patient or another designated person (such as spouse, relative, etc.) under direct site staff supervision. Patients will be monitored at the investigational site for at least 30 minutes after this first injection in this study.

Alirocumab subcutaneous injections will then be performed outside of the clinic, every two weeks up to the last injection. If the injection is scheduled to take place on the same date as the site visit, then the IMP should be administered after the blood sampling has been completed.

Alirocumab should be administered subcutaneously every two weeks ideally at approximately the same time of the day. The time of the day is based upon patient's preference; however it is acceptable to have a window period (see study procedures Section 10).

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.
- By 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 NONINVESTIGATIONAL MEDICINAL PRODUCT(S)

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

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

Please see Section 8.7 for further information.

8.3 BLINDING PROCEDURES

Not applicable.

This is an open-label study and every patient will receive alirocumab. Treatment kit numbers will be allocated via interactive voice/web response system (IVRS/IWRS).

8.4 PACKAGING AND LABELING

Each alirocumab treatment kit will be prepared to contain 6 pre-filled pens.

In addition to the alirocumab treatment kits, a training kit containing 1 placebo pre-filled pen will be prepared for the purpose of instructing patients or caregiver on injection administration.

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

8.5 STORAGE CONDITIONS AND SHELF LIFE

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

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

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

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

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

8.6 RESPONSIBILITIES

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

All IMP will be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of IMP issued and returned is maintained.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc.) should be promptly notified to the Sponsor. Deficiencies related to the pre-filled pen should be recorded through a complaint procedure.

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

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

8.6.1 Treatment accountability and compliance

- IMP accountability:
  - Used and unused treatment kits are returned by the patient at each visit,
  - The Investigator or designee counts the number of remaining unused pre-filled pens in the returned packs, fills in the Treatment Log Form,
  - The Investigator or designee records the dosing information on the appropriate page(s) of the CRF,
  - The monitor in charge of the study then checks the information by comparing the used or unused treatment kits with treatment log forms and source data.

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 10.1.1). The used and unused kit(s) should be brought back by the patient to such visits for accountability purposes.

- The Investigator or designee will complete the corresponding treatment log form.
- The monitor will check the data consistency between e-CRF pages, treatment log forms using patient's diary, IVRS transaction confirmations and returned unused pre-filled pen of a corresponding kit.

The patient will be instructed on the importance to stay under study treatment.

8.6.2 Return and/or destruction of treatments

A detailed treatment log of the destroyed IMP will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the monitoring team. The Investigator will not destroy the unused IMP unless the Sponsor provides written authorization.

Sharp containers containing all used pens will be brought back on site by the patient for destruction purpose.

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

8.7 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient concomitantly to the study.

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

8.7.1 Management of background lipid-modifying therapy

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

Throughout the whole treatment period, the patients should stay, as far as possible, on the stable maximally tolerated registered daily dose of statins, with or without other LMT that was received in the 4 weeks prior to screening visit.

Dose adjustment of LMT, including statins, might take place as per the investigator's judgment, for example in case of tolerability issue. Any adjustment will be documented in the e-CRF.

For adjustments based on LDL-C values, simultaneous adjustment in alirocumab dose and any LMT should be avoided, unless required for a safety/tolerability issue.

8.7.2 Contraception

Women of childbearing potential must take an effective contraceptive method throughout the study treatment and during the 10-week period after the last study treatment injection. In some participating countries, specific contraceptive methods must be used by women of childbearing potential participating in a clinical trial (see Protocol Appendix I and Appendix J).

8.7.3 Prohibited concomitant medications

Forbidden concomitant medications from the initial screening visit until the end of treatment visit include the following:

- Statins other than simvastatin, atorvastatin, rosuvastatin unless there is a documented intolerance to the above mentioned potent statins in which case other statins are allowed.
- Fibrates other than fenofibrate.
- Other PCSK9-inhibitor.
- Systemic corticosteroids, unless used as replacement therapy for pituitary/adrenal disease with a stable regimen for at least 6 weeks prior to randomization, are prohibited during the study duration.

8.7.4 Life style and dietary habits

Life styles and dietary habits should be maintained if possible throughout the entire study duration, as medically feasible, with minimum changes.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 PRIMARY ENDPOINTS

In this study, primary endpoints only relate to safety assessments.

Safety will be assessed throughout the study by the following parameters:

- Recording of adverse events (including serious adverse events and adverse events of special interest).
- Standard laboratory tests: hematology (hemoglobin, WBC, platelet count) and biochemistry (urea, creatinine, glucose, glycated hemoglobin A1c [HbA1c], total CK).
- Liver function tests: SGOT (AST), SGPT (ALT), alkaline phosphatase (ALP), total bilirubin.
- Physical examination and vital signs: height (only at screening), weight, heart rate, systolic and diastolic blood pressure
- Device related complaints will be recorded and described as well.

Reporting procedures for AEs, SAEs and AESI are detailed in Section 10.4, Section 10.5, Section 10.6, Section 10.7.

The assessment of tolerability refers to local injection site reactions (see Appendix H).

9.1.1 Adverse events

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 IMP.

TEAE period:

The TEAE period will include a study period of 2 weeks after last study treatment injection. This means that TEAE period will cover a period from first dose to + 14 days after last dose. Safety reporting under commercial alirocumab intake will be documented via spontaneous reporting.

Death observation period:

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

Adverse events, including AESIs and SAEs, will be collected from the time the patient signs the informed consent to the completion of the safety observation period.

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 Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of the considered database lock.

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

For this study, the following AEs are AESI:

- Increase in alanine transaminase (ALT): ALT ≥3 x ULN (if baseline ALT <ULN) or ALT ≥2 times the baseline value (if baseline ALT ≥ULN).
- Allergic events and/or local injection site reaction that are allergic in nature and that require consultation with another physician for further evaluation.
- Pregnancy.
- Symptomatic overdose with IMP.
- Neurologic events that require additional examinations/procedures and/or referral to a specialist.
- Neurocognitive events.

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

9.1.2 Safety laboratory

The clinical laboratory data consist of urinalysis and blood analysis:

- Hematology (RBC count, hemoglobin, hematocrit, platelets, WBC count with differential blood count).
- Standard chemistry (fasting plasma glucose, sodium, potassium, chloride, bicarbonate, CPK, calcium, phosphorous, urea nitrogen, creatinine and calculated creatinine clearance using Cockroft-Gault formula or eGFR using MDRD Study equation, uric acid, total protein, lactic dehydrogenase (LDH), albumin, γ Glutamyl Transferase [γGT] Hepatitis B antigen, Hepatitis C antibody).
- HbA1c.
- Liver panel (ALT, AST, ALP, and total bilirubin).

Some additional safety laboratory parameters may be reflexively measured, based on actual data (please refer to Section 10.4.5).

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

9.1.3 Vital signs measurement

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

9.2 SECONDARY ENDPOINTS

9.2.1 Secondary efficacy endpoints

The main efficacy secondary endpoint will be:

- The percent change in calculated LDL-C from baseline to Week 12 (main timepoint).

The key secondary efficacy endpoints will include:

- The proportion of patients reaching calculated LDL-C <100 mg/dL (2.59mmol/L) at Week 12.
- The proportion of patients reaching calculated LDL-C <70 mg/dL (1.81mmol/L) at Week 12.
- Proportion of patients with LDL-C <70 mg/dL (1.81 mmol/L) and/or ≥50% reduction from baseline in LDL-C (if LDL- C ≥70 mg/dL [1.81 mmol/L]) at Week 12.
- The percent change from baseline to Week 12 in non-HDL-C, total-C, HDL-C, and TG levels.

Since the study duration for each participating country will depend on when alirocumab becomes commercially available and reimbursed, with a minimum duration of patient's participation of 12 weeks and up to a maximum of 30 months, the secondary efficacy endpoints listed above will also be assessed at the following time points depending on countries: Weeks 4, 8, 12, 24, 48, 72, 96, 108, and EOT/EOS.

9.2.1.1 Efficacy assessment method

9.2.1.1.1 Lipid parameters

Total-C, HDL-C, TG, non-HDL-C will be directly measured by a local Laboratory as per the schedule in Section 10.1.

LDL-C will be calculated using the Friedewald formula at all site visits.

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

9.2.2 Other secondary endpoints

The other secondary efficacy endpoints will include:

- The proportion of patients who were up-titrated to 150 mg of alirocumab based on investigator's judgment.
- The proportion of patients who were down-titrated to 75 mg of alirocumab based on investigator's judgment.
- The reasons (ie, LDL-C threshold, AE) that triggered a down-titration or an up-titration of alirocumab.

9.2.3 Patient's reported outcomes: patient's acceptability of self-injection

Patient's acceptability of self-injection will be documented by using the Self Injection Assessment Questionnaire (version 2 SIAQ, Appendix G), to be completed only by those patients who give themselves an injection.

This paper questionnaire will be collected separately from the e-CRF.

The SIAQ is a patient reported outcome (PRO) measure that contains two modules; one to be completed before the first self-injection (PRE module) and another to be completed after self-injection (POST module). The response for each item is provided on a five point Likert scale where a score of one corresponds to the patient's worst experience and a score of five corresponds to the best experience.

Some instructions to complete the questionnaire:

1/ the PRE Module must be completed before the training self-injection with placebo.

The PRE module consists of seven items that can be grouped into three domains: feelings about injections (items 1-3); self-confidence (items 4-6); and satisfaction with self-injection (item 7).

2/ the POST Module must be completed preferably within 30 minutes (maximum 1hour) after the self-injection of a SC medication.

The POST module consists of 18 items that can be grouped into six domains: feelings about injections (items 1-3); self-image (item 4); self-confidence (items 5-7); pain and skin reactions (items 8-9); ease of use (items 10-11); and satisfaction with self-injection (items 12-18). Domain scores are calculated as the mean of the item scores included in the domain.

The POST module will be completed at week 4, week 8, week 12, week 24, week 48, and then every 12 weeks until last alirocumab injection.

9.3 APPROPRIATENESS OF MEASUREMENTS

See Section 4.

10 STUDY PROCEDURES

For all visits after Day 1/Week 0 (inclusion visit), a timeframe of a certain number of days will be allowed. The window period for Week 0 up to Week 12 included is ±3 days, then for Week 18 and Week 24 it is ±5 days and then for the subsequent visits it is ±7 days.

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

Blood samplings:

The blood samplings including the determination of lipid parameters (ie, total-C, LDL-C, HDL-C, TG, non-HDL-C, FPG and HbA1C) should be performed in the morning, in fasting condition (ie, overnight, at least 10 to 12 hours fast and refrain from smoking), and before IMP injection for all site visits throughout the study. Alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the blood sampling are discouraged.

Note: if the patient is not in fasting conditions, the blood sample will not be collected and a new appointment will be given the day after (or as close as possible to this date) to the patient with instruction to be fasted (see above conditions) and not having taken IMP (injection to be delayed accordingly).

In case the lipid results are made available during the visit, the lipid results performed at local laboratory will be reviewed at the on-site visit by the investigator, and, in case a dose adjustment is required, the dose will be modified immediately or the patient will be requested to come to the site within a few days for an unscheduled visit, so that the dose can be adjusted as needed.

The unscheduled dispensation visit will be similar to the “dispensation only” visits, eg, V10/W36.

Laboratory tests:

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

- Hematology: (all site visits except V2, V3/inclusion, V6/W8, dispensation visits and EOT/EOS: see Section 9.2 for details.
- Chemistry: (all site visits except V2, V3/inclusion, V6/W8, dispensation visits, EOT/EOT): see Section 9.2 for details.
- Lipid profile: (screening, Week 4, Week 8, Week 12, Week 24, Week 48, Week 72, Week 96, and EOT/EOS): see Section 9.2.1.1.1.
- Liver panel: in case of total bilirubin values above the normal range, differentiation into conjugated and non-conjugated bilirubin will occur automatically (screening, Week 4, Week 8, Week 12, Week 24, Week 48, Week 72, Week 96, EOT/EOS): see Section 9.2 for details.
- Hepatitis B surface antigen (screening).

- Hepatitis C antibody, at screening and EOT/EOS; in case of ALT increase during the study, hepatitis C antibody should be determined and if positive a reflexive testing should be performed).
- Serum pregnancy test (screening only).
- Urine pregnancy test (inclusion and EOT/EOS).

Urine samplings:

Urinalysis - dipstick will be performed at site or at the local Laboratory at screening, inclusion, W12, EOT/EOS visits and as needed during the study at investigator's discretion.

It will assess for pH, specific gravity, and for the presence of blood, protein, glucose, ketones, nitrates, leukocyte esterase, uro-bilinogen and bilirubin. If the dipstick is abnormal then standard microscopy will be conducted.

Notes: Any clinically relevant abnormal laboratory value should be immediately rechecked for confirmation before making any decision for the concerned patient. It should be documented as an AE/SAE if one or more criteria in Section 10.4.2 are met. Please also refer to Section 10.4.1.3.

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in Appendix E, Appendix F and should be followed by investigators. In case of ALT increase ≥3 x ULN (or ≥2 X baseline ALT if ALT elevated at baseline), the local Laboratory will perform the required additional testing.

Other assessments:

All other blood parameters will also be measured by a local 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 10 to 12 hours fast and refrain from smoking). Alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the blood sampling are discouraged.

- Glycemic parameters (HbA1c at screening, V7, V9, V11, V13, V15 and EOT/EOS visits and serum glucose at screening, V5, V7, V9, V11, V13, V15 and EOT/EOS visits) will be measured by a local Laboratory, as per the schedule in Section 1.2.

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

Physical examination:

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

Blood pressure (BP)/heart rate (HR):

BP should be measured in sitting position under standardized conditions, approximately at the same time of the day, on the same arm, with the same apparatus (after the patient has rested comfortably in sitting position for at least 5 minutes).Values are to be recorded in the electronic case report form (eCRF); both systolic BP and diastolic BP should be recorded. At the first screening visit, BP should be measured in both arms. The arm with the highest diastolic pressure will be determined at this visit, and BP should be measured on this arm throughout the study. This highest value will be recorded in the eCRF.

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

Notes: 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 Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8).

Body weight and height:

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

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

Self-injection assessment questionnaire (SIAQ):

The SIAQ is a patient reported outcome (PRO) measure that contains two modules; one to be completed before the first self-injection at training (PRE module) and another to be completed after self-injection (POST module). The response for each item is provided on a five point Likert scale where a score of one corresponded to the patient's worst experience and a score of five corresponded to the best experience.

See Section 9.2.3.

10.1 VISIT SCHEDULE

10.1.1 Screening period

Only patients who meet the inclusion criteria as noted in Section 7.1 should be screened. The screening period will take place up to 3 weeks or 21 days (and as soon as possible after receipt of laboratory eligibility criteria) prior to inclusion/Day 1 visit. The first screening visit (Week-3) can take place from 21 to 8 days before the inclusion visit. If it is planned to have another designated person administer the injections to the patient during the study, then this person should be present at the injection training.

Screening Visit (Visit 1 / Week -3 / Day -21 up to -8):

During screening visit the below will be performed:

- Complete informed consent - the patient will receive complete information about the study both verbally and in writing. Written informed consent for the study must be obtained prior to any study related investigations or procedures.
- Assess inclusion/exclusion criteria.
- Obtain patient demography – age, gender, race, and ethnicity.
- Obtain medical history (including menopausal status), surgical history, alcohol habits, and smoking habits.
- Obtain family medical history (including risk factors relating to premature CHD (before 55 years of age in a male, 65 years in a female first degree relative), allergy and Type 2 diabetes).
- Document prior medication history within the previous 12 weeks, especially for lipid modifying therapy (including statin) and nutraceutical products that may affect lipids (eg, omega-3 fatty acids, plant stanols such as found in Benecol, flax seed oil, psyllium).
- Record concomitant medication.
- Perform physical examination.
- Obtain body weight and height measurements.
- Take vital signs including HR and BP as per directions in Section 10 above.
- Collect AEs from informed consent form (ICF) signature onward:
  - All AEs and SAEs will be collected from the time of informed consent signature and throughout the study until the post study treatment follow up visit.
- Urinalysis (dipstick and if abnormal then microscopy).
- Obtain fasting blood sample for:
  - Lipids: measure or calculation of total-C, LDL-C, HDL-C, TG, non-HDL-C,
  - Hematology: red blood cell count including hematocrit, hemoglobin, red blood cell, WBC count with differential count and platelets,
  - Chemistry: sodium, potassium, chloride, bicarbonate, fasting glucose, calcium, phosphorous, urea, creatinine, uric acid, total protein, LDH, albumin, and γGT,
  - HbA1c,
  - Liver panel (ALT, AST, ALP, and total bilirubin),
  - CPK,
  - Hepatitis B surface antigen and hepatitis C antibody tests,
  - Serum pregnancy test (women of childbearing potential only),

  Note: All patients will be qualified for inclusion based on the laboratory results, including LDL-C value obtained at this visit, as well as other lab values where repeat is not allowed by protocol.
- Give instruction on diet.

Injection training during screening period (V2/D -7):

Injection training visit can take place at all time between V1/Screening and V3 Inclusion and also can be done during one of these two visits.

Injection training should be provided as outlined in Section 8.1. The placebo for alirocumab should be administered by the patient or another designated person (such as spouse, relative, etc) at the study site under supervision of site staff with appropriate feedback.

If it is planned to have another designated person administering the injections to the patient during the study, then this person should also be present at the next visit (injection training visit at Week -1). If feasible, it is acceptable that the injection training with placebo be performed at the inclusion visit (before the first IMP injection).

- Before injection training patient would be requested to complete SIAQ PRE self-injection module.
- Collect AEs.
- Record batch number allocated in eCRF.
- An appointment will be given for the next visit.

10.1.2 Open-label Treatment Period

10.1.2.1 Inclusion visit (Visit 3 / Week 0 / Day 1 +3)

During inclusion visit the below will be performed:

- Assess Inclusion/Exclusion Criteria: confirm eligibility and include the patient.
- Collect AEs.
- Record concomitant medication.
- Review patient's diet. Patient should be on a NCEP-ATPIII TLC diet or equivalent.
- Physical examination.
- Urine pregnancy test (females of childbearing potential only).
- Urinalysis.
- Injection training reminder could be performed at inclusion visit as needed.
- If the patient is confirmed eligible, the Investigator will start the next study procedures:
  - IVRS/IWRS contact for allocation of one 7-digit treatment kit number according to the list for the alirocumab injections. Investigators should never allocate a treatment kit number to a patient without contacting IVRS/IWRS,
  - 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 first open-label IMP injection will take place at the study site, but only after the assessment of all evaluations planned at that visit. Close supervision, feedback and further training to be provided for IMP administration. The patient should be observed for at least 30 minutes after the injection.
- Ask the patient to complete the SIAQ (post-module).

Reminders:

- An appointment will be given for the next study site visit.
- Remind patient to be in fasting conditions (ie, overnight, at least 10 to 12 hours fast and refrain from smoking) for next study site visit. Also, alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the next study site visit are discouraged.
- Patient will be provided with a diary and instructed on its completion. Patient will be asked to bring the diary to the next study site visit.
- Patient will be given a sharp container to discard all used pens.

10.1.2.2 Phone calls: Visit 4 / Week 2 (Day 15 ±3), Visit 8 / Week 18 (Day 127 ±5)

During phone calls the below will be checked:

- Vital status.
- Prior and concomitant medications.
- Safety and product-related complaint information.

In case of any safety concerns the investigator may request the patient to come back to the site for complementary assessments.

10.1.2.3 Visit 5 / Week 4 (Day 29 ±3), Visit 6 / Week 8 (Day 57 ±3), Visit 7 / Week 12 (Day 85 ±3), Visit 9 / Week 24 (Day 169 ±5), Visit 11 / Week 48 (Day 337 ±7), Visit 13 / Week 72 (Day 505 ±7), Visit 15 / Week 96 (Day 673 ±7)

During these visits the below will be performed:

- Collect AEs.
- Check product complaints.
- Check compliance on IMP (review patient diary and treatment kit) and data collection on IMP administration.
- Record concomitant medication.
- Perform physical examination.
- Take vital signs including HR and BP.
- Urinalysis (only at V7).
- Laboratory tests: Hematology, Biochemistry, Liver panel, Lipid profile (hematology and biochemistry not needed for V6), HbA1c (except at V5 and V6).

- Remind Nutritional Counseling (including reviewing patient's diet).
- Provide any injection training reminder as needed.
- IVRS contact for treatment kit dispensing (at V5 and V6, new treatment kit dispensing would be done as per titration needs).

Reminders:

- An appointment will be given for the next study site visit, to be done before next IMP administration.
- Remind patient to be in fasting conditions (ie, overnight, at least 10 to 12 hours fast and refrain from smoking) for next study site visit. Also, alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the next study site visit are discouraged.
- Ask the patient to complete the SIAQ POST (ie, after alirocumab injection).
- Patient to bring the diary to the next study site visit.
- If upon review of the laboratory blood test results, the investigator judges that a dose titration of the patient dose is necessary, then he/she will contact the patient and plan an unscheduled visit. The assessments of the unscheduled visit will be at minimum the same of the "dispensation only" visit (eg, V10/Week 36).

10.1.2.4 Dispensation visits: Visit 10 / Week 36 (Day 253 ±7), Visit 12 /Week 60 (Day 421 ±7), Visit 14 / Week 84 (Day 589 ±7), Visit 16 / Week 108 (Day 757 ±7)

During dispensation visits the below will be performed:

- Treatment compliance will be checked.
- Patient' diaries will be reviewed.
- Safety and concomitant medication will be reviewed.
- Check product complaints.
- Provide any injection training reminder as needed.
- Treatment kit dispensing.

10.1.2.5 End-of-treatment (EOT/EOS) visit: Visit 17 / Week 120 (Day 841 +7)

This EOT/EOS visit should occur at least 14 days (+7 days) after last injection (ie, within a 14-21 days' time window).

This visit may occur before Week 120 if the commercial alirocumab (Praluent) becomes available before this date in a given country.

During the EOT/EOS visit the below will be performed:

- Collect AEs.
- Check product complaints.
- Check compliance on IMP (review patient diary and treatment kit) and data collection on IMP administration.
- Record concomitant medication.
- Perform physical examination.
- Take vital signs including HR and BP.
- Laboratory tests: Hematology, Biochemistry, Liver panel (including Hepatitis C antibody, with reflexive testing if positive), Lipid profile, HbA1c. In case of abnormal results, a retest should be performed as soon as possible.
- Urinalysis (dipstick and if abnormal then microscopy).
- Urine pregnancy test (women of childbearing potential only).
- Document the end of treatment with collection of the following:
  - Last dose as per diary,
  - Reason for permanent treatment discontinuation,
  - Whether the patient switches to commercial alirocumab or to another therapy.
- Remind Nutritional Counseling (including reviewing patient's diet).
- IVRS/IWRS contact to register the patient's EOT/EOS.

Reminders:

- An appointment for lab sampling will be scheduled in case of any persistent laboratory abnormality at EOT/EOS visit.

10.2 DEFINITION OF SOURCE DATA

- Agreement, date, and signature of informed consent mentioning the study identification.
- Patient identification, last participation in a clinical trial, medical history, associated diseases, and data related to the studied pathology.
- Contraception methods for women of childbearing potential (WOCBP).
- Previous and concomitant medications (including the lipid modifying therapy, especially statins used, with doses, to document statin intolerance).
- Study identification.
- Treatment number, dates of administration.
- Dates of visits and assessments including the examination report.
- Vital signs (heart rate, blood pressure), height, body weight.
- Faxed lab reports (dated and signed by the Principal Investigator or Sub-Investigator documenting timeliness of review).

- IVRS/IWRS confirmation fax.
- 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.
- Laboratory and procedure reports.

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

The IMP should be continued whenever possible. In case the IMP is stopped, it should be determined whether the stop can be made temporarily; permanent IMP discontinuation should be a last resort. Any IMP discontinuation should be fully documented in the CRF. In any case, the patient should remain in the study as long as possible.

Pregnancy will lead to definitive treatment discontinuation in all cases.

10.3.1 Temporary treatment discontinuation with investigational medicinal product(s)

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

10.3.2 Permanent treatment discontinuation with investigational medicinal product(s)

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

Patient withdrawal from the study treatment or from the study should be avoided as much as possible.

10.3.2.1 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 e-CRF.

Patients should discontinue the IMP for the following reasons:

- Pregnancy, intention for pregnancy, or no longer with effective contraceptive method of birth control (females of childbearing potential only).
- Acute injection reaction of clinical concern.
- At patient request, ie, withdrawal of the consent for treatment;
- Serious adverse event (or non-serious but severe in intensity) of hypersensitivity reaction considered related to IMP.
- If, in the Investigator's opinion, continuation with the administration of the IMP would be detrimental to the patient's well-being.
- Intercurrent condition that requires discontinuation of the IMP (eg, laboratory abnormalities, please refer to decision tree Appendix F).
- At the specific request of the Sponsor.
- Any abnormal laboratory value will be immediately rechecked for confirmation before making a decision of permanent discontinuation of the IMP for the concerned patient.

10.3.2.2 Handling of patients after permanent treatment discontinuation

Patients who prematurely discontinue study treatment (regardless of the reason) should, at the time of treatment discontinuation:

- Have, as soon as possible, an unscheduled visit with assessments normally planned at end of treatment visit (this should take place within 5 days of treatment discontinuation, if possible).
- At a minimum, should then be followed up to recovery or stabilization of any AE as specified in this protocol.
- Undergo a final end of study visit (EOT/EOS) at least 2 weeks after the last study treatment injection.

All definitive discontinuation of study treatment should be recorded by the investigator in the appropriate screens of the e-CRF and in the patient's medical records when confirmed.

IVRS/IWRS should be notified when a patient prematurely discontinues study treatment.

10.3.2.3 Procedure and consequence for patient withdrawal from study

The patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-patient contact follow-up, eg, medical records check. Patients requesting withdrawal should be informed that withdrawal of consent for follow-up may jeopardize the public health value of the study. If possible, the patients should be assessed using the procedures defined above.

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

All study withdrawals should be recorded by the Investigator in the appropriate screens of the e-CRF and in the patient's medical records when considered as confirmed. In the medical record, at least the date of the withdrawal and the reason should be documented.

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

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

Patients who have withdrawn from the study cannot be included in the study again. Their inclusion and treatment numbers must not be reused.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

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

10.4.1.2 Serious adverse event

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

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

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

- Intensive treatment in an emergency room or at home for:
  - Allergic bronchospasm,
  - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc.),
  - Convulsions (seizures, epilepsy, epileptic fit, absence, etc.).
- Development of drug dependence or drug abuse.
- ALT >3 x ULN + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN.
- Suicide attempt or any event suggestive of suicidality.
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling).
- Bullous cutaneous eruptions.
- Cancers diagnosed during the study or aggravated during the study (only if judged unusual/significant by the Investigators in oncology studies).
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study (only if judged unusual/significant by the Investigators in studies assessing specifically the effect of a study drug on these diseases).
- Suspected transmission of an infection agent: if any suspected transmission of an infectious agent via a medicinal product (eg product contamination).

10.4.1.3 Adverse event of special interest

An adverse event of special interest (AESI) is an AE (serious or non-serious) that needs to be monitored, documented, and managed in a pre-specified manner described in the protocol.

For this study, the AESIs are the following (refer also to Section 10.4.4 for the reporting time frame, and the corresponding complementary forms in the e-CRF to be filled):

- **Increase in alanine aminotransferase (ALT):**
  - ALT ≥3 x ULN (if baseline ALT <ULN) or ALT ≥ 2 times the baseline value (if baseline ALT ≥ULN) (Please refer to related flowchart in Appendix F).
- **Allergic events that require consultation with another physician** for further evaluation of hypersensitivity/allergy as per the Investigator's medical judgment.
- **Local injection site reactions that are allergic in nature**:
  - Local injection site reactions deemed to be allergic by the Investigator (or have an allergic component) and that require consultation with another physician for further evaluation of hypersensitivity/allergy as per the Investigator's medical judgment should be reported as AESIs.
    Note: Other local injection site reactions are non-AESIs. Please see Section 10.4.1.4 for details.
    Note: The safety instructions on allergic events and local injection site reactions are detailed in Section 10.6.
- **Pregnancy:**
  - Pregnancy occurring in a female patient or the female partner of a male patient (if data collection is permitted by the female partner and by local regulatory authorities) during the study or within 70 days (10 weeks) following the last dose of IMP.
  - Pregnancy will be recorded as AESI in all cases. Pregnancy will be qualified as an SAE only if it fulfils one or more SAE criteria.
  - In the event of pregnancy of a female patient included in the study, the IMP should be permanently discontinued.
  - The follow-up of the pregnancy will be mandatory until the outcome is 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 of the study treatment are administered in <7 calendar days). The symptomatic overdose should be reported using the term "symptomatic overdose (accidental or intentional)", indicating the circumstance in parentheses (eg, "symptomatic overdose [accidental]" or "symptomatic overdose [intentional]"). The patient should be monitored and appropriate symptomatic treatment instituted,
  - The circumstances of the overdose should be clearly specified in the verbatim, and the symptoms, if any, entered on separate AE/SAE forms,
  - Of note, asymptomatic overdose should be reported as a standard AE.

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

10.4.1.4 Local injection site reactions (non-allergic or allergic not requiring consultation)

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

The definition of local injection site reactions, the reporting time frame, and the corresponding complementary forms in the e-CRF to be filled are summarized in Appendix E.

10.4.1.5 Device Deficiency

- A device Deficiency is any inadequacy related to the identity, quality, durability, reliability, safety or performance of the medical device including malfunctions, use errors, and inadequate labeling.
- Product Complaints (PC):
  - Product Complaints is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, efficacy or performance of a product after it is released for distribution. Patients will be instructed to contact their site for any questions or difficulties.
- All product complaints (PC) must be reported on a product complaint form when there is a reason to suspect a problem with the device.
- In case of a PC associated with the occurrence of an AE, the AE must be documented on an AE page in the CRF.
- In the case of a PC associated with the occurrence of a SAE, the SAE must be reported as in Section 10.4.3 in accordance with the serious adverse event reporting procedures.

10.4.2 General guidelines for reporting adverse events (and product complaints)

- All AEs, regardless of seriousness or relationship to investigational medical product (IMP)/ non investigational medical product (NIMP), spanning from the signature of the informed consent form until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding page(s) or screen(s) of the CRF.
- All products complaints associated or not to an AE are to be recorded immediately on the corresponding products (study medical device) complaints pages and reported to local Complaint Service immediately (within 24 hours).

- Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP or by the study procedure(s).
- The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the Sponsor.
- Patients who experience an ongoing SAE or an AESI, at the prespecified study end-date, should be followed until resolution, stabilization, or death and related data will be collected. The duration of post study follow-up and reporting of AEs will be specified (eg, until recovery).
- When treatment is prematurely discontinued, the patient will have an EOT (=EOS) visit at least 2 weeks after the last study treatment injection unless there is an AE to be followed until final outcome and related data will be collected.
- Laboratory or vital signs are to be recorded as AEs only if:
  - Symptomatic and/or,
  - Requiring either corrective treatment or consultation, and/or,
  - Leading to IMP discontinuation or modification of dosing, and/or,
  - Fulfilling a seriousness criterion, and/or,
  - Defined as an AESI.

  Instructions for AE reporting are summarized in Appendix E.
- Adverse event (injection site reactions) recorded in patient's questionnaire:

  The Investigator must compare the injection site reaction information recorded by the patient in the SIAQ to the information recorded in patient diaries. Based on his/her clinical assessment the investigator would complete an adverse event, when required.

10.4.3 Instructions for reporting serious adverse events

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

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send a notification to the monitoring team after approval of the Investigator within the e-CRF or after a standard delay.
- SEND (preferably by fax or e-mail) a photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring team whose name, fax number, and email address appear on the clinical trial protocol. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.

- All further data updates should be recorded in the e-CRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status, etc.) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life threatening within a week (7 days) of the initial notification.
- A back-up plan (using a paper CRF process) is available and should be used when the e-CRF system does not work.

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

10.4.4 Guidelines for reporting adverse events of special interest

For these AEs, the Sponsor must be informed immediately (ie, within 24 hours), as per SAEs notification described in Section 10.4.3, even if not fulfilling a seriousness criterion, using the corresponding screens in the e-CRF. Please refer to Section 10.4.1.3 for a listing of AESI and Appendix E for a summary of reporting adverse events.

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

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

10.4.5 Guidelines for management of specific laboratory abnormalities

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in Appendix F.

The following laboratory abnormalities should be monitored, documented, and managed according to the related flow chart in protocol appendices.

- Neutropenia.
- Thrombocytopenia.
- Increase in ALT.
- Acute renal insufficiency.
- Increase in CPK and suspicion of rhabdomyolysis.

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 Reactions, SUSAR), to the regulatory authorities, independent ethics committees (IECs)/institutional review boards (IRBs) as appropriate and to the Investigators.
- All SAEs that are expected and at least reasonably related to the IMPs to the regulatory authorities, according to local regulations.

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

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

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

10.6 SAFETY INSTRUCTIONS

10.6.1 Local injection site reactions (non-allergic or allergic not requiring consultation)

The classification of local injection site reactions, the reporting time frame, and the corresponding complementary forms in the e-CRF to be filled are summarized in Appendix H.

In case the Investigator or the patient recognizes any signs of local intolerability, the patient should be treated and followed-up as per the Investigator's medical judgment.

Specific e-CRF screens (General Allergic Reaction and/or Local Injection Site Reaction Complementary Form) are to be filled (Appendix E). The local symptoms should be reported in the "local injection site reaction" section of the complementary form. If the injection site reaction progress/expand/worsen/etc, both "local injection site reaction" and "general allergic reaction" of the complementary form should be completed.

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.

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

The patient has erythema, redness, and/or swelling, that is <2.5 cm in diameter, AND

- The swelling does not interfere with activity, AND
- No other signs or symptoms are involved.

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

10.6.2 Allergic Adverse Events

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 mechanics of injection) should only be recorded on the Local Injection Site Reaction Complementary Form. However, injection site reactions that progress/expand/worsen/etc should be evaluated as recommended in Section 10.6.3 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.

10.6.3 Allergic adverse event with cutaneous involvement

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

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

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

10.6.4 Acute allergic injection reactions

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

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

10.7 ADVERSE EVENTS MONITORING

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

11 STATISTICAL CONSIDERATIONS

The material of this Section is the basis for the Statistical Analysis Plan for the study. This plan may be revised during the study to accommodate clinical trial protocol amendments and to make changes to adapt to unexpected issues in study execution and data that affect planned analysis. Thus a final plan should be issued before database lock.

11.1 DETERMINATION OF SAMPLE SIZE

No formal sample size calculation has been done. The Safety analyses of this study will be descriptive. The table below provides the precision (95% CI) associated to a variety of AE event rates for a targeted sample size of 1300 patients:

Table 1 - Expected 95% CI for various event rates

Adverse event rates	10%	20%	30%	40%	50%
95%CI	[8.4%; 11.6%]	[17.8%; 22.2%]	[27.5%; 32.5%]	[37.3%; 42.7%]	[47.3%; 52.7%]

For a rare non observed event, by using the rule of three, it can be estimated that the upper limit of the 95% confidence interval of the event rate is approximately 0.23% (1 per 433).

11.2 DISPOSITION OF PATIENTS

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

Enrolled patients consist of all screened patients, with a treatment kit number allocated and recorded in the IVRS/IWRS database, regardless of whether treatment kit was used or not.

Reasons for treatment discontinuation as well as reasons for withdrawal from the study will be summarized.

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy population

11.3.1.1 Modified intent-to-treat population

Modified intent-to-treat population (mITT): all enrolled patients who took at least one dose or part of a dose of alirocumab and had an evaluable efficacy endpoint during the efficacy treatment period. The main efficacy endpoint will be evaluable provided that the two following conditions are met:

- Availability of a baseline calculated LDL-C value (last value available prior to the first injection of alirocumab).
- Availability of at least one calculated LDL-C value during the efficacy treatment period and within one of the analysis windows up to Week 12.

The efficacy treatment period is defined as the time period from the first injection of alirocumab up to the day of last injection +21 days.

11.3.2 Safety population

The safety population will consist of the patients who have signed the informed consent form and who have received at least one dose or partial dose of alirocumab.

11.3.3 Other analysis population

The analysis of the "POST-self-injection" module of the SIAQ will be performed in the patients of the safety population who gave themselves at least one alirocumab injection.

11.4 STATISTICAL METHODS

All statistical analyses described in this section will be provided at the time of the final analysis.

The number and percentage of patients will be provided for qualitative variables. The following information will be provided for continuous variables: number of patients (N), mean, standard deviation, median, as well as minimum and maximum. The first quartile (Q1) and the third quartile (Q3) will also be provided for some baseline lipid and laboratory parameters.

Analyses will also be performed on some sub-groups of interest such as patients with HeFH, Type 1 and Type 2 diabetes mellitus, established CHD or other CVD (including patients suffering from progressive cardiovascular disease).

For the final analysis, the results will be displayed globally and in some cases per country or region if the sample size is deemed sufficiently large.

Final analysis will be performed after the global Data Base Lock.

11.4.1 Extent of alirocumab exposure and compliance

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

11.4.1.1 Extent of investigational medicinal product exposure

The total exposure will be assessed by:

- Duration of alirocumab exposure in weeks defined as: (last alirocumab injection date + 14 - first alirocumab injection date) / 7, regardless of unplanned intermittent discontinuations.
- The total number of injections by patient.

11.4.1.2 Compliance

Compliance will be assessed using the following parameters:

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

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

- 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):
  - 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. For example, if a patient takes a dose 18 days after his/her previous injection, then 1 day is counted as a day under-planned dosing,
  - 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 divided by the duration of IMP injection exposure in days. For example, if a patient takes a dose 9 days after his/her previous injection, then 2 days are counted as a days above-planned dosing.

11.4.2 Analyses of safety data (see Section 9.1)

All safety analyses will be performed on the Safety population. For each of safety parameter, the baseline value will be defined as the last available value before the first injection.

The safety analysis will focus on the Treatment Emergent Adverse Events (TEAE) period defined as the time from the first dose of alirocumab to the last dose of IMP +14 to 21 days.

The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests and vital signs.

Potentially clinically significant abnormality (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.

11.4.2.1 Analysis of adverse events

Adverse event incidence tables will be presented by system organ class (SOC), high-level group term (HLGT), high level term (HLT) and preferred term (PT) sorted in alphabetical order, 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 will be the safety population.

Adverse event incidence table will be provided for all types of TEAEs: all TEAEs, all treatment emergent AESI, 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, exploration of time to onset could be performed for these selected TEAEs as described below to account for the differential exposure time in all patients.

Selected TEAEs will be also analyzed using time-to-event approach (Kaplan-Meier methodology). Time from the first dose of 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 different time points of exposure will be presented and Kaplan-Meier curves will be provided.

Death:

The following deaths summaries will be generated:

- Number (%) of patients who died by study period (TEAE, on-study, post-study) summarized on the safety population.
- TEAE leading to death (death as an outcome on the AE CRF page as reported by the Investigator) by primary SOC , HLGT, HLT and PT showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT.

11.4.2.2 Analysis of 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. For selected parameters, mean changes from baseline with the corresponding standard error will be plotted over time (at same time points).

- The incidence of PCSAs at any time during the TEAE period (on-treatment PCSAs) will be summarized 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.

The absolute change in HbA1c (%) will be assessed from baseline to Week 12, 24, 72, 96 and EOT/EOS.

11.4.3 Analyses of efficacy data (see Section 9.2.1)

Efficacy variables will be explored through descriptive statistics.

Percent changes from baseline will be summarized at Weeks 4, 8, 12 and 24 and at Week 48, 72, 96, EOT/EOS in the mITT population using number of available data, mean, SD, median, minimum, and maximum. For percent changes, 95% confidence intervals of the mean will also be provided.

All measurements, scheduled or unscheduled will be assigned to analysis windows defined in the statistical analysis plan (SAP).

The proportions of patients reaching the different targets defined for LDL-C will be provided with their corresponding 95% confidence intervals.

11.4.4 Analysis of other endpoint(s) (see Section 9.2.2)

The number (n) and percentage (%) of patients with an up-titration to 150 mg of alirocumab will be described as well as the detailed reasons that triggered the up-titration.

The number (n) and percentage (%) of patients with a down-titration to 75 mg of alirocumab will be described as well as the detailed reasons that triggered the down-titration.

Further details will be provided in SAP.

11.4.5 Analyses of patient's acceptability of self-injection (see Section 9.2.3)

Analysis of the SIAQ will be conducted on the safety population.
A descriptive summary of total and domain scores will be provided for each visit and change from baseline at Weeks 4, 8, 12, 24, 48, 72 and 96.

Further details will be provided in the SAP.

11.5 INTERIM ANALYSIS

No formal interim analysis is planned for this study. However some descriptive analyses might be performed before the end of the study in order to support the submission of a reimbursement dossier if requested by local health authorities.

12 ETHICAL AND REGULATORY CONSIDERATIONS

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 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, delegated Investigator staff and Sub-investigator, in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, and the ICH guidelines for GCP, all applicable laws, rules and regulations.

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

12.4 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 must be reviewed and approved by the Sponsor prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval/favorable opinion.

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

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

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

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

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

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

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

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

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

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

13.2 RESPONSIBILITIES OF THE SPONSOR

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

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

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, the monitoring team must check the CRF entries against the source documents, except for the pre-identified source data directly recorded in the CRF. The informed consent form will include a statement by which the patient allows the Sponsor's duly authorized personnel, the Ethics Committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the CRFs (eg, patient's medical file, appointment books, original laboratory records). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

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

It is the responsibility of the Investigator to maintain adequate and accurate CRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner.

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

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

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

13.5 USE OF COMPUTERIZED SYSTEMS

The complete list of computerized systems used for the study is provided in a separate document which is maintained in the Sponsor and Investigator study files.

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

- For data management activities, Inform 5.0.
- For statistical activities, SAS.
- For pharmacovigilance activities, AWARE, Business Object XI.
- For monitoring activities, Clubnet.
- For medical writing activities, DOMASYS.

External data loading is planned for this clinical trial.

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

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

14.2 RECORD RETENTION IN STUDY SITES

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

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

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

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

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

14.3 CONFIDENTIALITY

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

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

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

14.4 PROPERTY RIGHTS

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

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

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

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

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

14.5 DATA PROTECTION

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

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

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

14.6 INSURANCE COMPENSATION

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

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

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

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

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

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

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

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

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

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

14.8.1 By the Sponsor

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

- The information on the product leads to doubt as to the benefit/risk ratio.
- Patient enrollment is unsatisfactory.
- The Investigator has received from the Sponsor all IMP, means and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon.
- Non-compliance of the Investigator or Subinvestigator, delegated staff with any provision of the clinical trial protocol, and breach of the applicable laws and regulations or breach of the ICH GCP.
- The total number of patients is included earlier than expected.

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

14.8.2 By the Investigator

The Investigator may terminate his/her participation upon thirty (30) days' prior written notice if the study site or the Investigator for any reason becomes unable to perform or complete the clinical trial.

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

14.9 CLINICAL TRIAL RESULTS

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

14.10 PUBLICATIONS AND COMMUNICATIONS

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

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

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

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

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

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

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

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

In some instances, an amendment may require a change to the 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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17 APPENDICES

Appendix A Summary of TLC Diet for High Cholesterol

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

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

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

Appendix B WHO Criteria (Dutch Lipid Network clinical criteria) for diagnosis of Heterozygous Familial Hypercholesterolemia (heFH)

Diagnostic Scoring for Heterozygous Familial Hypercholesterolemia			
Family history			
a First degree relative with known premature (men <55 yrs, women <60 yrs) coronary and vascular disease. OR			1
b First degree relative with known LDL-cholesterol >95th percentile for age and sex.			
and/or			
a First degree relative with tendon xanthomata and/or arcus cornealis. OR			2
b Children below 18 yrs. with LDL-cholesterol >95th percentile for age and sex.			
Clinical history			
a Patient has premature (men <55 yrs, women <60 yrs) coronary artery disease			2
b Patient has premature (men <55 yrs, women <60 yrs) cerebral or peripheral vascular disease.			1
Physical examination			
a Tendon xanthomata			6
b Arcus cornealis below the age of 45 yrs.			4
Laboratory analysis			
	mmol/L	mg/dL	
a LDL-cholesterol	>8.5	>325	8
b LDL-cholesterol	6.5-8.4	251-325	5
c LDL-cholesterol	5.0-6.4	190-250	3
d LDL-cholesterol	4.0-4.9	155-190	1
Deoxyribonucleic acid (DNA)-analysis			
a Functional mutation low-density lipoprotein receptor gene present			8
Diagnosis of heFH is:			
Definite When		>8 points	
Probable When		6-8 points	
Possible When		3-5 points	

Appendix C Simon Broome Register Diagnostic Criteria for Heterozygous Familial Hypercholesterolemia

Definite familial hypercholesterolemia is defined as:

- Total-C >6.7 mmol/L (260 mg/dL) or LDL cholesterol above 4.0 mmol/L (155 mg/dL) in a child <16 years or Total-C >7.5 mmol/L (290 mg/dL) or LDL cholesterol above 4.9 mmol/L (190 mg/dL) in an adult. (Levels either pre-treatment or highest on treatment).

  PLUS

- Tendon xanthomas in patient, or in 1st degree relative (parent, sibling, child), or in 2nd degree relative (grandparent, uncle, aunt).

  OR

- DNA-based evidence of an LDL receptor mutation or familial defective apo B-100.

Possible familial hypercholesterolemia is defined as:

- Total-C >6.7 mmol/L (260 mg/dL) or LDL cholesterol above 4.0 mmol/L (155 mg/dL) in a child <16 years or Total-C >7.5 mmol/L (290 mg/dL) or LDL cholesterol above 4.9 mmol/L (190 mg/dL) in an adult. (Levels either pre-treatment or highest on treatment).

And at least one of the following:

- Family history of myocardial infarction below 50 years of age in 2nd degree relative or below 60 years of age in 1st degree relative.
- Family history of raised cholesterols >7.5 mmol/L (290 mg/dL) in adult 1st or 2nd degree relative or >6.7 mmol/L (260 mg/dL) in child or sibling under 16 years of age.

Appendix D The Stages of Heart Failure – NYHA classification

Physicians often assess the stages of heart failure according to the New York Heart Association (NYHA) functional classification system. This system relates to symptoms to everyday activity and the patient's quality of life.

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

Appendix E Summary of Adverse Events reporting instructions at Sanofi

EVENT CATEGORY	REPORTING TIMEFRAME	SPECIFIC EVENTS IN THIS CATEGORY	CASE REPORT FORM COMPLETION		
			AE form	Safety complementary Form [a]	Other specific forms
Adverse event (non-SAE, non-AESI)	Routine	Any AE that is not SAE or AESI	Yes	No	No
Serious Adverse Event (non-AESI or AESI)	Expedited (within 24 hours)	Any AE meeting seriousness criterion per Section 10.4.1.2	Yes	Yes	No, unless applicable
Adverse Event of Special Interest (AESI)	Expedited (within 24 hours)	Pregnancy of female patient/subject (including male subject's partner as described in Section 10.4.1.3)	Yes	Yes	Yes
		Symptomatic overdose with IMP	Yes	Yes	No
		Increase in ALT as follows: - ALT ≥3 ULN (if baseline ALT <ULN) or - ALT ≥2 times the baseline value (if baseline ALT ≥ULN) Please refer to related flowchart (per Appendix C)	Yes	Yes	Yes
		Allergic drug reactions and/or local injection site reactions deemed to be allergic and requiring consultation with another physician as specified in Section 10.4.1.3.	Yes	Yes	Yes [b]
		Neurologic events (requiring additional examinations/procedures and/or consultation with a specialist as specified in Section 10.4.1.3)	Yes	Yes	Yes
		Neurocognitive events (Section 10.4.1.3)	Yes	Yes	Yes
Local injection site reaction	Routine	Non-allergic or allergic not requiring consultation with another physician, as described in Section 10.4.1.4.	Yes	No	Yes [b]

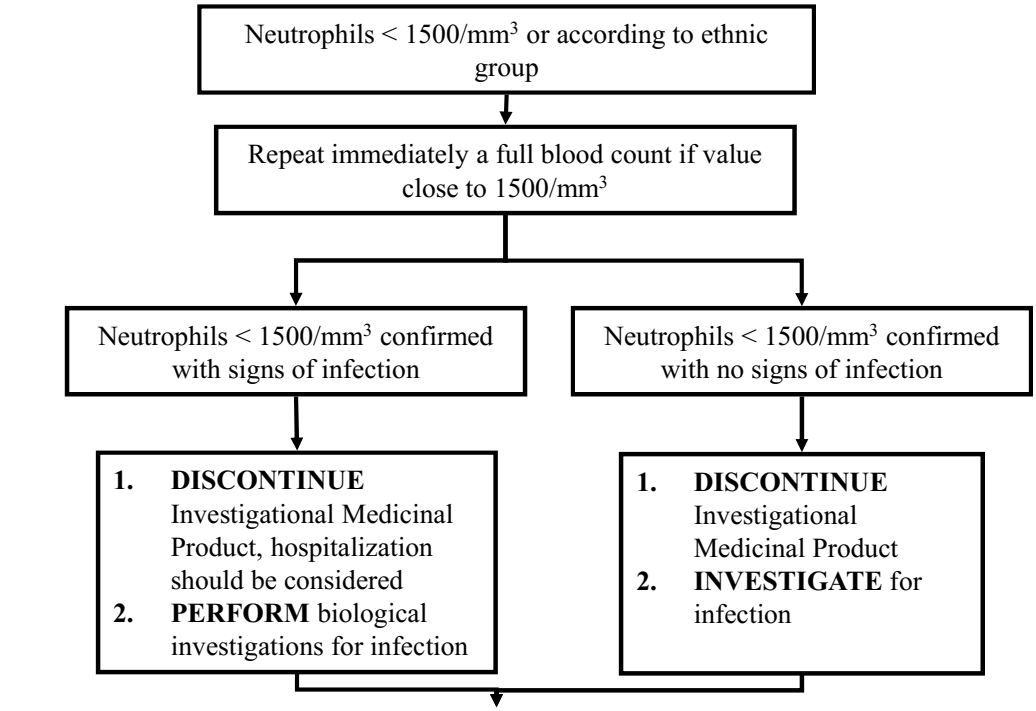
EVENT CATEGORY	REPORTING TIMEFRAME	SPECIFIC EVENTS IN THIS CATEGORY	CASE REPORT FORM COMPLETION		
			AE form	Safety complementary Form [a]	Other specific forms
Laboratory or vital sign abnormality (non-SAE, non-AESI) that is: - Symptomatic - Requiring corrective treatment or consultation - Leading to IMP discontinuation or dose regimen modification	Routine	- Neutropenia - Thrombocytopenia - Acute renal insufficiency - Increase in CPK and suspicion of rhabdomyolysis Per Appendix C.	Yes	No	No

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

b. General allergic reaction or local site reaction sections of the Complementary Form should be completed as applicable according to the type of reaction (general or local). However, for local injection site reactions that progress/expand/worsen/etc, both sections (local and general) of the Complementary Form should be completed.

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

NEUTROPENIA

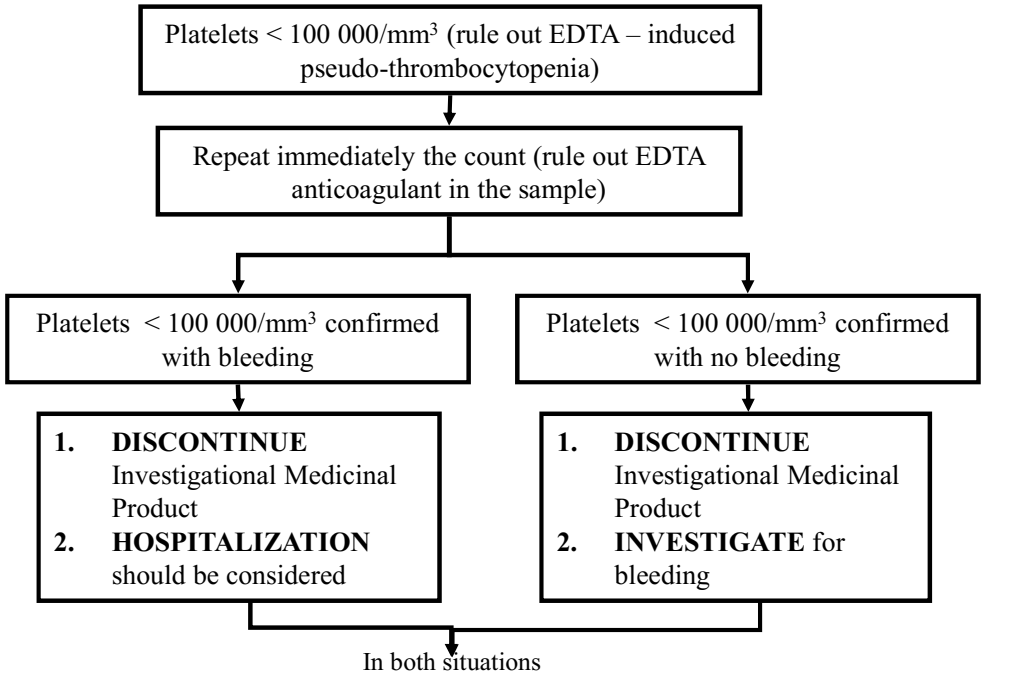


3. **INFORM** the local monitor
4. **INVESTIGATE** previous treatments particularly long-term, even a long time ago, exposure to toxic agents, e.g., benzene, X-rays, etc.
5. **PERFORM** and collect the following investigations (results):
   - RBC and platelet counts
   - Serology: EBV, (HIV), mumps, measles, rubella
6. **DECISION** for bone marrow aspiration: to be taken in specialized unit
7. **COLLECT/STORE** one sample following handling procedures described in PK sections **(for studies with PK sampling)** and freeze one serum sample (5 mL) on Day 1 (cessation of investigational medicinal product) and Day 5 (for further investigations)
8. **MONITOR** the leukocyte count 3 times per week for at least one week, then twice a month until it returns to normal

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

Neutropenia is to be recorded as AE only if at least one of the criteria listed in Section 10.4.3 is met

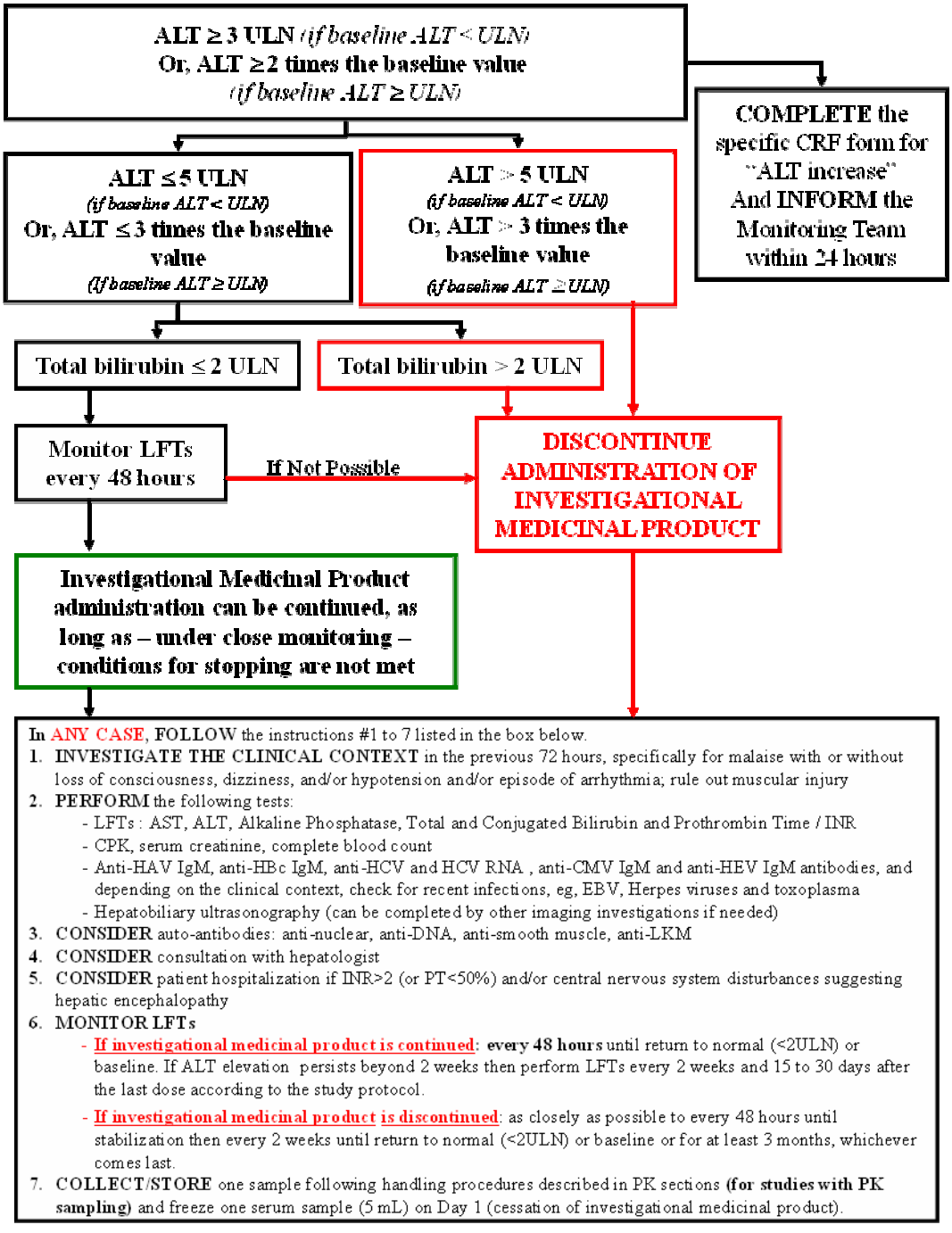
THROMBOCYTOPENIA



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

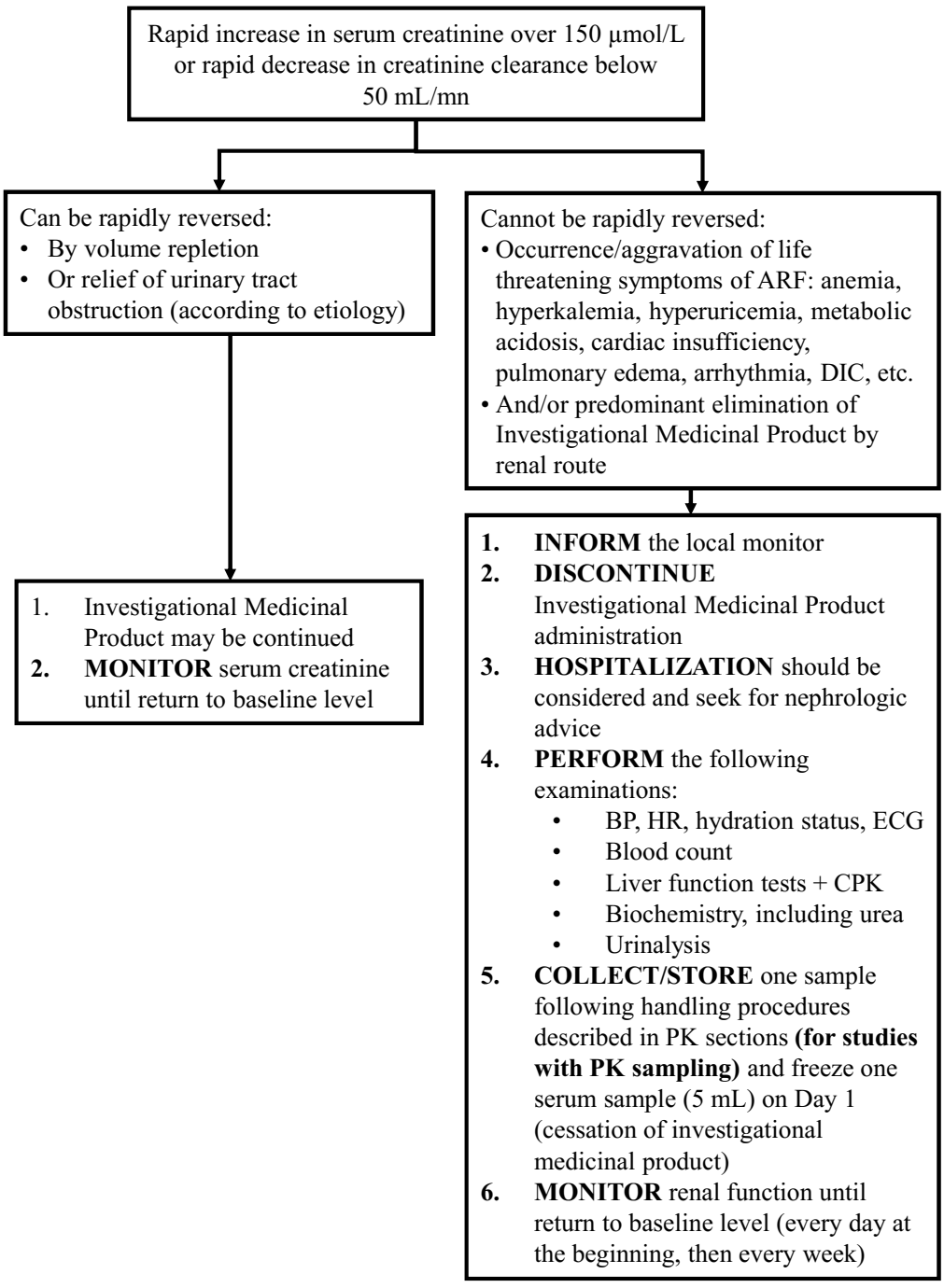
Thrombocytopenia is to be recorded as AE only if at least one of the criteria listed in Section 10.4.3 is met

INCREASE IN ALT



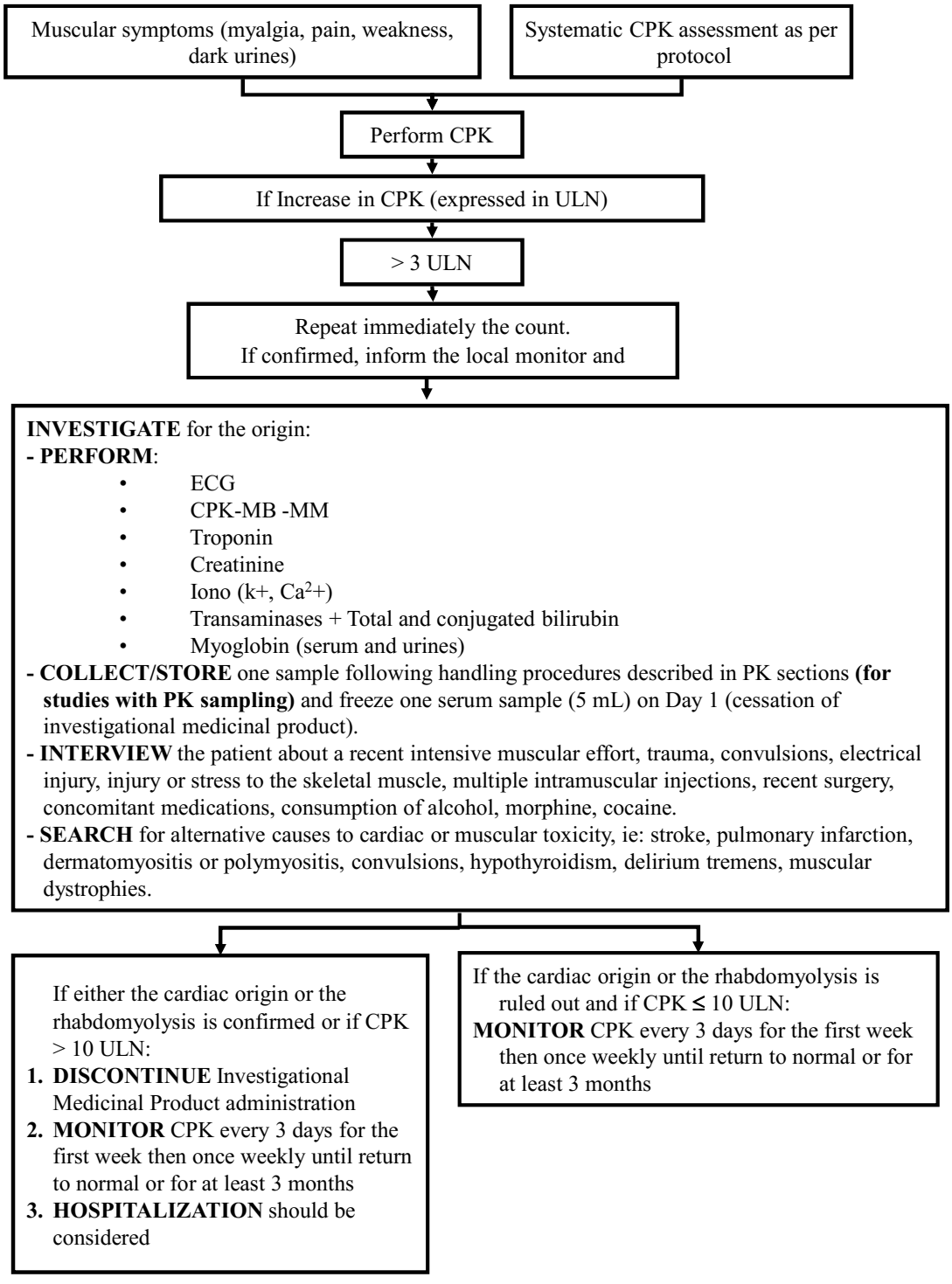
NOTE: ALT ≥ 3 ULN (if baseline ALT < ULN) or ALT ≥ 2 TIMES THE BASELINE VALUE (if baseline ALT ≥ ULN) SHOULD BE NOTIFIED WITHIN 24 HOURS TO THE MONITORING TEAM (SEE Section 10.4.1.3, Section 10.4.4, and Section 10.4.5). IN ADDITION, IF ALT < 3 ULN MEETS A SERIOUSNESS CRITERION, THE EVENT SHOULD BE NOTIFIED WITHIN 24 HOURS TO THE MONITORING TEAM

ACUTE RENAL FAILURE



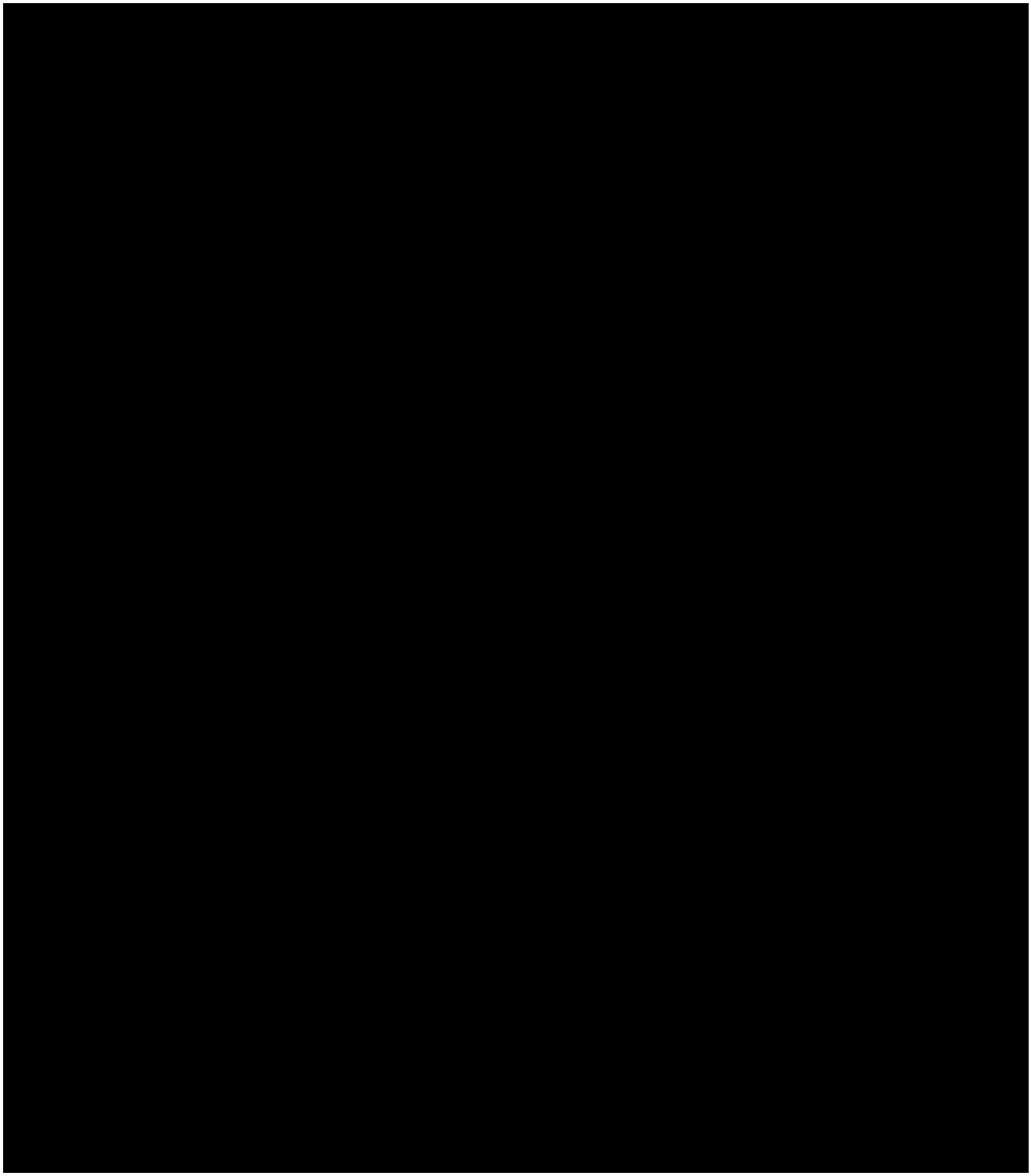
Acute renal failure is to be recorded as AE only if at least one of the criteria listed in Section 10.4.3 is met

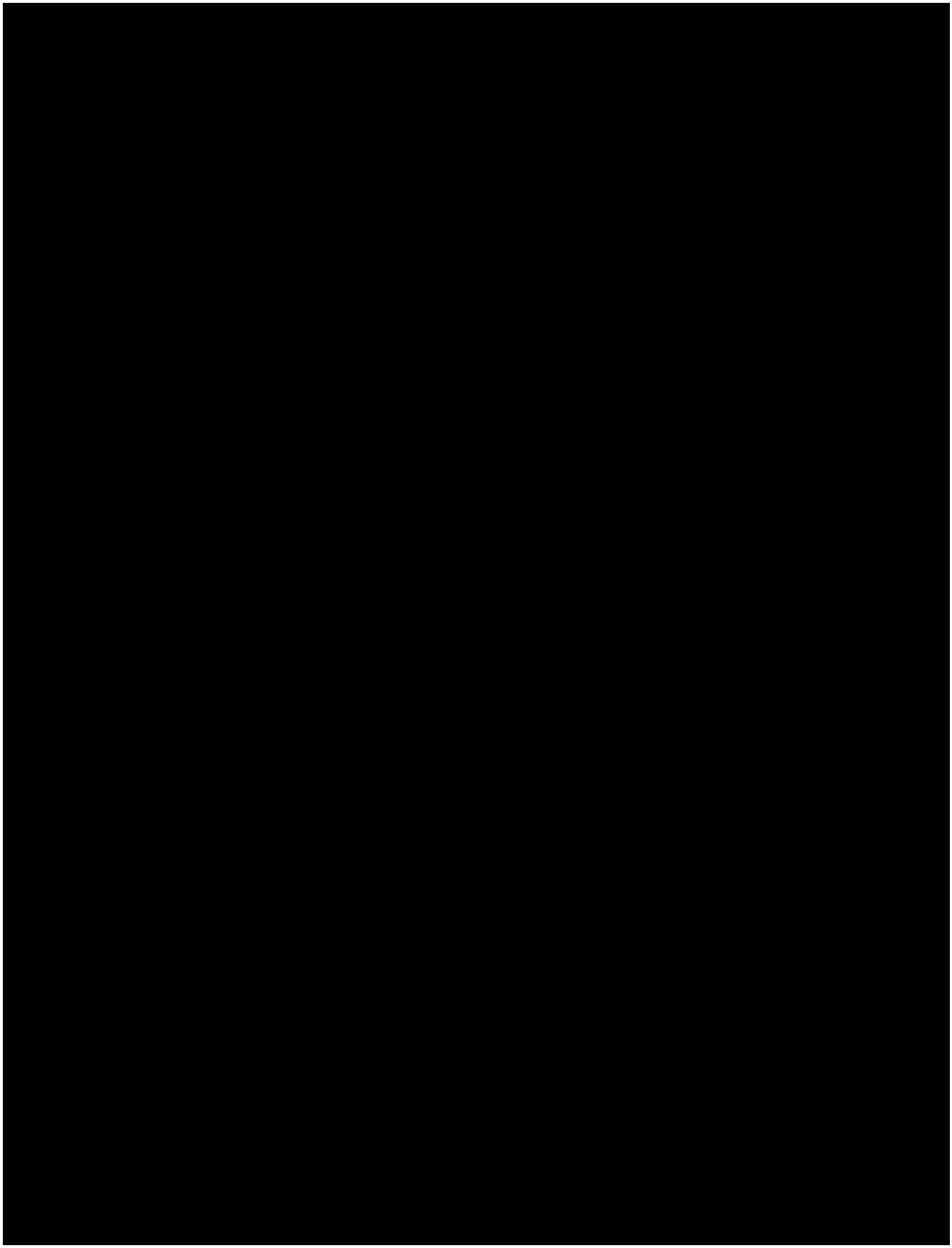
SUSPICION OF RHABDOMYOLYSIS

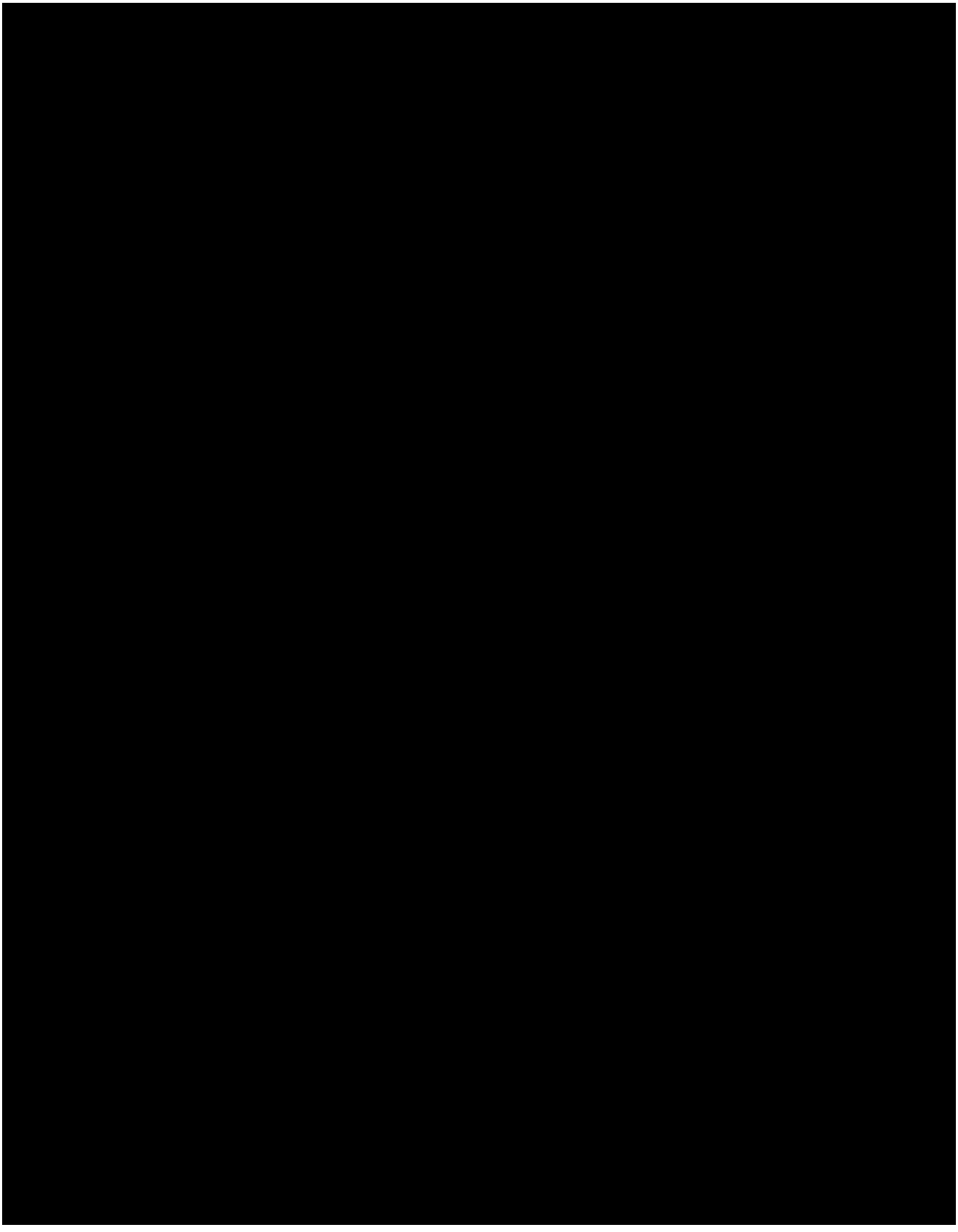


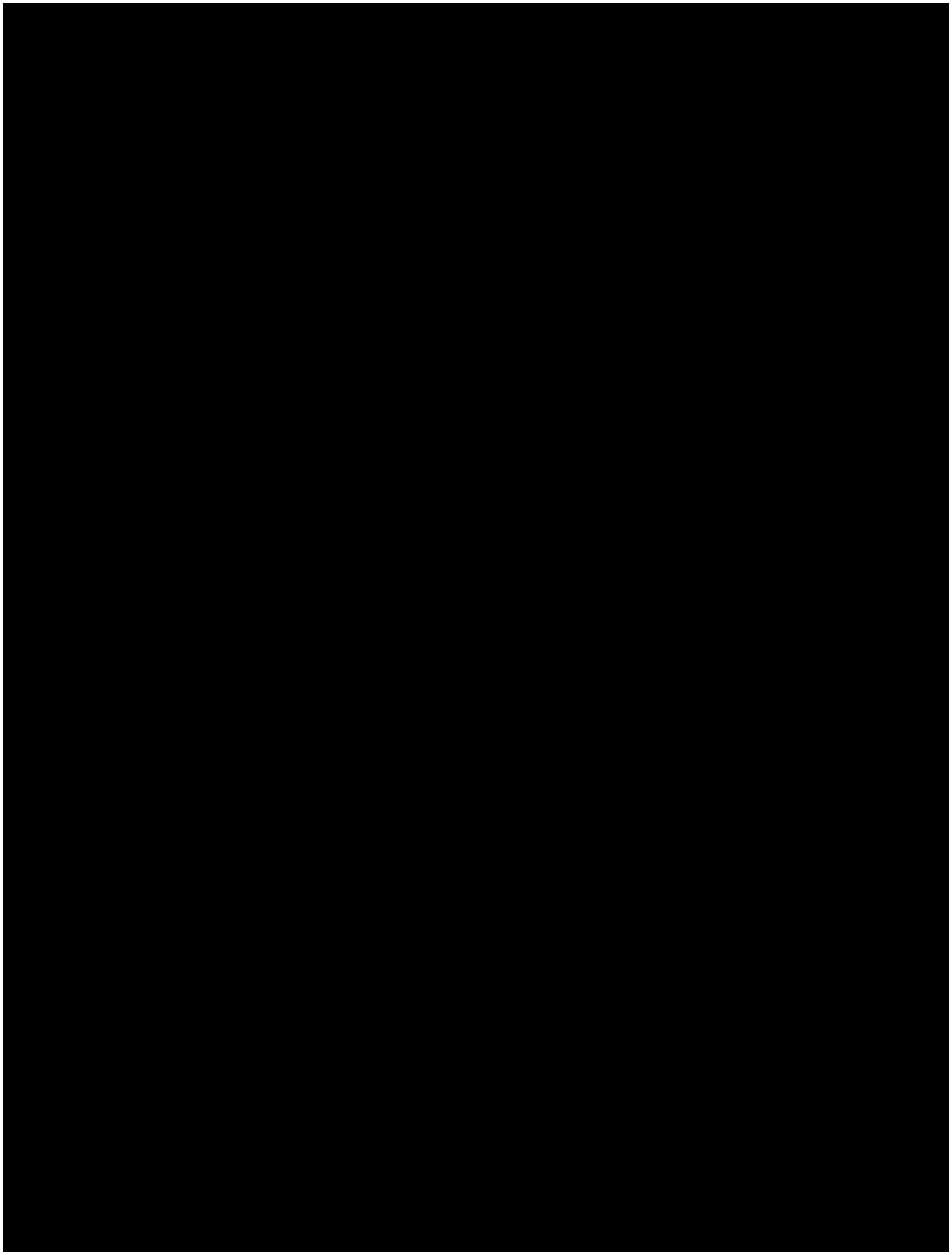
Suspicion of rhabdomyolysis is to be recorded as AE only if at least one of the criteria listed in Section 10.4.3 is met

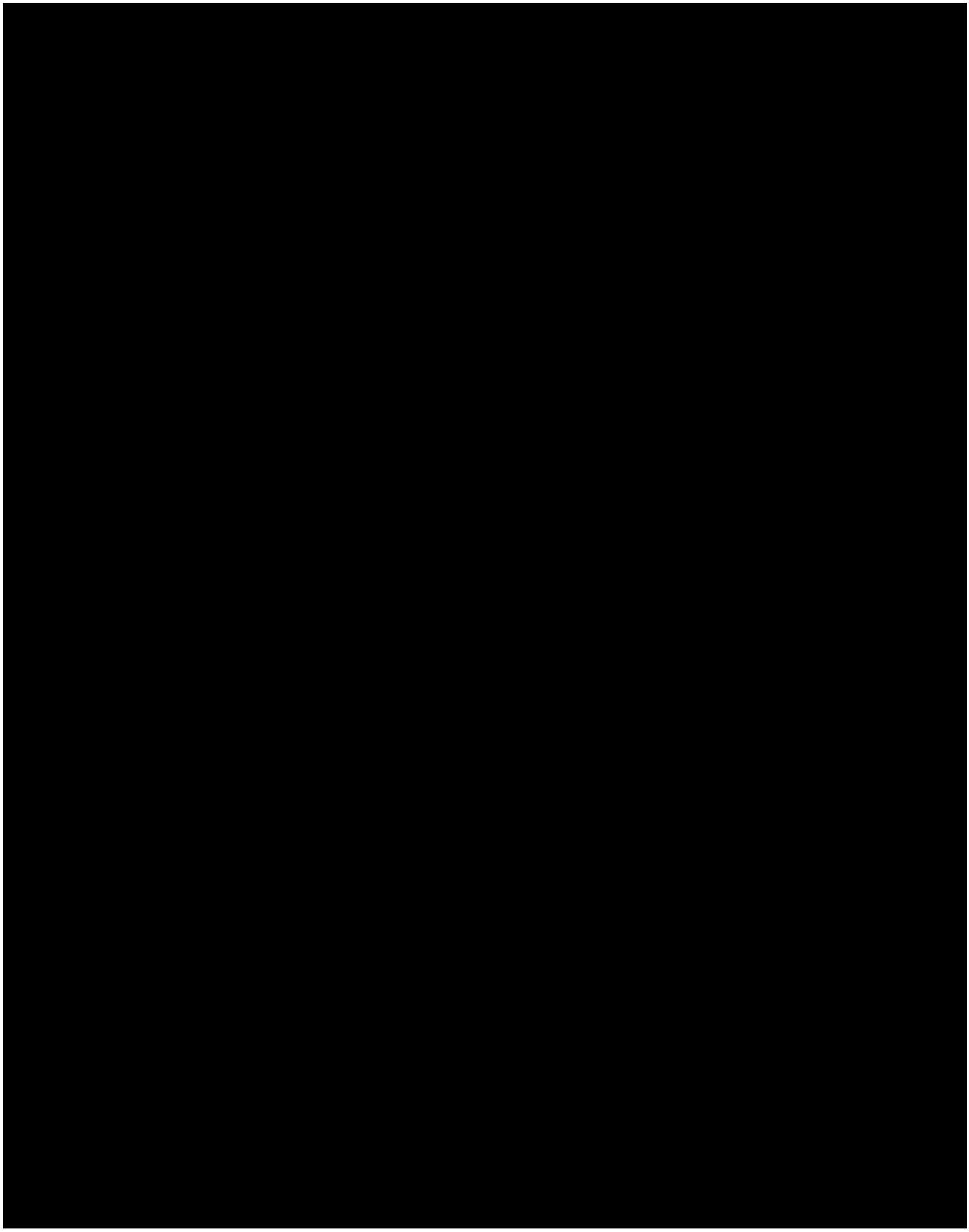
Appendix G Self-injection Assessment Scale (SIAQ)

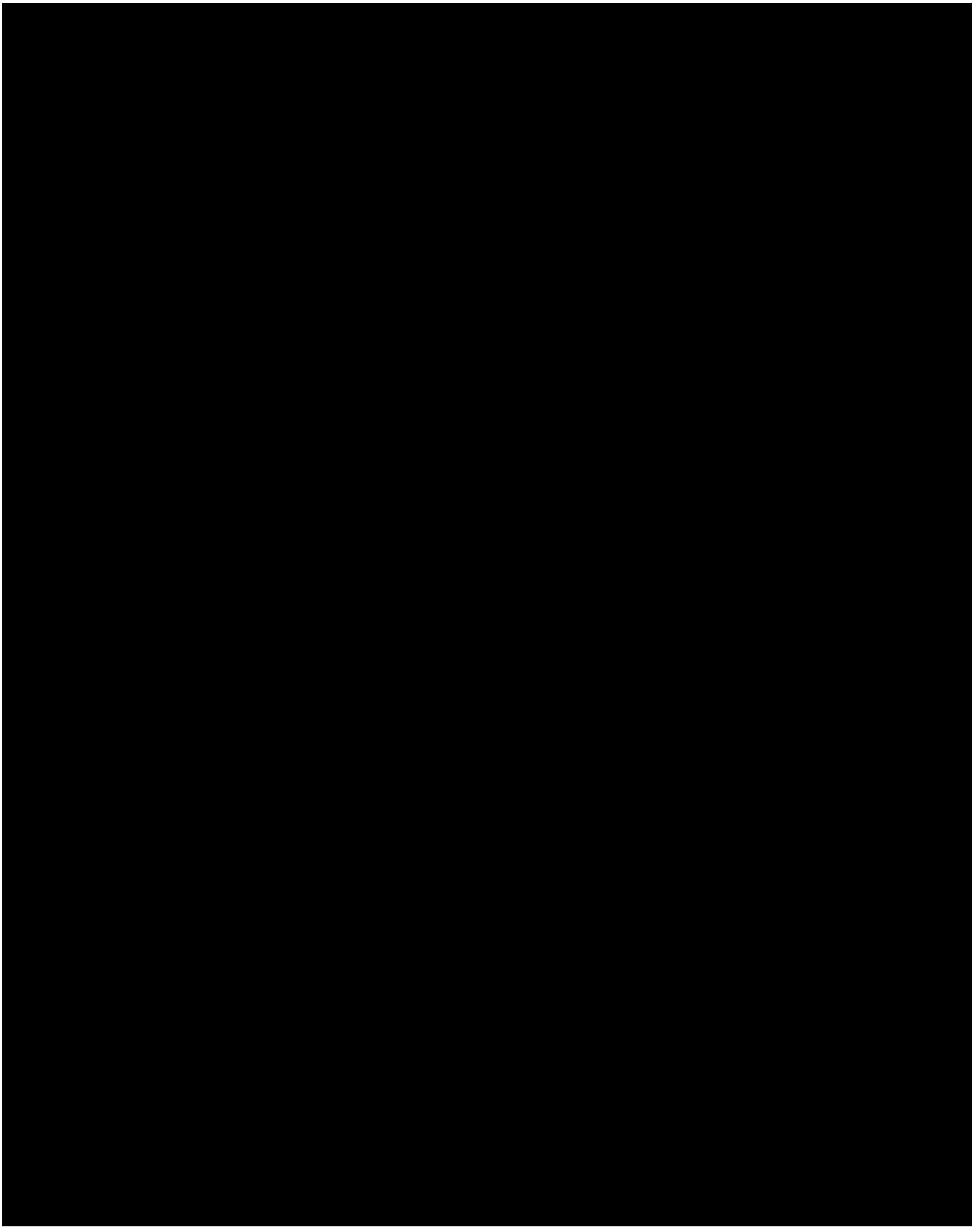


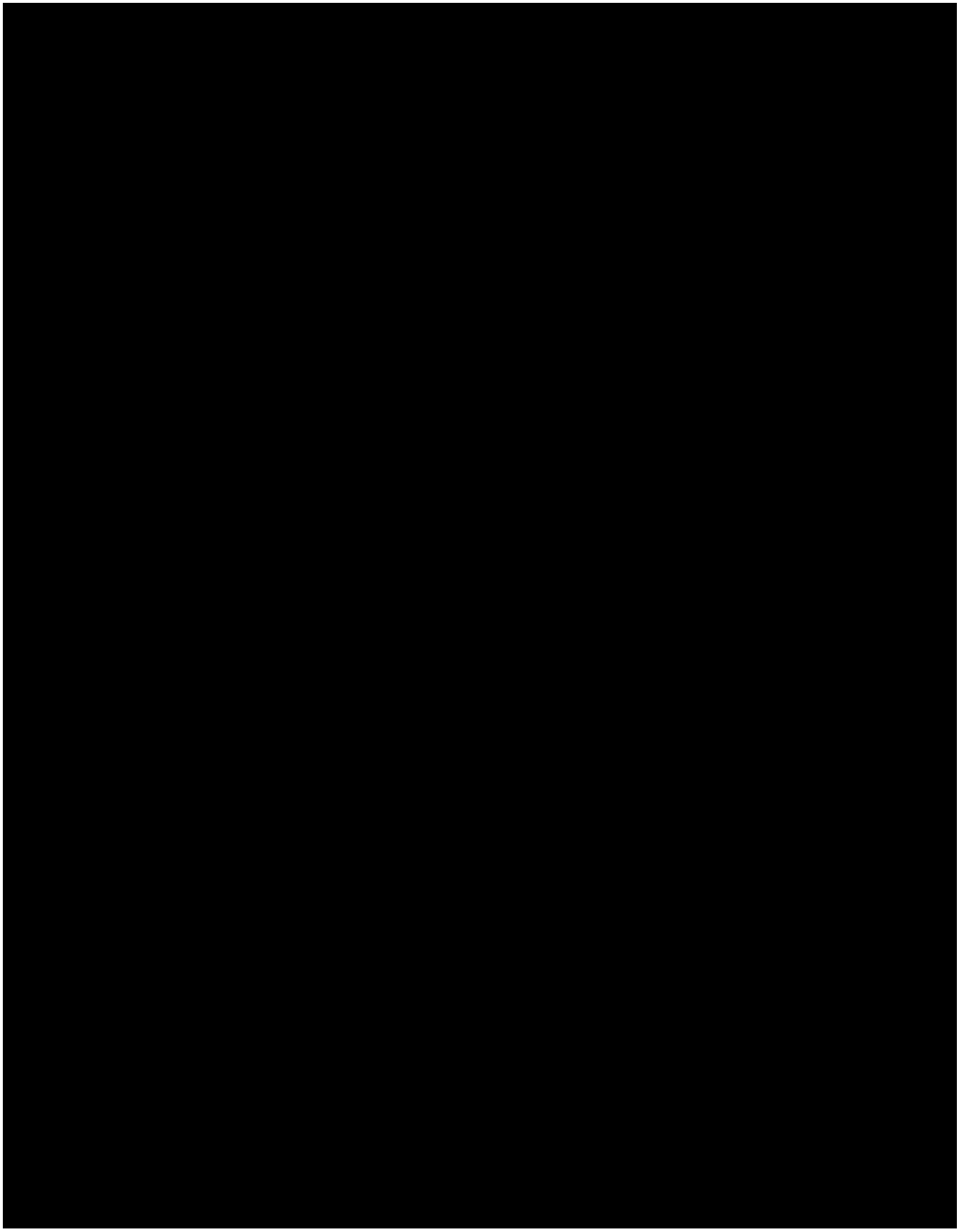


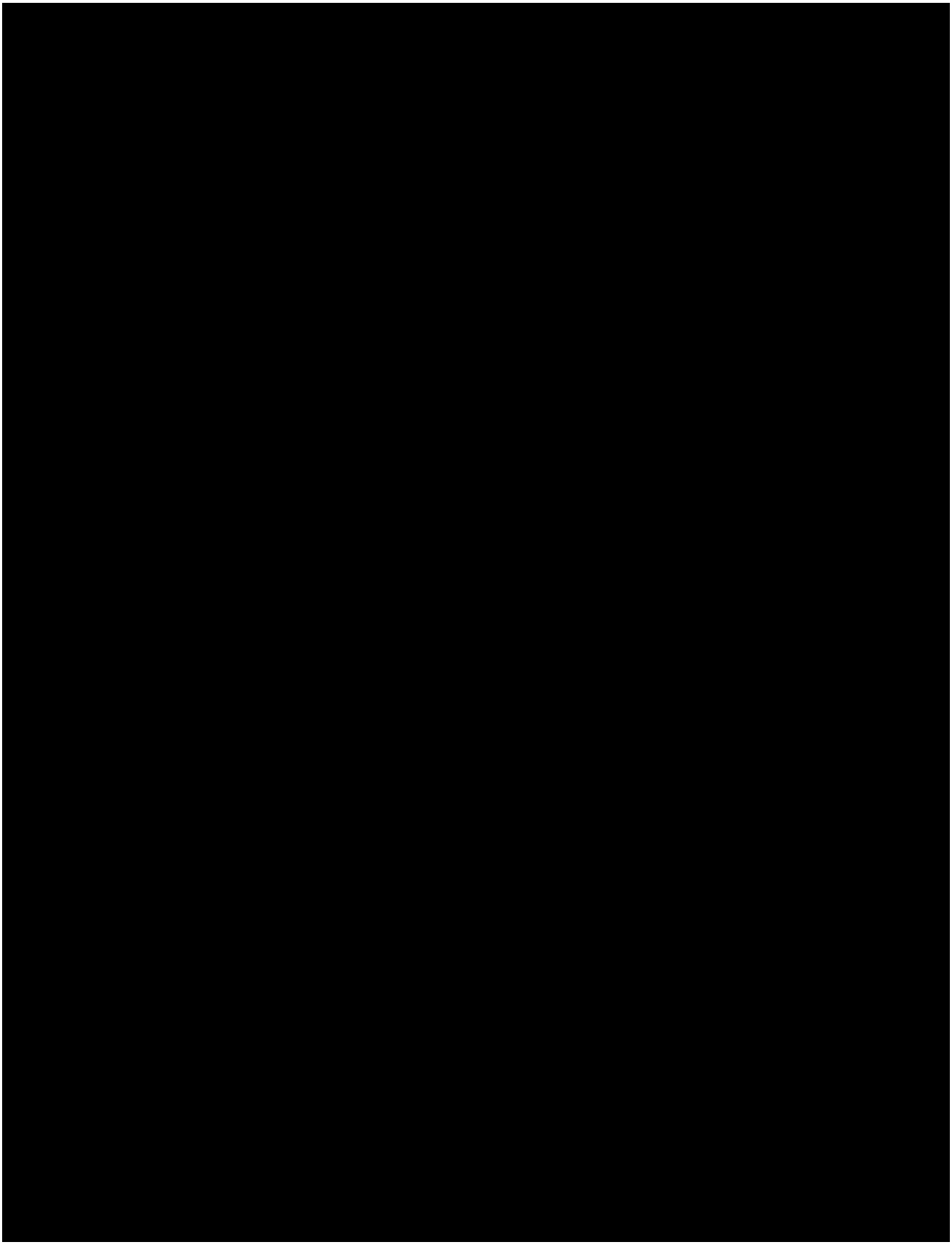












Appendix H Assessment of Local Injection Site Reactions

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

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

*** Please specify the other signs or symptoms (for example, hematoma, discoloration, reactivation, etc.).

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

Appendix I Guidance on contraceptive methods for Denmark only

The acceptable methods of contraception for female subjects included in this study in Denmark will include the following:

- Intra-uterine devices (IUD).
- Hormonal contraceptives (contraceptive pills, implants, transdermal patches, hormonal vaginal devices or injections with prolonged release).
- Subjects using a double-barrier contraceptive method (condom used with a diaphragm for example). However, this is limited to exceptional cases or conditions where the patient cannot use other contraceptive methods (ie, hormonal contraceptives or IUD).
- Subjects having a sterilized permanent partner may be allowed to participate.

The allowed methods of contraception can also be described in the patient's information (subject information leaflet.

Appendix J Guidance on contraceptive methods for Sweden only

The acceptable methods of contraception for female subjects included in this study in Sweden will include the following:

Women of childbearing potential must use a highly-effective contraceptive method throughout the study treatment, and for 10 weeks after the last IMP injection for those patients who discontinue prematurely.

Below a list of contraceptive methods considered as highly-effective method for birth control:

- Oral (except low-dose gestagen (lynestrenol and norestisteron)), injectable, or implanted hormonal contraceptives.
- Intrauterine device.
- Intrauterine system (for example, progestin-releasing coil).
- Vasectomized male (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate) for 10 weeks after the last IMP injection for those patients who discontinue prematurely.

Appendix K Guidance on contraceptive methods and collection of pregnancy information

DEFINITIONS

Nonreproductive potential

1. Premenopausal female with 1 of the following:
   - Documented hysterectomy,
   - Documented bilateral salpingectomy,
   - Documented bilateral oophorectomy.
2. Postmenopausal
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use 1 of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

Reproductive potential (WOCBP)

A woman is considered of reproductive potential (WOCBP), ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

CONTRACEPTIVE GUIDANCE

Male subjects

- Male subjects with heterosexual partners of reproductive potential (WOCBP) are eligible to participate if they agree to use the following during the protocol defined timeline:
  - Refrain from donating sperm,

    and
  - At least 1 of the following conditions applies:
    - Are and agree to remain abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle,

      or
    - Agree to use a male condom plus an additional contraceptive method with a failure rate of <1% per year (see table for female subjects).
- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom for the time defined in the protocol.

Highly Effective Contraceptive Methods That Are User Dependent
Failure rate of <1% per year when used consistently and correctly [a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation b - oral - intravaginal - transdermal
• Progestogen-only hormone contraception associated with inhibition of ovulation [b] - oral - injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation [b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method(s) of contraception should be used. Spermatogenesis cycle is approximately 90 days.)*
• Sexual abstinence (Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case TWO highly effective methods of contraception should be used during the treatment period and for at least [XX, corresponding to time needed to eliminate study treatment plus 30 days for study treatments with genotoxic potential] after the last dose of study treatment.

Female subjects:

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly* [a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation [b] - oral - intravaginal - transdermal
• Progestogen-only hormone contraception associated with inhibition of ovulation [b] - oral - injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation [b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method(s) of contraception should be used. Spermatogenesis cycle is approximately 90 days.)*
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)*
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case TWO highly effective methods of contraception should be used during the treatment period and for at least [XX, corresponding to time needed to eliminate study treatment plus 30 days for study treatments with genotoxic potential] after the last dose of study treatment.

COLLECTION OF PREGNANCY INFORMATION

Male subjects with partners of reproductive potential who become pregnant

- The Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. This applies only to subjects who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor.
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure

Female subjects who become pregnant

- The Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on participant and neonate, which will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the Investigator, will be reported to the Sponsor as described in Section 10.4. While the Investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

Appendix L Country-specific requirement

Will be added as necessary by the concerned country.