CLINICAL TRIAL PROTOCOL

COMPOUND: Praluent® (alirocumab)

A multicenter, randomized, open-label, parallel-group usability study of the commercial 1 mL alirocumab auto-injector device (AI) and the new 2 mL auto-injector device (SYDNEY) in high or very high cardiovascular risk patients with hypercholesterolemia not adequately controlled with their lipid-modifying therapy

STUDY NUMBER: MSC14864

NCT Number: NCT03415178

Version Number:	1	EudraCT IND Number(s) WHO universal trial number:	Not applicable 105574 Not applicable
Date:	20-Nov-2017	Total number of pages:	100

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CLINICAL TRIAL SUMMARY

COMPOUND: PRALUENT® (alirocumab)	**STUDY No.: MSC14864**
TITLE	A multicenter, randomized, open-label, parallel-group usability study of the commercial 1 mL alirocumab auto-injector device (AI) and the new 2 mL auto-injector device (SYDNEY) in high or very high cardiovascular risk patients with hypercholesterolemia not adequately controlled with their lipid-modifying therapy
INVESTIGATOR/TRIAL LOCATION	Multicenter, USA
PHASE OF DEVELOPMENT	Phase 3
STUDY OBJECTIVE(S)	**Primary objective**: • To collect 12 weeks of real-use (usability) data assessing the robustness and user interaction of the new alirocumab auto-injector device (which is referred to as SYDNEY), in unsupervised settings on Weeks 4, 8, and 12. **Secondary objectives:** Device-related: • To collect real-use (usability) data assessing the robustness and user interaction of SYDNEY and the current 1 mL alirocumab auto-injector device (which is referred to as AI) in supervised settings on Week 0 (Day1). Pharmacokinetics: • To compare alirocumab pharmacokinetics (PK) 300 mg every 4 weeks (Q4W) administered using SYDNEY and AI, from baseline until Week 4. • To evaluate alirocumab PK 300 mg Q4W administered using SYDNEY, until Week 16. Anti-drug antibodies: • To evaluate the development of anti-drug (alirocumab) antibodies (ADA). Efficacy/pharmacodynamics: • To compare the percent and absolute change in LDL-C from baseline to Week 4 using SYDNEY and AI. • To evaluate the percent and absolute change in LDL-C from baseline to Weeks 8, 12 and 16, using SYDNEY. Safety: • To evaluate the safety and tolerability of alirocumab 300 mg Q4W, using both SYDNEY and AI.
STUDY DESIGN	This is a multicenter, randomized, open-label, 16-week study, with 2 parallel arms (parallel-arms period) for the first 4 weeks, and then only one arm (single-arm period) for the subsequent weeks until Week 16. Patients will be randomized to receive self-administered alirocumab 300 mg Q4W via either SYDNEY or AI for the first injection on Week 0 (Day 1).

	Subsequently, all patients will receive self-administered alirocumab 300 mg Q4W via SYDNEY for the 2nd, 3rd and 4th injections on Week 4 (Day 29), Week 8 (Day 57) and Week 12 (Day 85).
STUDY POPULATION **Main selection criteria**	**Main Inclusion Criteria:** • Patients are in either category A or B (below), and are not adequately controlled with a stable daily dose of atorvastatin (20 mg or 40 mg), or rosuvastatin (10 mg or 20 mg) for at least 4 weeks prior to the screening visit (Week -2), with or without other lipid-modifying therapy (LMT). A) Patients with heterozygous familial hypercholesterolemia (heFH)** ***Diagnosis of heFH must be made either by genotyping or by clinical criteria. For those patients not genotyped, the clinical diagnosis may be based on either the WHO criteria/Dutch Lipid Clinical Network criteria with a score >8 points or the Simon Broome register diagnostic criteria with a criterion for definite FH.* **OR** B) Non-FH patients at high or very high cardiovascular (CV) risk. High and very high cardiovascular risk patients include patients with coronary heart disease (CHD), non-CHD cardiovascular disease (CVD), and other risk factors. • Patient willing and able to self-inject for the duration of the study. • Signed Written Informed Consent Form. **Key Exclusion Criteria:** • LDL-C <70 mg/dL (<1.81 mmol/L) at the screening visit (Week-2). • Currently taking a daily dose of statin that is not atorvastatin 20 mg or 40 mg, or rosuvastatin 10 mg or 20 mg. • Not on a stable dose of LMT (including statin) for at least 4 weeks, prior to the screening visit (Week- 2) and from screening to randomization. • Having previously used any device for the proprotein convertase subtilisin/kexin type 9 (PCSK9)) inhibitor administration, or having participated in any clinical trial for a PCSK9 inhibitor. • Fasting serum Triglyceride (TG) >400 mg/dL (>4.52 mmol/L) at the screening visit (Week-2).
Total expected number of patients	66 randomized patients : • A group of 33 patients using SYDNEY in the entire study treatment period, • A group of 33 patients using AI for the first 4 weeks (parallel-arms period), then switching to SYDNEY (during the single-arm period).

STUDY TREATMENT(s) **Investigational Medicinal Product A (new auto-injector device)**	Alirocumab delivered via the new 2 mL auto-injector device (SYDNEY).
Formulation:	Sterile alirocumab drug product supplied at a concentration of 150 mg/mL in histidine (6 mM), polysorbate 20 (0.1 mg), sucrose (100 mg), and Water for Injection USP, to pH 6.0.
Route(s) of administration: **Dose regimen:**	Subcutaneous (SC) in the abdomen or thigh (site of injection to be documented). 300 mg Q4W administered as 1 single injection of 2 mL. Self-administration on: • Week 0 (Day 1), at the investigator site, supervised. • Week 4 (Day 29) and Week 8 (Day 57) at the investigator site, or at home , unsupervised. • Week 12 (Day 85) at the investigator site, observed only (also considered unsupervised).
Investigational Medicinal Product B (current auto-injector device) **Formulation:** **Route(s) of administration:** **Dose regimen:**	Alirocumab delivered via the current (commercial) 1 mL auto-injector device (AI). Sterile alirocumab drug product supplied at a concentration of 150 mg/mL in histidine (6 mM), polysorbate 20 (0.1 mg), sucrose (100 mg), and Water for Injection USP, to pH 6.0. Subcutaneous (SC) in the abdomen or thigh (site of injection to be documented). 300 mg Q4W administered as 2 injections of 1 mL. Self-administration on: • Week 0 (Day 1), at the investigator site, supervised.
ENDPOINT(S)	**Primary endpoint:** Number (%) and types of SYDNEY-associated product technical complaints* (PTCs) at the unsupervised injections on Weeks 4, 8, and 12. **Secondary endpoints:** Device-related endpoints: • For both devices: - Number (%) of patients with auto-injector associated PTCs (overall and by type) at the supervised injections (Week 0, Day 1). - Injection experience questionnaire. • For SYDNEY only: - Number (%) of patients with a SYDNEY - associated PTC (overall and by type) at the unsupervised injections on Weeks 4, 8, and 12. - Patient perspective questionnaire. - Injection-Treatment Acceptance Questionnaire (I-TAQ©). Pharmacokinetics: • Alirocumab PK parameters after the first and the last dosing.

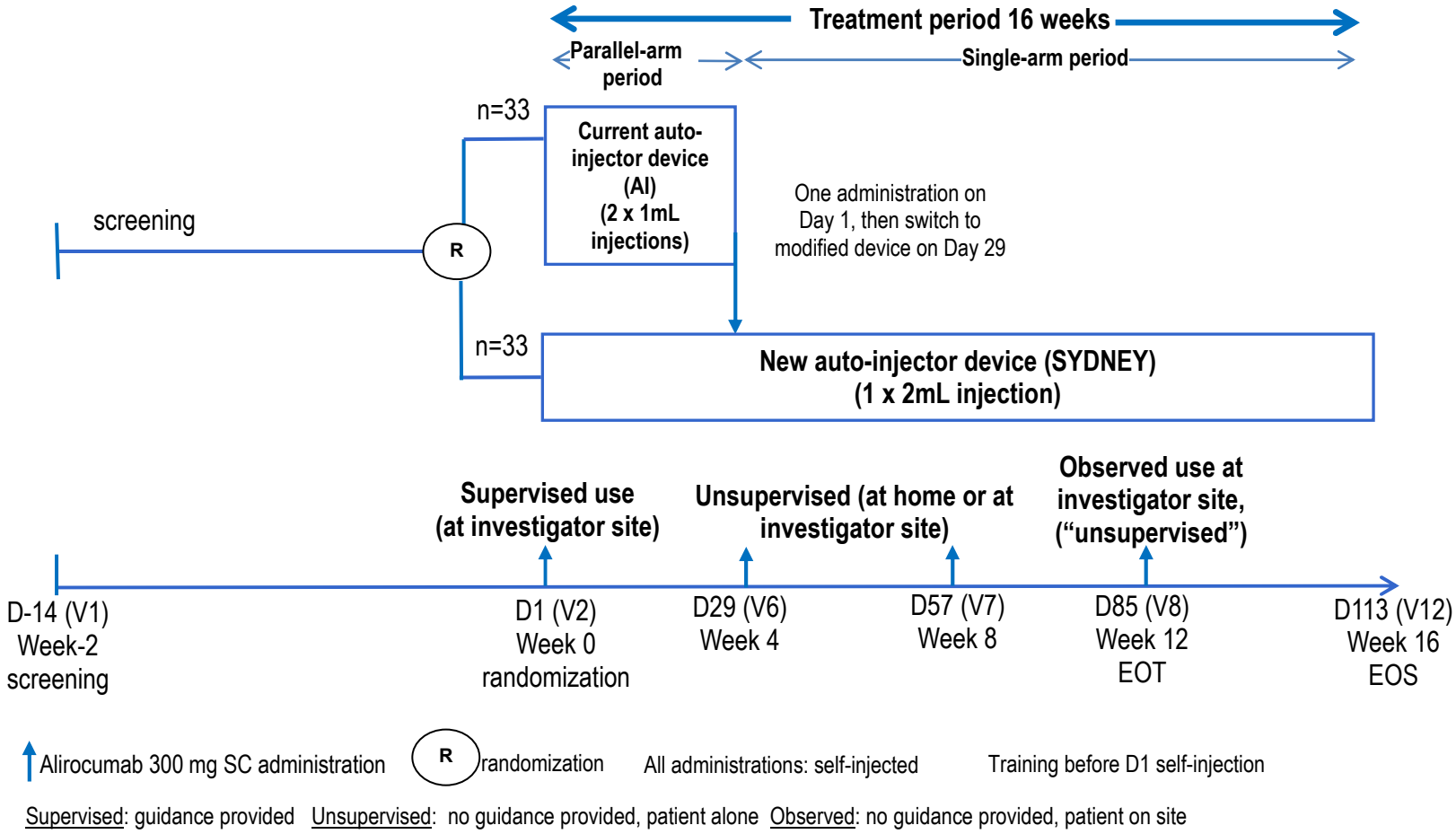
	• Free and total PCSK9 levels measured using PK serum samples. Anti-drug antibodies: • ADAs assessed throughout the study. Efficacy/pharmacodynamics: • Percent and absolute change from baseline in LDL-C at Weeks 4, 8, 12 and 16. Safety: • Adverse events (AEs), including Serious Adverse Events (SAEs) and Adverse events of special interest (AESIs), laboratory data, vital signs assessed throughout the study. ***PTC <u>Definition</u>**: All complaints that triggered an investigation by the Device Department will be categorized as device-related, patient- related, undetermined, or not related to device nor patient. **In this study, a PTC is defined as** any complaint reported on the Patient Complaint form that triggered an investigation by the Device Department and was categorized as either device-related, patient-related or undetermined, whether or not associated with an AE. Of note, the complaints categorized as not related to device nor patient will not be considered as a PTC. This definition will be used for both primary and secondary endpoints. ** In case a PTC is associated with the occurrence of an AE, the AE must be documented on an AE page in the electronic case report form (e-CRF) and the PTC must be described. In case a PTC is associated with the occurrence of a SAE, the SAE must be reported to the Monitoring Team in accordance with the SAE reporting procedures.*
ASSESSMENT SCHEDULE	The study will consist of the following visits: • Visit 1 (between Week -2 and Week 0), screening visit, on-site visit. • Visit 2 (Week 0, D1): randomization, baseline visit, on-site visit. • Visits 3 through 11 (Week 1 through Week 15): - Visits 3, 4, 5, 9, 10, and 11: PK sampling will be collected at these visits. These visits may be performed on site or as home-visits. - Visits 6 and 7 (Weeks 4 and 8): These visits may be performed on site or as home-visits. • Visit 8 (Week 12): end-of-treatment (EOT) Visit, on site • Visit 12 (Week 16): end-of-study (EOS) Visit, on site.
STATISTICAL CONSIDERATIONS	**Sample size determination** No formal sample size was calculated for this study: sample size is based on empirical considerations. Considering a drop-out rate of 10% it is proposed to randomize 66 patients overall (33 in each group) in order to ensure 60 evaluable patients overall (30 in each group) resulting in

	180 unsupervised planned injections using SYDNEY. Patients in the AI group will switch to SYDNEY group at the time of the second injection; therefore, it will ensure to have 60 evaluable patients using SYDNEY for the 2nd, 3rd and 4th unsupervised injections. With 60 evaluable patients using SYDNEY, a total of 180 unsupervised injections is expected to be achieved during the study. Expecting a maximum of 3 observed PTC over the 180 injections (observed PTC rate of 1.67%) with SYDNEY, the upper bound of the 2-sided 95% confidence interval (CI) calculated with the Wilson score method will be no higher than 5.2%. **Analysis population** The primary endpoint will be analyzed on the safety population of the single-arm period that will consist of all randomized patients who continue in the single-arm period (from Week 4, to Week 16), and receive at least 1 dose or part of a dose of Investigational Medicinal Product (IMP) during this period. **Analysis of the primary endpoint** The primary endpoint (ie, number (%) and type of SYDNEY-associated PTCs at the unsupervised injections) will be described on the safety population for the single-arm period. The number and % of PTCs will be provided with the 95% CI using Wilson score method. If applicable, the number of PTCs per patient will be described. **Analysis of secondary endpoints** All secondary device-related endpoints will be analyzed on the safety population using descriptive statistics. In addition, 95% CI for the number of PTCs, number and % of patients with any PTCs will be provided using Wilson score method. **Pharmacokinetics** PK parameters and levels of PCSK9 (total and free) will be summarized descriptively by auto-injector device group. After the first administration only, for log-transformed maximum plasma concentration (C_{max}), area under the curve concentration versus time curve extrapolated to infinity ($AUC_{0\text{-}tau}$) and trough concentration (C_{trough}), the difference between auto-injector devices will be assessed using a linear fixed effects model. Estimate and 90% CI for the ratio of geometric means (SYDNEY/current AI) will be computed for C_{max}, $AUC_{0\text{-}tau}$ and C_{trough}. **Anti-drug antibodies** Results of ADA will be summarized by auto-injector device group using descriptive statistics. **Pharmacodynamics** Percent and absolute change from baseline in LDL-C will be summarized descriptively for each auto-injector device. At Week 4 only, statistical analyses will compare auto-injector devices using an ANCOVA model to determine the estimates and 95% confidence intervals for the difference between means of percent LDL-C change for AI versus SYDNEY.

	Safety and tolerability The safety analysis will be based on the review of the individual data and descriptive statistics. Adverse events will be classified using Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. The number of treatment-emergent adverse events (TEAEs) will be tabulated by auto-injector device, as well as treatment-emergent AESIs (including in particular local injection site reactions LISR), treatment-emergent SAEs, TEAEs leading to permanent treatment discontinuation. For vital signs and laboratory parameters, the number of patients with abnormalities and/or potentially clinically significant abnormalities (PCSAs) will be summarized by auto-injector device.
DURATION OF STUDY PERIOD (per patient)	Total study duration (per patient) is expected to be up to 18 weeks: • Up to 2 weeks of screening period • 16 weeks of study treatment period (auto-injector device assessment phase).

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



1.2 STUDY FLOW CHART

Phase	Screening	Treatment Phase										
Day[a]	D-14 to D-1	D1	D8 (±1)	D15 (±1)	D22 (±1)	D29 (±3)	D57 (±3)	D85 (±3) EOT	D92 (±1)	D99 (±1)	D106 (±1)	D113 (±3) EOS
Week	Wk-2 to Wk 0	Wk 0	Wk 1	Wk 2	Wk 3	Wk 4	Wk 8	Wk 12	Wk 13	Wk 14	Wk 15	Wk 16
Visit (visit number)	1	2	3[b]	4[b]	5[b]	6[b]	7[b]	8	9[b]	10[b]	11[b]	12
Place where visits may occur	On-site	On-site	On-site or home	On-site or home	On-site or home	On-site or home	On-site or home	On-site	On-site or home	On-site or home	On-site or home	On-site
Informed consent	X											
Inclusion/exclusion criteria	X	X										
Patient demography	X											
Medical/surgical history	X											
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X										
Study treatment administration[c]												
Training injection with both devices (prior to randomization)[d]		X										
alirocumab SC injection using SYDNEY		X[e]				X[f]	X[f]	X[e]				
alirocumab SC injection using AI		X[e]										
Dispense/Complete/Review patient diary		X				X[f]	X[f]	X				
Contact IRT		X				X	X	X				X
Dispense alirocumab device		X				X[f]	X[f]	X				
Collect devices post-injection		X					X	X				
Treatment compliance		X					X	X[g]				
End user data recording												
Product Technical Complaints		X				X[f]	X[f]	X				
Patient perspective questionnaire[h]								X				
Injection-Treatment Acceptance Questionnaire (I-TAQ©)[i]								X				
Injection Experience questionnaire[j]		X				X	X	X				

Phase	Screening	Treatment Phase										
Day[a]	D-14 to D-1	D1	D8 (±1)	D15 (±1)	D22 (±1)	D29 (±3)	D57 (±3)	D85 (±3) EOT	D92 (±1)	D99 (±1)	D106 (±1)	D113 (±3) EOS
Week	Wk-2 to Wk 0	Wk 0	Wk 1	Wk 2	Wk 3	Wk 4	Wk 8	Wk 12	Wk 13	Wk 14	Wk 15	Wk 16
Visit (visit number)	1	2	3[b]	4[b]	5[b]	6[b]	7[b]	8	9[b]	10[b]	11[b]	12
Place where visits may occur	On-site	On-site	On-site or home	On-site or home	On-site or home	On-site or home	On-site or home	On-site	On-site or home	On-site or home	On-site or home	On-site
Safety												
Physical examination	X											X
Height	X											
Body weight	X											X
Vital signs (Blood Pressure[k], Heart Rate)	X	X				X	X	X				X
Hematology[m], biochemistry[m] (including fasting plasma glucose)	X	X										X
Creatine phosphokinase	X	X				X	X	X				X
Liver function panel (ALT, AST, ALP & total bilirubin[l])	X	X				X	X	X				X
Serum pregnancy test (if applicable)	X											
Urine pregnancy test (if applicable)		X										X
Adverse event collection	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetics												
alirocumab pharmacokinetic samples[n]		X	X	X	X	X	X	X	X	X	X	X
ADA		X[o]				X[o]						X
Pharmacodynamics /efficacy												
Lipid parameters (LDL-C, total-C, HDL-C, triglyceride)	X	X[o]				X[o]	X[o]	X[o]				X

Abbreviations: EOT: end-of-treatment, EOS: end-of-study, SC: subcutaneous, IRT: Interactive response technology, ADA: anti (alirocumab) - drug antibody, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase , LDL-C: Low density lipoprotein cholesterol, total-C: Total cholesterol, HDL-C: High density lipoprotein cholesterol, AI: Autoinjector, PCSK9: Proprotein convertase subtilisin/kexin type 9, γGT: gamma-glutamyl transferase.

a Day is expressed in reference to the 1st administration of alirocumab (D1).

b Visits 3, 4, 5, 6, 7, 9, 10 and 11: PK sample to be collected, these visits can be either done on site or be home-visits.

c The self-administration on Day 1 only will be done under supervision (guidance provided) on site. Self-administrations on Week 4 (Day 29) and Week 8 (Day 57) will be done at home or on site, unsupervised and without any guidance. The self-administration on Week 12 (Day 85) will be done at the site and will be observed (no guidance provided, considered unsupervised). Injection site will be documented.

d Patients will first receive paper- based training with each device by the site. They will then practice one injection with each device (SYDNEY and AI) into a training pad.

e Self-injection at the site on Days 1 (supervised) and 85 (observed, considered unsupervised). Device collected immediately after dosing.

f Self-injection at home or on-site: If self –injection is performed at home, a visiting Nurse will bring supplies for blood draw, diary, and dispensed IMP kit to subject's home and collect IMP materials post injection. The Visiting Nurse will not observe or provide guidance and therefore the injection will be unsupervised. After the completion of the visit the Visiting Nurse will collect all study supplies and return them to the site.

g Treatment compliance at Week 12 applies for injection done at Week 8 and injection done at Week 12.

h Patient perspective questionnaire: Completed by the patient after the last injection to record patient experience and satisfaction associated with use of SYDNEY to administer the 300 mg dose.

i Injection-Treatment Acceptance Questionnaire (I-TAQ©): Completed by the patient after the last injection, to measure their acceptance of self-injection treatment.

j Injection Experience questionnaire: Completed by the patient after each self-injection (AI or SYDNEY) addressing specific aspects of using the device.

k Blood pressure after 5 minutes in seating resting position.

l Total bilirubin (and, in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin).

m Hematology includes: red blood cell count, hematocrit, hemoglobin, white blood cell count with differential count (neutrophils, eosinophils, basophils, monocytes, and lymphocytes), and platelets. Biochemistry includes: sodium, potassium, chloride, plasma glucose, calcium, urea nitrogen, creatinine, total proteins, albumin, γGT.

n When alirocumab is to be administered, PK samples will be takien prior to alirocumab injection (Includes assay of total and free PCSK9).

o Prior to dosing with any IMP.

2 TABLE OF CONTENTS

2.1 LIST OF TABLES

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3 LIST OF ABBREVIATIONS

ADA: anti-drug (alirocumab) antibodies
AE: adverse event
AESI: adverse event of special interest
AI: auto-injector, refers to the current 1mL alirocumab auto-injector only
ALP: alkaline phosphatase
ALT: alanine aminotransferase
ASCVD: atherosclerotic cardiovascular disease
AST: aspartate aminotransferase
$AUC_{0\text{-}tau}$: area under the curve concentration versus time curve extrapolated to infinity
CHD: coronary heart disease
CI: confidence interval
C_{max}: maximum plasma concentration
CPK: creatinine phosphokinase
CRF: case report form
C_{trough}: trough concentration
CV: cadiovascular
CVD: cadiovascular disease
DRF: Discrepancy Resolution Form
e-CRF: electronic case report form
eGFR: estimated glomerular filtration rate
EOS: end-of-study
EOT: end-of-treatment
EU: European Union
FH: familial hypercholesterolemia
GCP: good clinical practice
HDL-C: high-density lipoprotein cholesterol
heFH: heterozygous familial hypercholesterolemia
HLT: high-level term
ICH: International Conference on Harmonization
IEC: Independent Ethics Committee
IMP: investigational medicinal product
IRB: Institutional Review Board
IRT: Interactive Response Technology
I-TAQ: Injection-Treatment Acceptance Questionnaire
LDL-C: low-density lipoprotein chlesterol
LDLR: low-density lipoprotein receptor
LISR: local injection site reactions
LMT: lipid modifying therapy
MedDRA: Medical Dictionary for Regulatory Activities
mITT: modified intent-to-treat
NIMP: noninvestigational medicinal product

PCSA:	potentially clinically significant abnormality(ies)
PCSK9:	proprotein convertase subtilisin/kexin type 9
PD:	pharmacodynamic
PFP:	pre-filled pen
PK:	pharmacokinetics
PTC:	product technical complaint
Q4W:	every 4 weeks
SAE:	serious adverse event
SAP:	statistical analysis plan
SOC:	system organ class
SYDNEY:	new alirocumab 2 mL auto-injector
TEAE:	treatment-emergent adverse event
TG:	triglyceride
Total-C:	total cholesterol
ULN:	upper limit of normal
US:	United States
WOCBP:	women of child bearing potential
γGT:	gamma-glutamyl transferase

4 INTRODUCTION AND RATIONALE

4.1 INTRODUCTION

Alirocumab is a fully human monoclonal antibody (mAb) that binds with high affinity to proprotein convertase subtilisin kexin type 9 (PCSK9) across several species. PCSK9 binds to low-density lipoprotein receptors (LDLRs) and promotes the internalization and removal of LDLR on hepatocytes. By blocking PCSK9 from binding to LDLR, alirocumab increases the number of LDLR available to remove low-density lipoprotein cholesterol (LDL-C) from circulation. Hence, alirocumab is an effective treatment to lower LDL-C and may reduce the risk for cardiovascular disease (CVD).

Alirocumab (also referred to as SAR236553 and REGN727) has been developed for the treatment of primary hypercholesterolemia or mixed dyslipidemia and is currently being developed for the reduction of cardiovascular (CV) events. Alirocumab is approved in many countries, in particular in the United States (US) and the European Union (EU).

More detailed information is provided in the latest version of Investigator's Brochure.

4.2 RATIONALE

4.2.1 Study Rationale

The 300 mg every 4 weeks (Q4W) dosing regimen administered as 2 injections of 150 mg has been established as an effective, safe dosing regimen for alirocumab. In order to support the 300 mg Q4W dosing regimen, a new auto-injector device (which is referred to as SYDNEY) with a volume of 2 mL has been developed.

This larger volume device will allow delivering the 300 mg monthly dosing as a single injection of 2 mL of the 150 mg/mL alirocumab solution, rather than 2 separate injections of 1 mL of the 150 mg/mL alirocumab solution with the currently marketed device. In this study, usability and acceptability of the large volume 2 mL SYDNEY device will be assessed when used by patients in an unsupervised setting. The current 1 mL auto-injector device (which is referred to as AI,) will be used as a calibrator for pharmacokinetics (PK), efficacy and safety.

In order to assess usability and acceptability of this new 2 mL SYDNEY device, any PTC with respect to the use of SYDNEY reported by the patients will be collected. In this study, a PTC is defined as any complaint reported on the Patient Complaint form that triggered an investigation by the Device Department and was categorized as either device-related, patient- related, or undetermined, whether or not associated with an AE.

PTCs will also be collected for AI. To allow a proper assessment, only self-administration will be allowed and therefore patients will be instructed to self-inject in the abdomen or thigh.

4.2.2 Study description and design rationale

The objective of this study is to assess the usability of SYDNEY in high or very high cardiovascular risk patients with hypercholesterolemia not adequately controlled with their lipid-modifying therapy (LMT).

Study population should include patients with either heterozygous familial hypercholesterolemia (heFH) or non-FH patients at high or very high cardiovascular risk (including patients with coronary heart disease [CHD], non-CHD CVD, and other risk factors) , not adequately controlled with a stable daily dose of atorvastatin (20 mg or 40 mg), or rosuvastatin (10 mg or 20 mg) for at least 4 weeks prior to the screening visit, with or without LMT.

This is a randomized, open-label, 16-week study, after a screening period of up to 2 weeks:

Treatment periods include:

- A parallel-arms period with one of the 2 devices (SYDNEY or AI) for the first 4 weeks.

  Patients will be randomized to receive alirocumab 300 mg Q4W, self-administered using either SYDNEY or AI on Week 0 (Day 1) for the first injection, that will be done on site, under supervision and guidance of the Investigator or designee.

- A single-arm period (with SYDNEY only) for the subsequent weeks until Week 16

  All patients will receive alirocumab 300 mg Q4W, self-administered using only SYDNEY, for the 2^{nd}, 3^{rd} and 4^{th} injections on Week 4, Week 8 and Week 12 respectively.

  The Week 4 and Week 8 injections will be performed at home or on-site without supervision or guidance. The Week 12 injection will be performed at the site and will be under observation only; there will be no guidance provided. Therefore the Week 12 injection is also considered to be unsupervised.

Patients assigned to the AI will switch to SYDNEY after the first self-injection to allow for the maximum use of SYDNEY in this study (ie, a total of 180 unsupervised injections to be performed with the new device), for the evaluation of safety, efficacy and ease of use of the 2 mL device in all the study participants.

The proposed design would support bridging the data for the alirocumab 300 mg monthly dosing regimen obtained with the currently marketed 1 mL AI to the new 2 mL SYDNEY.

It also allows for a descriptive comparison of the two devices up to Week 4 only (after the first dose) for pharmacokinetic/pharmacodynamic (PK/PD) and safety (including local injection site reactions [LISR]).

5 STUDY OBJECTIVES

5.1 PRIMARY

To collect 12 weeks of real-use (usability) data assessing the robustness and user interaction of the new alirocumab auto-injector device (which is referred to as SYDNEY), in unsupervised settings on Weeks 4, 8, and 12.

5.2 SECONDARY

Device-related:

- To collect real-use (usability) data assessing the robustness and user interaction of SYDNEY and the current 1 mL alirocumab auto-injector device (which is referred to as AI) in supervised settings on Week 0 (Day 1).

Pharmacokinetics:

- To compare alirocumab PK 300 mg Q4W administered using SYDNEY and AI, from baseline until Week 4.
- To evaluate alirocumab PK 300 mg Q4W administered using SYDNEY, until Week 16.

Anti-drug antibodies:

- To evaluate the development of anti-drug (alirocumab) antibodies (ADA).

Efficacy/pharmacodynamics:

- To compare the percent and absolute change in LDL-C, from baseline to Week 4 using SYDNEY and AI.
- To evaluate the percent and absolute change in LDL-C from baseline to Weeks 8, 12 and 16, using SYDNEY.

Safety:

- To evaluate the safety and tolerability of alirocumab 300 mg Q4W, using both SYDNEY and AI.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

This is a multicenter, randomized, open-label, 16-week study conducted in the US, with 2 parallel arms (parallel-arm period) for the first 4 weeks, and then only one arm (single-arm period) for the subsequent weeks until Week 16.

After a screening period of up to 2 weeks, all patients will be trained in self-injection using both devices at clinical site on Week 0 (Day 1) before randomization. They will first receive paper-based training with each device by the site. They will then practice one injection with each device (SYDNEY and AI) into a training pad.

Randomization will occur when training is completed and considered satisfactory by the site.

Eligible patients will then be randomly allocated to receive alirocumab 300 mg Q4W, self-administered using either SYDNEY or AI for the first injection on Week 0 (Day 1). This injection will be performed at the site under supervision and guidance.

Subsequently, from Week 4 (Day 29), all patients will receive alirocumab 300 mg Q4W self-administered using only SYDNEY for the 2nd, 3rd and 4th injections on Week 4 (Day 29), Week 8 (Day 57) and Week 12 (Day 85) respectively.

The Week 4 and Week 8 injections may be performed at home or on site without supervision or guidance. The Week 12 injection will be performed at the site and will be under observation only; there will be no guidance provided by the investigator or designee, and is therefore also considered unsupervised. This observation will assess whether the self-injection is performed adequately with this information recorded in the e-CRF.

On Week 0 (Day1), Week 1 (Day 8), Week 2 (Day 15), Week 3 (Day 22), Week 4 (Day 29), Week 8 (Day 57), Week 12 (Day 85), Week 13 (Day 92), Week 14 (Day 99), and Week 15 (Day 106), Week 16 (Day 113), PK collection, AE reporting, and concomitant medication reporting will be required. At the above mentioned time points, the patient has a choice to complete the assessment at the study site or in the patient's home (home visit). Should a patient prefer that sample collection be done at home instead of at the site, a research nurse will visit the patient's home to complete the required PK blood draw and management prior to the sample being shipped to the central lab. The Visiting Nurse will also bring the IMP and supplies (including diary) for the patient to administer unsupervised (the nurse will not provide any guidance or be in the room while the dose is self administered). After the completion of the visit the Visiting Nurse will collect all study supplies and return them to the site.

The Week 12 visit will be the end-of-treatment (EOT) visit. The Week 16 visit will be the end-of-study (EOS) visit.

A possible complaint identified by the investigator following the patient diary review and the patient interview, will trigger the completion of the Patient Complaint form by the investigator.

The completed Patient Complaint form and the corresponding device (both elements referred as "complaint sample") will be sent to the Research & Development (R&D) complaint office, where the type of complaint will be determined: whether the complaint is packaging related or potentially due to device issue or patient use. All complaint samples which are potentially due to device issue or patient use will be sent to Site Frankfurt Devices (SFD)/PTC Center where, after an investigation, the complaint will be classified as device-related, or patient- related, or undetermined (in case it cannot be determined whether the PTC is device or patient related), or not related to device nor patient (see Appendix B).

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

The total study duration (per patient) is expected to be up to 18 weeks:

- Up to 2 weeks of screening period.
- 16 weeks of study treatment period (auto-injector device assessment phase).

6.2.2 Determination of end of clinical trial (all patients)

The end of the study is defined as being the last patient last visit/contact as scheduled per protocol.

6.3 INTERIM ANALYSIS

No interim analysis is planned.

6.4 DISCUSSION OF STUDY DESIGN AND CHOICE OF CONTROL GROUPS

See Section 4.2 and Section 6.1.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

Patients meeting all of the following criteria will be considered for enrollment into the study:

I 01. Patients are in either category A or B (below), and are not adequately controlled with a stable daily dose of atorvastatin (20 mg or 40 mg), or rosuvastatin (10 mg or 20 mg) for at least 4 weeks prior to the screening visit (Week-2), with or without other lipid modifying therapy (LMT).

A) Patients with heterozygous familial hypercholesterolemia (heFH)**.

***Diagnosis of heFH must be made either by genotyping or by clinical criteria. For those patients not genotyped, the clinical diagnosis may be based on either the WHO criteria/Dutch (*see Appendix H*)*

Lipid Clinical Network criteria with a score >8 points or the Simon Broome register diagnostic criteria with a criterion for definite FH.

OR

B) Non-FH patients with high and very high cardiovascular risk*, include patients with coronary heart disease (CHD), non-CHD CVD, and other risk factors. Definitions for CHD, non-CHD CVD, and other risk factors are provided below:

a) A documented history of CHD (includes 1 or more of the following):

i. Acute myocardial infarction.

ii. Silent myocardial infarction.

iii. Unstable angina.

iv. Coronary revascularization procedure (eg, percutaneous coronary intervention or coronary artery bypass graft surgery).

v. Clinically significant CHD diagnosed by invasive or non-invasive testing (eg, coronary angiography, stress test using treadmill, stress echocardiography or nuclear imaging).

b) Non-CHD CVD (includes 1 or more of the following criteria):

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

ii. Peripheral arterial disease.

iii. Abdominal aortic aneurysm.

iv. Atherosclerotic renal artery stenosis.

v. Carotid artery disease (transient ischemic attacks or >50% obstruction of a carotid artery).

c) Other risk factors

i. Documented moderate chronic kidney disease as defined by 30≤ Estimated Glomerular Filtration Rate (eGFR) <60 mL/min/1.73 m² for 3 months or more, including the screening visit.

ii. Type 1 or type 2 diabetes mellitus.

iii. A calculated 10-year fatal CVD risk SCORE ≥5% (European Society of Cardiology [ESC] and the European Atherosclerosis Society [EAS] Guidelines for the management of dyslipidemias [1]).

* For CVD risk categories, see Appendix D.

I 02. Patient willing and able to self-inject for the duration of the study.

I 03. Signed Written Informed Consent Form.

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 three sub-sections:

7.2.1 Exclusion criteria related to study methodology

E 01. LDL-C <70 mg/dL (<1.81 mmol/L) at the screening visit.

E 02. Currently taking a daily dose of statin that is not atorvastatin 20 mg or 40 mg, or rosuvastatin 10 mg or 20 mg.

E 03. Not on a stable dose of LMT (including statin) for at least 4 weeks prior to the screening visit and from screening to randomization.

E 04. Use of fibrates, other than fenofibrate within 4 weeks of the screening visit or between screening and randomization visits.

E 05. Use of red yeast rice products within 4 weeks of the screening visit or between screening and randomization visits.

E 06. Patients who have received plasmapheresis treatment within 2 months prior to the screening visit, or have plans to receive it.

E 07. Patients who are planned to undergo scheduled percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), carotid or peripheral revascularization during the study.

E 08. History of New York Heart Association (NYHA) Class III or IV heart failure within the past 12 months.

E 09. Age <18 years or legal age of majority at the screening visit, whichever is greater.

E 10. Known history of homozygous FH.

E 11. Having previously used any device for PCSK9 inhibitor administration, or having participated in any clinical trial for a PCSK9 inhibitor.

E 12. Conditions/situations such as:

A) 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.

B) Patients considered by the Investigator or any sub-Investigator as inappropriate for this study for any reason, eg:

i) Those deemed unable to meet specific protocol requirements, such as scheduled visits,

ii) Those deemed unable to administer or tolerate long-term injections as per the patient or the investigator,

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

iv) 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 13. Patients who have taken any investigational drugs within 1 month or 5 half-lives, whichever is longer.

E 14. Patients who withdraw consent during the screening period (patient who is not willing to continue or fails to return).

E 15. Laboratory findings during the screening period (not including randomization labs) with the following values:

A) Triglycerides (TG) >400 mg/dL (>4.52 mmol/L) at the screening visit (Week-2). Note: 1 repeat lab is allowed.

B) Positive serum pregnancy test in women of childbearing potential.

C) eGFR <30 mL/min/1.73 m^2 according to 4-variable modification of diet in renal disease (MDRD) equation.

D) ALT or AST >3 x upper limit of normal (ULN) (1 repeat lab is allowed).

E) Creatinine kinas (CK) >3 x ULN (1 repeat lab is allowed).

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

E 16. All contraindications to the background therapies or warning/precaution of use (when appropriate) as displayed in the respective National Product Labeling.

7.2.3 Exclusion criteria related to the current knowledge of alirocumab

E 17. History of a serious hypersensitivity reaction to alirocumab (including hypersensitivity vasculitis and hypersensitivity reactions requiring hospitalization).

E 18. Pregnant or breast-feeding women.

E 19. 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 serum pregnancy test at screening and urine pregnancy test at randomization visit. They must use effective contraceptive methods throughout the study and agree to repeat urine pregnancy test at designated visits. The applied methods of contraception have to meet the criteria for a highly effective method of birth control according to the "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" (2). Please refer to Appendix A.

Postmenopausal women must be amenorrheic for at least 12 months.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

Sterile alirocumab drug product will be supplied at a concentration of 150 mg/mL in an aqueous buffer, pH 6.0, containing sucrose, histidine, and polysorbate 20 as 1 mL or 2 mL volume respectively in a current auto-injector or in a new auto-injector.

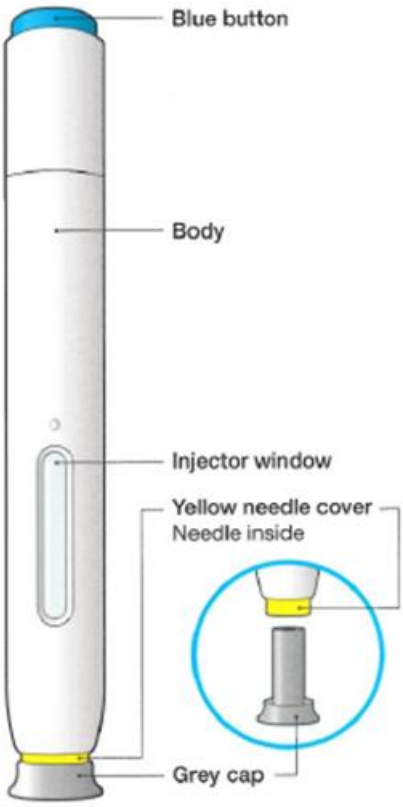
8.1.1 Description of the auto-injectors

In this study protocol, AI refers to the current commercial 1 mL device only, SYDNEY refers to the new 2 mL device.

8.1.1.1 Current auto-injector: AI

The currently marketed device, 1 mL AI, delivers 2 separate 1 mL injections of the 150 mg/mL Praluent® (alirocumab) for the 300 mg Q4W dosing regimen.

Figure 1 - 1 mL Clinical pre-filled pen/auto-injector – disposable PFP/AI



8.1.1.2 New auto-injector: SYDNEY

The new 2 mL AI, SYDNEY, is a two-step disposable auto-injector designed to deliver 2 mL of 150 mg/ mL Praluent® (alirocumab) subcutaneously in ≤20 seconds.

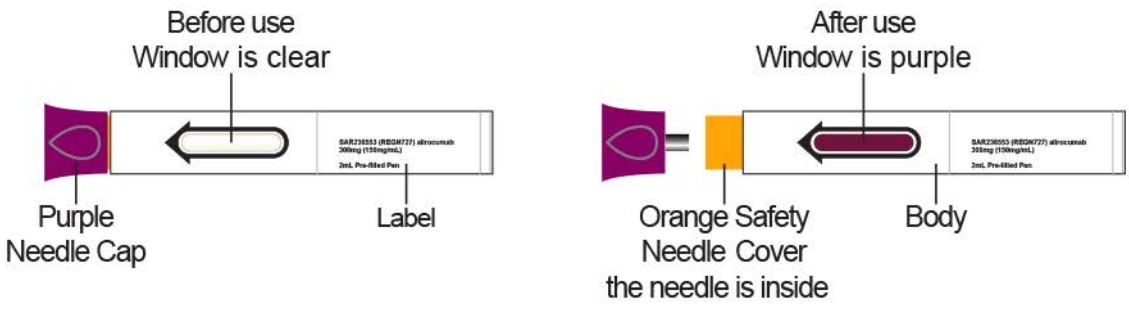
The main features of SYDNEY include:

- An easy to use buttonless device for the patients
- A needle safety cover that shields the needle at start of injection and extends to cover the needle when the AI is removed from the skin, which helps preventing needle stick injury
- An inspection window to allow visibility of the medication and provide feedback before and after injection (window changes from transparent to purple)
- Visible and audible cues to signal the start and end of injection
- A single-use, disposable device
- Self-disabling feature to prevent re-use
- An arrow around the inspection window (indicating the direction to push the pen against the skin)

The main functional difference other than the injected volume between the new and the current device is that there is one step less for preparation of the injection with the new device, there is no longer the need to push a button to start the injection.

This new 2 mL AI, SYDNEY, is illustrated in Figure 2.

Figure 2 - 2 mL Clinical SYDNEY pre-filled pen



8.1.2 Route and method of administration

An Instructions for Use sheet will be provided to patients containing detailed instructions on use.

The IMP will be administered by self-injection. The used auto-injector will be returned to the site for accountability and reconciliation.

It is recommended that the IMP injections be rotated within an anatomical area (eg, right thigh then left thigh or right abdomen then left abdomen). Patients also have the option to inject in a different anatomical area (eg, thigh then abdomen) during the study. Patients should not inject into areas where the skin is bruised, tender, hard, red, or hot.

It should be noted that if patients have problems activating the auto-injector by pressing the needle cover against their belly (eg, soft tissue), it is recommended to inject into the thigh, where the skin is firmer than the belly. If another concomitant drug is being injected at the same site planned for the IMP injection, then the patient should be advised to use an alternate location for administration of the IMP.

Patients will be asked to store the IMP in a refrigerator. Prior to administration, the IMP should be set outside in a safe location at room temperature for about 45 minutes. Thereafter, the IMP should be administered as soon as possible.

8.1.3 Timing of administration

On Day 1, prior to the randomization, all patients will be trained in self-injection using both devices at clinical site. They will first receive paper-based training with each device by the investigator or designee. They will then practice one injection with each device (current and new auto-injector devices) into a training pad.

Randomization will occur when training is completed and considered satisfactory by the investigator or designee.

Patients will be randomized to receive self-administered alirocumab 300 mg Q4W subcutaneously via either SYDNEY or AI for the first injection on Week 0 (Day 1).

The treatment period will start as soon as possible after the call for randomization using the treatment kit number provided by the Interactive Response Technology (IRT). The first injection after randomization will be done at the investigational site by the patient under direct site staff supervision. Patients will be monitored at the investigational site for at least 30 minutes after this first injection.

Subsequently, all patients will receive self-administered alirocumab 300 mg Q4W via SYDNEY for the 2nd, 3rd and 4th injections on Week 4 (Day 29), Week 8 (Day 57) and Week 12 (Day 85).

- The 2nd and 3rd injections will be done unsupervised at home or on site.
- The 4th injection will be done on site under observation by a caregiver (considered unsupervised), as no direction or prompting will be given. This observation will assess whether the self-injection is performed adequately with this information recorded in the e-CRF.

IMP should ideally be administered subcutaneously at approximately the same time of the day Q4W; however it is acceptable to have a window period of ± 3 days. The time of the day is based on patient's preference.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCT(S)

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

- Atorvastatin 20 mg or 40 mg, rosuvastatin 10 mg or 20 mg.
- Cholesterol absorption inhibitors (ezetimibe),
- Bile acid-binding sequestrants (such as cholestyramine, colestipol, colesevelam),
- Nicotinic acid,
- Fenofibrate,
- Omega-3 fatty acids (≥1000 mg daily).

8.3 BLINDING PROCEDURES

Not applicable, this study is an open-label design.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

The randomized treatment kit number list is generated centrally by Sanofi. The IMPs are packaged in accordance with this list.

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

Patients will be randomized to receive either SYDNEY or AI for the first injection at Week 0 (on Day 1) using a ratio 1:1.

The treatment kit numbers will be allocated using the centralized treatment allocation system (IRT) on randomization visit Week 0 (Day 1), Week 4 (Day 29), Week 8 (Day 57) and Week 12 (Day 85).

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

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

8.5 PACKAGING AND LABELING

The treatment kit with AI will be prepared to contain 2 auto-injectors (2 x 1 mL) whereas the treatment kit with SYDNEY will be prepared to contain 1 auto-injector (1 x 2 mL).

In addition to the open-label treatment kits, a dummy kit for practice containing 1 auto-injector each will be prepared for the purpose of instructing patients on injection administration which is to be performed prior to randomization. These training injections will be performed on site at randomization Week 0 (Visit 2, Day1).

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

8.6 STORAGE CONDITIONS AND SHELF LIFE

At the investigational site, stored IMP should be kept in an appropriate locked room, under the responsibility of the investigator or designee or other authorized person in accordance with local regulations, labeling specifications, policies and procedures. Control of IMP storage conditions, especially control of temperature (eg, refrigerated storage between +2°C and +8°C [36°- 46° F] at the site) and information on in-use stability and instructions for handling the alirocumab should be managed according to the rules provided by the Sponsor (eg, the temperature of the site refrigerator should be checked daily and recorded on a log sheet).

IMP will be either given to the patient for self-administration while on site or the supplies will be brought and collected by the Visiting Nurse in an appropriate transport bag at the refrigerated temperature.

The IMP must be administered in accordance with the Instructions for Use. If the storage and in use conditions described in the Instructions for Use are not followed, do not administer the IMP.

8.7 RESPONSIBILITIES

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

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

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) should be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 6.1) .

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 the IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party (except for the Visiting Nurse who has been approved by the Sponsor), allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

8.7.1 Treatment accountability and compliance

IMP administration data will be recorded by the Investigator or designee on the e-CRF.

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

- The Investigator or designee will obtain via IRT the treatment kit number(s) and he/she will dispense the treatment kit(s) to the patient.
- The Investigator or designee will enter the treatment kit packaging number(s) and the kit numbers in the e-CRF, if applicable.
- The accountability is to be performed at IMP kit re-supply visits only. The used and unused kit(s) should be brought back to such visits for accountability purposes.
- The monitor will check the data consistency between e-CRF pages, treatment log forms using patient’s diary, and returned unused IMPs of a corresponding kit.

The patient will be instructed on the importance to take the study treatment as planned for the remainder of the treatment duration, as well as the need to return all used and unused IMP kits at each site visit.

8.7.2 Return and/or destruction of treatments

All treatments kits will be retrieved from the site by the Sponsor. A detailed treatment log of the returned IMP will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the monitoring team.

8.8 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient concomitantly to any IMP(s) during the study. This medication is not provided by the Sponsor.

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

8.8.1 Management of background lipid-modifying therapy

For background LMT, including statins (atorvastatin 20 and 40 mg, rosuvastatin 10 and 20 mg), sites must follow the national product label for the safety monitoring and management of patients.

Patients will be on stable dose of statin therapy with or without other LMT during the study as indicated in Section 7.

From the screening visit until the Week 16 visit, the background LMT should not be changed. No dose adjustment, discontinuation or initiation of other statins or other LMT should take place during this time, barring exceptional circumstances whereby overriding concerns warrant such changes, as per the Investigator's judgment.

Should the patient require the introduction of a fibrate during the course of the study (ie, as rescue treatment) only fenofibrate will be allowed to be added.

8.8.2 Contraception

Women of childbearing potential must use an effective contraceptive method throughout the entire duration of the study treatment. It is also recommended to continue using an effective contraceptive method for at least 4 weeks after the last injection of IMP. The applied methods of contraception have to meet the criteria for a highly effective method of birth control according to the "International Conference on Harmonization 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" (2).

8.8.3 Prohibited concomitant medications

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

- Red yeast rice products
- Fibrates, other than fenofibrate
- Other PCSK9 inhibitors

Note: while red yeast rice is considered a dietary supplement/nutraceutical, it contains HMG CoA reductase inhibitor activity (mechanism of action of statins), along with other active ingredients. Because such products lack standardization, varying amounts of the active substance could lead to alterations in lipids during the study and potentially confound the LDL-C assessment.

8.9 LIFESTYLE AND DIETARY HABITS

Lifestyle and dietary habits should be maintained if possible throughout the entire study duration, as medically feasible, with minimum changes. There shall be no significant changes in nutritional composition of the diet or in the quantity/pattern of food consumed.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 PRIMARY ENDPOINT

The primary endpoint is the number (%) and types of SYDNEY-associated product technical complaints (PTCs)* at the unsupervised injections on Weeks 4, 8, and 12.

*** Product technical complaints (PTC)**

In this study, all complaints that triggered an investigation by the Device Department will be categorized as device-related, patient- related, undetermined, or not related to device nor patient, whether or not associated with an AE. **In this study, a PTC is defined as** any complaint reported on the Patient Complaint form that triggered an investigation by the Device Department and was categorized as either device-related, patient- related or undetermined. The complaints categorized as not related to device nor patient will not be considered as a PTC. This definition will be used for both primary and secondary endpoints.

Patient diaries

Patients will be given diaries to complete after each self-injection they perform using the auto-injector device. The diary will include specific questions about the self-injection process.

At each visit, the Investigator will review the diary with the patient, and confirm more particularly whether there were any problems associated with the auto-injector during study treatment administration and record the experience in the e-CRF.

Following interview with the patient, in the event the Patient complaints form is completed by the investigator, this form and the corresponding auto-injector device (both elements referred as “complaint sample”) will be sent to the Sponsor for identification of as described in Section 6.1.

In case a PTC is associated with the occurrence of an AE, the AE must be documented on an AE page in the e-CRF. In case a PTC is associated with the occurrence of a SAE, the SAE must be reported to the Monitoring Team in accordance with the SAE reporting procedures.

9.1.1 Collection of devices

All used auto-injector devices will be collected by the site. In case a Patient Complaints form is completed, the concerned device will be sent to the Sponsor along with the Patient Complaints form.

9.2 SECONDARY ENDPOINTS

- Secondary endpoints include: Device-related endpoints
- Pharmacokinetics
- Anti-drug antibodies
- Efficacy/pharmacodynamics:
- Safety:
  - Adverse events (AEs), including Serious Adverse Events (SAEs) and Adverse events of special interest (AESIs), laboratory data, and vital signs assessed throughout the study.

  AESIs and other groupings of interest will include: general allergic reactions (GARs) requiring consultation with another physician, LISR requiring consultation with another physician, neurologic events that require additional examinations/procedures and/or referral to a specialist, neurocognitive events, pregnancy, symptomatic overdose with IMP, alanine aminotransferase (ALT) increase: ALT ≥3 x Upper Limit of Normal (ULN) (if baseline ALT <ULN) or ALT ≥2 times the baseline value (if baseline ALT ≥ULN).

9.2.1 Device-related endpoints

For both devices:

- Number (%) of patients with current AI- associated PTCs (overall and by type) at the supervised injections (Week 0, Day 1).
- Patient questionnaires (see Appendix C):
  - **Injection Experience Questionnaire**: patients will be given an Injection Experience Questionnaire to complete after the self-injection they perform using SYDNEY or AI on Week 0 (Day 1). The questionnaire will include questions about specific aspects of using the device.

For SYDNEY only:

- Number (%) of patients with a SYDNEY- associated PTC (overall and by type) at the unsupervised injections on Weeks 4, 8, and 12.
- Patient questionnaires (see Appendix C):
  - **Patient Perspective Questionnaire**: the aim of the Patient Perspective Questionnaire (to be completed by the patient after the last injection) will be to generate data to support an understanding of the patient experience and satisfaction associated with use of the large volume 2 mL SYDNEY to administer the 300 mg dose.

- **Injection-Treatment Acceptance Questionnaire**: the I-TAQ© (to be completed by the patient after the last injection) is a 22-item, self-administered questionnaire administered to patients in order to measure their acceptance of the injection. The aim is to generate data to show patient acceptance of self-injection treatments.

Assessment schedule

The assessment timing can be found in the study flow chart (Section 1.2).

9.2.2 Pharmacokinetics assessments

Total serum alirocumab concentrations, as well as total and free PCSK9 concentrations will be measured:

- Alirocumab PK parameters after the first and the last dosing.
- Free and total PCSK9 levels measured using PK serum samples.

9.2.2.1 Sampling time

The sampling times for blood collection can be found in the study flow chart (Section 1.2).

9.2.2.2 Number of pharmacokinetic samples

Table 1 - Number of serum samples

	ALIROCUMAB
By patient / Total	11
Total current auto-injector (AI) arm (33 patients)	33 * 5 samples = 165
Total new auto-injector (SYDNEY) arm (33 patients)	33 * 11 samples = 363 + 33 patient * 6 samples = 198
Total for study	165+363+198 = 726

9.2.2.3 Pharmacokinetic sample handling procedure

The sample handling procedure is summarized in the below table.

Special procedures for collection, storage, and shipment will be provided in Appendix F of the protocol.

Table 2 - Summary of handling procedures

Blood Sample Volume	5 mL
Anticoagulant	None
Handling Procedures	To be described in Appendix F of the protocol
Serum Aliquot Split	Two equal aliquots
Serum Storage Conditions	-20°C (-68°F) or below
Serum Shipment Conditions	Dry ice

9.2.2.4 Bioanalytical method

All PK samples will be analyzed by Bioanalytical Sciences group at Regeneron Pharmaceuticals, Inc.

PK samples will be analyzed using a validated enzyme-linked immunosorbent assay (ELISA) to determine total concentrations of alirocumab (ie, free SAR236553 and SAR236553 present in PCSK9:SAR236553 complexes) in acid-treated human serum as summarized in Table 3.

Alirocumab PK samples will also be analyzed to determine total and free PCSK9 levels using validated ELISA. [redacted]

Table 3 - Summary of bioanalytical method

Analyte	ALIROCUMAB
Matrix	Serum
Analytical Technique	ELISA
Lower limit of Quantification	[redacted]
Site of Bioanalysis	Regeneron Pharmaceuticals, Inc
Method Reference	[redacted]

9.2.2.5 Pharmacokinetics parameters

The pharmacokinetic parameters listed in Table 4 will be calculated, using non-compartmental methods for alirocumab serum concentrations after single and multiple doses. The parameters will include, but not be limited to the following.

Table 4 - List of pharmacokinetic parameters and definitions

Parameters	Drug/Analyte	Matrix	Definition/Calculation
C_{max}	SAR236553	Serum	Maximum serum concentration observed
C_{trough}	SAR236553	Serum	Serum concentration observed just before treatment administration during repeated dosing
t_{max}	SAR236553	Serum	Time to reach C_{max}
$AUC_{0\text{-}tau}$	SAR236553	Serum	Area under the serum concentration versus time curve calculated using the trapezoidal method during a dosage interval

9.2.3 Anti-drug (alirocumab) antibody (ADA) assessments

9.2.3.1 Sampling times

Anti-drug antibodies will be assessed throughout the study. The sampling times for blood collection of ADA samples can be found in the study flow chart (See Section 1.2).

9.2.3.2 Number of ADA samples

Table 5 - Number of serum samples

	Anti-ALIROCUMAB antibodies
By patient	3
Number of patients	66
Total for study	3*66 = 198

9.2.3.3 Sample handling procedure

The sample handling procedure is summarized in Table 6. Special procedures for collection storage and shipment will be provided in Appendix F of the protocol.

Table 6 - Summary of handling procedures

Blood sample volume	5 mL
Anticoagulant	None
Handling procedures	Will be provided in Appendix F of the protocol
Serum aliquot split	Two equal aliquots
Serum storage conditions	-20°C (-68°F) or below
Serum shipment conditions	Dry ice

9.2.3.4 Bioanalytical methods

All PK samples will be analyzed by Bioanalytical Sciences group at Regeneron Pharmaceuticals, Inc.

ADA samples will be analyzed using a validated electrochemiluminescence assay for the determination of anti- alirocumab antibodies in human serum as summarized in Table 7.

Table 7 - Summary of bioanalytical method

Analyte	Anti-ALIROCUMAB
Matrix	Serum
Analytical technique	Electrochemiluminescence
Sensitivity	approx. 5.6 ng/mL
Site of bioanalysis	Regeneron Pharmaceuticals, Inc.
Method reference	[redacted]

9.2.4 Efficacy/Pharmacodynamics assessments:

The efficacy secondary endpoint is represented by the percent and absolute change from baseline in LDL-C at Weeks 4, 8, 12 and 16.

At all visits LDL-C will be calculated using the Friedewald formula (3). For the purpose of calculating LDL-C through the Friedewald formula, blood sampling will be done for determination of Total-cholesterol (Total-C), high-density lipoprotein cholesterol (HDL-C), and TG. If TG values exceed 400 mg/dL (4.52 mmol/L) then the central lab will reflexively measure (via the beta quantification method) the LDL-C rather than calculating it.

The blood sampling for lipid parameters should be performed in the morning, in fasting condition (at least 10 to 12 hours fast and refrain from smoking). Alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the blood sampling are discouraged. The sample handling procedure will be provided separately in a Central Lab manual.

9.2.4.1 Pharmacodynamic parameter

The pharmacodynamic endpoint will be the percent change in LDL-C value from baseline to Week 4 defined as: 100x (LDL-C value at Week 4 - LDL-C value at baseline) / LDL-C value at baseline.

The baseline LDL-C value will be the last LDL-C level obtained before the first injection of IMP. The LDL-C at Week 4 will be the LDL-C level obtained within the Week 4 analysis window.

All calculated and measured LDL-C values (scheduled or unscheduled, fasting or not fasting) may be used in the analyses if appropriate according to above definition and analysis windows used to allocate a time point to a measurement. Analysis windows will be defined in the statistical analysis plan (SAP). In case both calculated and measured LDL-C are provided for the same sampling, the measured LDL-C will be considered.

Percent and absolute change from baseline in LDL-C will also be calculated at Week 8, 12 and 16. They will be summarized descriptively.

9.2.5 Safety assessments

Adverse events, spontaneously reported by the subject or observed by the Investigator, will be monitored at each visit. This includes SAEs, detailed in Section 10.4.1.2, AEs of special interest (AESIs) detailed in Section 10.4.1.3, laboratory data, vital signs assessed throughout the study. Specific additional forms will be completed for AESI. For any Local Injection Site Reactions (LISR), and general allergic AEs, whether or not reported as AESI, special forms on symptoms will have to be completed (see Section 10.6).

Assessment of safety will be based on clinical safety endpoints, laboratory safety variables, vital signs, and physical examination.

9.2.5.1 Adverse events

Refer to Section 10.4 up to Section 10.7 for details.

9.2.5.2 Laboratory safety variables

The clinical laboratory data consist of blood analysis including the following:

- Hematology: red blood cell count, hematocrit, hemoglobin, white blood cell count with differential count (neutrophils, eosinophils, basophils, monocytes, and lymphocytes), platelets.
- Biochemistry: sodium, potassium, chloride, calcium, plasma glucose, urea nitrogen, creatinine, albumin, total proteins, gamma-glutamyl transferase (γGT).
- Liver function panel: aspartate aminotransferase (AST), Alanine aminotransferase (ALT), alkaline phosphatase (ALP), and total bilirubin (and, in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin).
- Creatine phosphokinase (CPK).
- Urine and serum (beta-human chorionic gonadotropin [β-HCG]) pregnancy test for women of child bearing potential (WOCBP) only.

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

9.2.5.3 Vital signs

Vital signs include heart rate, systolic and diastolic blood pressure measured after 5 minutes in seating resting position.

9.2.5.4 Physical examination

Physical examination, including body weight (kg), height (only at screening visit).

9.3 SAMPLED BLOOD VOLUME

The volume of blood sampled in the study is shown in Table 8.

Table 8 - Sampled blood volume

Type	Volume per sample	Sample number	Total
Hematology	2 mL	3	6 mL
Biochemistry	2 mL	3	6 mL
Creatine phosphokinase	2 mL	6	12 mL
Liver function panel	1 mL	6	6 mL
Pharmacodynamics	3 mL	6	18 mL
β-HCG (if applicable)	5 mL	1	5 mL
Pharmacokinetics alirocumab	5 mL	11	55 mL
Anti-alirocumab antibody	5mL	3	15 mL
Total if male or female post menopausal			**118 mL**
Total if WOCBP			**123 mL**

Abbreviations: β-HCG: beta-human chorionic gonadotropin, WOCBP: Women of childbearing potential

9.4 FUTURE USE OF SAMPLES

Stored samples may be used for safety analysis, even after study completion. Unused or left over samples after testing may be used for other research purposes (excluding genetic analysis) related to cardiovascular diseases, other than those defined in the present protocol. Information on these stored samples will be included in the informed consent form.

9.5 APPROPRIATENESS OF MEASUREMENTS

The primary endpoint is the number (%) and types of PTCs associated with the use of SYDNEY during the 3 unsupervised injections at Week 4, Week 8 and Week 12. This will allow to assess the robustness, usability and acceptability of the new 2 mL SYDNEY device. With an estimation of 60 evaluable patients using SYDNEY (30 patients in the SYDNEY group since Day 1 and 30 additional patients from the AI group switching to SYDNEY group after the 1st injection), a total of 180 unsupervised injections with SYDNEY will be assessed.

The data collected will also allow for evaluation of PK, safety, efficacy and use in real world setting of the 2 mL SYDNEY device in all study participants, from Week 4 injection.

Up to Week 4, the parallel arm design will allow for PK, PD and safety (including LISR) to be compared between SYDNEY and AI.

10 STUDY PROCEDURES

10.1 VISIT SCHEDULE

10.1.1 Visit 1: Screening/Day-14 (Week -2) to Day-1 (Week 0)

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 procedures.

The following procedures will then be performed:

- Contact IRT to assign a patient number
- Assess eligibility by review of Inclusion/Exclusion Criteria. Patients who fail to meet the eligibility criteria based on this preliminary review should not continue the screening process and a screen failure notification should be done through the IRT
- Interview to collect:
  - Patient demography
  - Medical/surgical history
- Record prior/concomitant medications
- Perform a physical examination including weight (kg) and height (cm) (collected for body mass index [BMI] calculation)
- Record vital signs including systolic and diastolic blood pressure (measured after 5 minutes in a seated resting position) and heart rate
- Obtain blood samples in fasting conditions for
  - Lipids panel: LDL-C, Total-C, HDL-C, TG
  - Hematology: red blood cell count, hematocrit, hemoglobin, white blood cell count with differential, platelets
  - Biochemistry: sodium, potassium, chloride, calcium, plasma glucose, urea nitrogen, creatinine, albumin, total proteins, γGT
  - Liver function panel: AST, ALT, ALP, and total bilirubin (and, in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin)
  - CPK
  - Serum pregnancy test (for WOCBP, only).
- Record AEs (including SAE and AESI) if any after informed consent signed
- Schedule a visit within 2 weeks maximum (Visit 2, Week 0, Day 1)

- 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 visit are discouraged.

10.1.2 Visit 2: Day 1, Week 0

The following procedures will be performed:

- Confirm eligibility by review of Inclusion/Exclusion Criteria. Patients who fail to meet the eligibility criteria based on this preliminary review should not continue the screening process and a screen failure notification should be done in the IRT
- Record vital signs including systolic and diastolic blood pressure (measured after 5 minutes in a seated resting position) and heart rate
- Contact IRT for allocation of a number for training kit, and alirocumab device (SYDNEY or AI)
- Record the kit number allocated in the e-CRF
- Record concomitant medications
- Record AEs (including SAE and AESI)
- Dispense training for both SYDNEY and AI, and perform injection-training as outlined in Section 8.1.3.
- Prior to dosing with IMP, collect blood sample in fasting conditions for:
  - Lipids panel
  - Hematology
  - Biochemistry
  - Liver function panel
  - CPK
  - Pharmacokinetics: PK parameters including assay of total and free PCSK9
  - Detection of anti-alirocumab antibodies.
- Obtain urine sample for pregnancy test (for WOCBP, only)
- Dispense patient diary
- Contact IRT for allocation of a kit number for alirocumab (SYDNEY or AI)
- Record the kit number allocated in the e-CRF
- Dispense alirocumab device (SYDNEY or AI)
- IMP injection using SYDNEY or AI (dependent on randomization) to be performed by the patient under staff supervision
- Collect used auto-injector device (as described in Section 9.1)

- Patient to complete diary
- Patient to complete the injection experience questionnaire
- Record Patient complaint (including PTC) in the Patient complaints form, if any occurred
- Record treatment compliance
- Schedule home-visits or on-site visits according to patient preference for Visit 3 (Week 1), Visit 4 (Week 2), and Visit 5 (Week 3)
- Schedule a visit for Week 4 (Day 29 [± 3 day]; Visit 6) and Week 8 (Day 57 [± 3 days], Visit 7) either on site or at home, based on the patient's preference.
- Schedule an on-site visit for Week 12 (Day 85 [± 3 days]; Visit 8) and remind patient to be in fasting conditions (ie overnight, at least 10 to 12 hours fast and refrain from smoking) for the visit. Also, alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the next visit are discouraged
- Review patient diary and record patient complaint (including PTC) in the Patient complaints form (for the Day 1 injection), if any (as described in Section 9.1)

10.1.3 Visit 3: Day 8 ± 1 day, Week 1; Visit 4: Day 15 ± 1 day, Week 2; Visit 5: Day 22 ± 1 day, Week 3

These visits may be performed on site or as home-visits

- Record concomitant medications
- Record AEs (including SAE and AESI)
- Obtain blood samples for
  - Pharmacokinetics: PK parameters including assay of total and free PCSK9
- Remind patient to be in fasting conditions (ie overnight, at least 10 to 12 hours fast and refrain from smoking) for next study visit (Visit 6). Also, alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the next visit are discouraged

10.1.4 Visit 6: Day 29 ± 3 days, Week 4

This visit may be performed on site or as a home-visit.

The following procedures will be performed:

- Record vital signs including systolic and diastolic blood pressure (measured after 5 minutes in a seated resting position) and heart rate
- Record concomitant medications
- Record AEs (including SAE and AESI)

- Obtain fasting blood samples for:
  - Lipids panel
  - Liver function panel
  - CPK
  - Pharmacokinetics: PK parameters including assay of total and free PCSK9
  - Detection of anti-alirocumab antibodies.
- Contact IRT for allocation of a kit number for SYDNEY
- Record the kit number allocated in the e-CRF
- Dispense the SYDNEY device to the patient if the injection is to be administered on site or to the Visiting Nurse, if the injection to be administered at home
- Dispense patient diary, to be completed after the injection
- Dispense Injection Experience Questionnaire, to be completed after the injection
- Collect and return the study supplies and diary (performed by the Visiting Nurse if the visit is completed at home)
- Confirm scheduled visit for Week 8 (Day 57 [± 3 days], Visit 7)
- Remind patient to be in fasting conditions (ie overnight, at least 10 to 12 hours fast and refrain from smoking) for next study visit (Vist 7). Also, alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the next visit are discouraged
- Review patient diary and record patient complaint (including PTC) in the Patient complaints form (for the Week 4 injection), if any (as described in Section 9.1), after received from the patient or theVisiting Nurse.

10.1.5 Visit 7: Day 57 ± 3 days, Week 8

This visit may be performed on site or as a home-visit.

The following procedures will be performed:

- Record vital signs including systolic and diastolic blood pressure (measured after 5 minutes in a seated resting position) and heart rate
- Record concomitant medications
- Record AEs (including SAE and AESI)
- Obtain fasting blood samples for:
  - Lipids panel
  - Liver function panel
  - CPK

  - Pharmacokinetics: PK parameters including assay of total and free PCSK9.
- Collect used auto-injector device (as described in Section 9.1)
- Record treatment compliance
- Contact IRT for allocation of a kit number for SYDNEY
- Record the kit number allocated in the e-CRF
- Dispense the SYDNEY device to the patient if the injection is to be administered on site, or to the Visiting Nurse if the injection is to be administered at home
- Dispense patient diary, to be completed after the injection
- Dispense Injection Experience Questionnaire, to be completed after the injection
- Collect and return the study supplies and diary (performed by the Visiting Nurse if the visit is completed at home)
- Dispense the SYDNEY device, injection to be administered at home
- Confirm scheduled visit for Week 12 (Day 85 [± 3 days]Visit 8)
- 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 visit are discouraged
- Review patient diary and record patient complaint (including PTC) in the Patient complaints form (for the Week 8 injection), if any (as described in Section 9.1), after received from the patient or the Visiting Nurse.

10.1.6 Visit 8 (end-of-treatment): Day 85 ± 3 days, Week 12

This visit must be performed on site.

The following procedures will be performed:

- Record vital signs including systolic and diastolic blood pressure (measured after 5 minutes in a seated resting position) and heart rate
- Record concomitant medications
- Record AEs (including SAE and AESI)
- Prior to dosing with IMP, obtain fasting blood samples for:
  - Lipids panel
  - Liver function panel
  - CPK
  - Pharmacokinetics: PK parameters including assay of total and free PCSK9
- Collect used auto-injector device (as described in Section 9.1)

- Collect previous diary
- Collect previous injection experience questionnaire
- Record treatment compliance
- Dispense injection experience questionnaire to be completed on site
- Dispense patient perspective questionnaire to be completed on site
- Dispense Injection-Treatment Acceptance Questionnaire (I-TAQ©) to be completed on site
- Contact IRT for allocation of a kit number for SYDNEY
- Record the kit number allocated in the e-CRF
- Dispense the SYDNEY device, injection to be administered on site under observation by the site staff, without any guidance (considered unsupervised)
- Dispense patient diary to be completed on site
- Record in the appropriate e-CRF page if the self-injection was performed appropriately with the full injection done
- Review patient diary and record patient complaint (including PTC) in the Patient complaints form, if any reported for this injection (as described in Section 9.1)
- Schedule home-visits or on-site visits according to patient preference for Visit 9 (Week 13), Visit 10 (Week 14), and Visit 11 (Week 15)
- Schedule a visit for Week 16 (Day 113 [± 3 day],Visit 12)

10.1.7 Visit 9: Day 92 ± 1 day, Week 13; Visit 10: Day 99 ± 1 day, Week 14; Visit 11: Day 106 ± 1 day, Week 15

These visits may be performed on site or as home-visits.

- Record concomitant medications
- Record AEs (including SAE and AESI)
- Obtain blood samples for:
  - Pharmacokinetics: PK parameters including assay of total and free PCSK9
- 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 visit are discouraged.

10.1.8 Visit 12 (end-of-study): Day 113 ± 3 days, Week 16

This visit must be performed on site.

The following procedures will be performed:

- Perform a physical examination, including body weight
- Record vital signs including systolic and diastolic blood pressure (measured after 5 minutes in a seated resting position) and heart rate
- Record concomitant medications
- Record AEs (including SAE and AESI)
- Obtain fasting blood samples for:
  - Lipids panel
  - Hematology
  - Biochemistry
  - Liver function panel.
  - CPK
  - Pharmacokinetics: PK parameters including assay of total and free PCSK9
  - Detection of anti-alirocmab antibodies.
- Obtain urine sample for pregnancy test (for WOCBP, only)
- Contact IRT to update the patient's status (study completion).

10.2 DEFINITION OF SOURCE DATA

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

- Agreement, date, and signature of informed consent mentioning the study identification.
- Patient identification, medical history, associated diseases, and data related to the studied pathology.
- Contraception methods for women of childbearing potential.
- Previous and concomitant medications (including the LMT).
- Study identification.
- Treatment number, dates of administration.
- Dates of visits and assessments including the examination report.
- Vital signs, height, body weight.

- IRT confirmation (screening, screen failure, training kit allocation, randomization, treatment reallocation, discontinuation, EOT, EOS).
- AEs and follow-up:
  - In case of SAE, the site should file in the source document at least copies of the hospitalization reports and any relevant examination reports documenting the follow-up of the SAE.
- Date of premature study discontinuation (if any) and reason
- Visiting Nurse records.

Source documentation may be found in the following:

- Patient's chart
- Patient diaries
- Patient perspective questionnaire
- Injection experience questionnaire
- Injection-Treatment Acceptance Questionnaire (I-TAQ©)
- Central and local laboratory 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 e-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 10.3.3 and Section 10.3.4).

For all temporary treatment discontinuations, duration should be recorded by the Investigator in the appropriate pages of the e-CRF.

Temporary treatment discontinuation is defined as one or more scheduled injections that are not administered to the patient as decided by the Investigator

10.3.2 Permanent treatment discontinuation with investigational medicinal product(s)

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

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

10.3.3 List of criteria for permanent treatment discontinuation

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

Patients should discontinue IMP for the following reasons:

- Pregnancy, intention for pregnancy, or no longer using effective contraceptive method of birth control (females only).
- Acute injection reaction of clinical concern.
- Serious or severe hypersensitivity reaction considered related to IMP.
- At patient request, ie, withdrawal of consent for treatment.
- If, in the Investigator's opinion, continuation with the administration of the IMP would be detrimental to the patient's well-being.
- Intercurrent condition that requires discontinuation of the IMP.
- At the specific request of the Sponsor.

Any abnormal laboratory value will be immediately rechecked for confirmation (after 24 hours) before making a decision of permanent discontinuation of the IMP for the concerned patient.

10.3.4 Handling of patients after permanent treatment discontinuation

Patients will be followed-up according to the study procedures specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

If possible, and after the permanent discontinuation of treatment, the patients will be assessed using the procedures normally planned for the last dosing day with the IMP (this EOT visit should take place within 5 days of treatment discontinuation, if possible) including a PK sample, if appropriate.

The patient, at a minimum, should then be followed-up for 4 weeks from the last administration of IMP or until recovery or stabilization of any AE as specified in this protocol, whichever comes last. A final end of study visit will take place 4 weeks after the premature discontinuation.

All cases of permanent treatment discontinuation should be recorded by the Investigator in the appropriate pages of the e-CRF when considered as confirmed. IRT should be notified when a patient prematurely discontinues study treatment. In the medical record, at least the date of the withdrawal and the reason should be documented.

10.3.5 Procedure and consequence for patient withdrawal from study

The patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason without any effect on their care. However, if patients no longer wish to take the IMP, they will be encouraged to remain in the study. If possible, the patients are assessed using the procedure normally planned for the EOS visit including a PK sample.

The Investigators should discuss with them key visits to attend. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study.

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.

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, unless the patient withdraws consent for follow-up, the Investigator should make the best effort to recontact 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 contact, receipt for sending a registered letter).

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

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

An **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 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
  - Suicide attempt or any event suggestive of suicidality
  - Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
  - Bullous cutaneous eruptions
  - Required Intervention to Prevent Permanent Impairment or Damage (Devices):
    If you believe that the intervention was necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure, either situation suspected to be due to the use of a medical product.

10.4.1.3 Adverse event of special interest

An adverse event of special interest (AESI) is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified or removed during a study by protocol amendment.

Adverse Events of Special Interest (AESI) are AEs (serious or non-serious) that need to be monitored, documented, and managed in a pre-specified manner described in the protocol.

For these AEs, the Sponsor will be informed immediately (ie within 24 hours), as per SAEs notification described in Section 10.4.1.2 even if not fulfilling a seriousness criterion, using the corresponding screens in the e-CRF.

The following AEs are considered as AESIs in the study:

- **Pregnancy** occurring in a female patient entered in the clinical trial or in a female partner of a male patient entered in the clinical trial.
  - It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Section 10.4.1.2).
  - In the event of pregnancy in a female participant, IMP should be discontinued.
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined.
- **Symptomatic overdose** (serious or nonserious) with IMP/NIMP
  - An overdose (accidental or intentional) with the IMP/NIMP is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic pills count) and defined as at least twice the intended dose within the intended therapeutic interval
  - Of note, asymptomatic overdose has to be reported as a standard AE.
  - The circumstances (ie, accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on separate AE forms.
- **Increase in alanine transaminase (ALT):** ALT ≥3 x ULN (if baseline ALT <ULN) or ALT ≥2 times the baseline value (if baseline ALT ≥ULN) (see the "Increase in ALT" flow diagram in Appendix E.
- **General allergic events:**
  - Any general allergic events regardless of the cause that require consultation with another physician for further evaluation of hypersensitivity/allergy as per the Investigator's medical judgment should be reported as an AESI.
  - All general allergic events require completion of the specific e-CRF screen.

- **Local injection site reactions:**
  - Local injection site reactions that require consultation with another physician for further evaluation of hypersensitivity/allergy as per the Investigator's medical judgment should be reported as an AESI.

  All LISR require completion of the specific e-CRF screen.

  Note:

  - Other LISR are non-AESIs. Please see Section 10.6 for details.
  - The safety instructions on allergic events and LISR are detailed in Section 10.6.
- **Neurologic events**: neurologic events that require additional examinations/procedures and/or referral to a specialist should be reported as an AESI. If the event does not require additional examinations/procedures and/or referral to a specialist, it should be reported as a standard AE.
- **Neurocognitive events:** All neurocognitive events will be considered as AESI.

10.4.2 General guidelines for reporting adverse events

- All AEs, regardless of seriousness or relationship to IMP/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 e-CRF.
- Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP 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.
- When treatment is prematurely discontinued, the patient, at a minimum, should then be followed-up for 4 Weeks from the last administration of IMP or until recovery or stabilization of any AE as specified in this protocol, whichever comes last. A final end of study visit will take place 4 weeks after the premature discontinuation.

- Laboratory and vital signs abnormalities are to be recorded as AEs only if:
  - Symptomatic and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI

Instructions for AE reporting are summarized in Table 9.

10.4.3 Instructions for reporting serious adverse events

In the case of occurrence of an SAE, the Investigator or any designees 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. If the e-CRF system does not work, the investigator must report an SAE to the Sanofi representative within 24 hours, and the Sanofi representative must report the SAE to Global Pharmacovigilance & Epidemiology (GPE) within 1 working day.

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 AESIs, the Sponsor must be informed immediately (ie, within 24 hours), as per SAE notification guidelines described in Section 10.4.3, even if not fulfilling a seriousness criterion, using the corresponding pages of the CRF (to be sent) or screens in the e-CRF.

Instructions for AE reporting are summarized in Table 9.

Table 9 - Summary of adverse event reporting instructions

Event category	Reporting timeframe	Specific events in this category	Case Report Form completion		
			AE form	Safety Complementary Form	Other specific forms
Adverse Event (non-SAE, non-AESI)	Routine	Any AE that is not SAE or AESI	Yes	No	No
Serious Adverse Event (non-AESI or AESI)	Expedited (within 24 hours)	Any AE meeting seriousness criterion per Section 10.4.1.2	Yes	Yes	No
Adverse Event of Special Interest	Expedited (within 24 hours)	Acute hypersensitivity/ anaphylaxis	Yes	Yes	No
		Pregnancy	Yes	Yes	Yes
		Symptomatic overdose	Yes	Yes	No
		ALT increase as defined in the protocol	Yes	Yes	Yes
		General allergic event requiring consultation with another physician	Yes	Yes	Yes
		Local injection site reactions requiring consultation with another physician	Yes	Yes	Yes
		Neurologic events that require additional examinations/procedures and/or referral to a specialist	Yes	Yes	Yes
		Neurocognitive events (any)	Yes	Yes	Yes

10.4.5 Guidelines for reporting product complaints

Any patient complaint related to the device (SYDNEY or AI)/ injection process must be reported in the Patient complaints form as soon as possible by the Investigator.

Appropriate information in addition to the device (eg, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered.

The completed Patient Complaints form and the corresponding device (both elements referred as "complaint sample") will be sent to the R&D complaint office.

The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

10.5 OBLIGATIONS OF THE SPONSOR

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

- All SAEs that are both unexpected and at least reasonably related to the IMP (SUSAR), to the regulatory authorities, Independent Ethics Committee (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.

Adverse events that are considered expected will be specified by the reference safety information (Investigator's brochure).

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

10.6 SAFETY INSTRUCTIONS

10.6.1 Local tolerability (local injection site reactions)

In case the Investigator or the patient recognizes any signs of local intolerability, then this should be treated and followed-up as per the Investigator's medical judgment. Specific e-CRF screens are to be filled in. Information on classifying the reaction is provided in Section 10.4, and on reporting these reactions is given in Appendix G.

Local injection site reactions that are related to the alirocumab injection, as opposed to another injectable agent, should be further characterized by evaluating the related symptoms that comprise an injection site reaction such as but not limited to redness, pain, etc. If the patient experiences a local injection site reaction with no signs or symptoms except for erythema/redness, and/or swelling, and the diameter of the erythema/ redness, or swelling measure <2.5 cm, no AE for local injection site reaction needs to be reported as this is not typically considered a clinically important finding. However, if the patient has a reaction of swelling with a diameter <2.5 cm that interferes with activity, then it should be considered as a clinically relevant finding and should be reported as an AE with a corresponding grade of moderate or severe, in accordance with Appendix G.

10.6.2 General allergic adverse events

Specific e-CRF screens are to be filled in to assess allergic AEs or allergic-like AE 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 Event and/or Local Injection Site Reaction Complementary Form.

Adverse events that are obviously not of allergic origin (eg, LISR related to mechanics of injection) should only be recorded on the Local Injection Site Reaction Complementary Form. However, injection site reactions that progress/expand/worsen/etc should be evaluated as recommended in Appendix G and General Allergic Reaction Complementary form should be completed.

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

10.6.2.1 Allergic adverse event with cutaneous involvement

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

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

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

10.6.2.2 Acute allergic injection reactions

Acute allergic injection reaction (which are considered under the category of general allergic events) 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.

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

10.7 ADVERSE EVENTS MONITORING

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

11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

No formal sample size was calculated, the sample size is based on empirical considerations. Considering a drop-out rate of 10% it is planned to randomize 66 patients overall (33 in each group) in order to ensure 60 evaluable patients overall (30 in each group) resulting in 180 unsupervised planned injections using SYDNEY, including the 2nd, 3rd and 4th unsupervised injections with SYDNEY for patients randomized in the AI group who will switch to SYDNEY group just before the second injection.

With 60 evaluable patients using SYDNEY, a total of 180 unsupervised injections is expected to be achieved during the study. Expecting a maximum of 3 observed PTC over the 180 injections (observed PTC rate of 1.67%) with SYDNEY, the upper bound of the 2-sided 95% confidence interval calculated with the Wilson score method will be no higher than 5.2%.

11.2 DISPOSITION OF PATIENTS

Screened patients are defined as any patient who met the inclusion criteria and none of the exclusion criteria, and signed the informed consent.

Randomized patients are all screened patients with a treatment kit number allocated and recorded in the IRT database, regardless of whether or not the treatment kit was used. These patients form the randomized population. Patients treated without being randomized will not be considered as randomized.

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

11.3 ANALYSIS POPULATIONS

11.3.1 Modified intent-to-treat populations

The primary efficacy analysis population that will be used for the analyses of LDL-C will be the modified intent-to-treat (mITT) population.

The mITT population of the parallel arms period will consist of all randomized patients who receive at least 1 dose or part of a dose of IMP visit during this period and who had an evaluable value of LDL-C at baseline and an on-treatment LDL-C value within Week 4 analysis window. The treatment period for the parallel arms period is defined as the time period from the first IMP injection up to 35 days after this injection or up to the day before the second injection, whichever comes first. Patients in this mITT population will be analyzed according to the auto-injector device group allocated by randomization (ie, as-randomized treatment group).

The mITT population of the single-arm period will consist of all randomized patients who continue in single-arm period and receive at least 1 dose or part of a dose of IMP of this period and who had an evaluable value of LDL-C at baseline and at least one on-treatment LDL-C within one of the analysis windows from Week 8 to Week 16. The treatment period for the single-arm period is defined as the time period from the second IMP injection up to 35 days after the last IMP injection for patients entering into the single arm period.

11.3.2 Safety populations

The safety population of the parallel arms period will consist of all randomized patients who receive at least 1 dose or part of a dose of IMP during this period. Patient data will be analyzed according to the auto-injector device actually used.

The safety population of the single-arm period will consist of all randomized patients who continue in the single-arm period and receive at least 1 dose or part of a dose of IMP during this period.

All safety and PTC analyses will be performed on these populations.

In addition:

- Nonrandomized but treated patients will not be part of the safety population, but their safety data will be presented separately
- Randomized patients for whom it is unclear whether they took the IMP will be included in the safety population as randomized
- For a patient receiving injections with an auto-injector device different than the randomized auto-injector device during the parallel-arms period, the auto-injector device group allocation for as-treated analysis will be the auto-injector device actually used.

11.3.3 Pharmacokinetic populations

The PK population of the parallel-arms period will consist of all randomized patients who receive at least at least 1 dose or part of a dose of IMP and had at least one evaluable blood sample for PK during this period. All patients will be analyzed according to the auto-injector device that they actually used.

The PK population of the single-arm period will consist of all randomized patients who receive at least 1 dose or part of a dose of IMP and had at least one evaluable blood sample for PK during this period.

These PK populations will be used for the analyses of alirocumab concentrations and PCSK9 concentrations.

11.3.4 Anti-alirocumab antibody population

The anti-alirocumab antibody population of the parallel-arm period will consist of all randomized patients who receive at least 1 dose or part of a dose of IMP during this period (safety population) with an available ADA sample at baseline and at least one post-baseline available ADA sample during this period.

The anti-alirocumab antibody population of the single-arm period will consist of all randomized patients who receive at least 1 dose or part of a dose of IMP during this period (safety population) with an available ADA sample at baseline and at least one post-baseline available ADA sample during this period.

11.4 STATISTICAL METHODS

Unless otherwise specified, analyses will be performed by auto-injector device group in the parallel-arms period and overall in the single-arm period.

The baseline value is defined as the last available value obtained up to the date and time of the first IMP administration.

11.4.1 Extent of study treatment exposure and compliance

The extent of study treatment exposure and compliance will be assessed and summarized by actual auto-injector device used within the safety population for each study period.

11.4.1.1 Extent of investigational medicinal product exposure

No duration of IMP exposure will be calculated for the parallel-arms period since patients will receive only one injection during this period. The proportion of patients having received the first injection will be summarized.

The duration of IMP exposure for the single-arm period is defined as: last IMP injection date - first IMP injection date during this period + 28 days (regardless of unplanned intermittent discontinuations). The number of injections received during the single-arm period will also be summarized.

11.4.1.2 Compliance

No treatment compliance to the IMP will be calculated for the parallel-arms period since patients will receive only one injection during this period.

Treatment compliance to the IMP for the single-arm period will be assessed using the mean injection frequency, defined for each patient, as the average number of days between 2 consecutive injections, that is: (last injection date – first injection date during this period)/(number of injections -1) for patients receiving at least 2 injections during this period.

11.4.2 Analyses of primary endpoint

The primary endpoint (ie, number (%) and types of SYDNEY-associated PTCs related to the unsupervised injections [Section 9.1]) will be described on the safety population for the single arm period. The number and % of PTCs will be provided with the 95% CI using Wilson score method. If applicable, the number of PTCs per patient will be described. In addition the type of PTCs will be described.

11.4.3 Analyses of secondary efficacy endpoints

All secondary device-related endpoints (Section 9.2.1) will be analyzed on the safety population using descriptive statistics. In addition, 95% CI for the number of PTCs, number and % of patients with any PTCs will be provided using Wilson score method.

11.4.4 Analyses of safety data

Safety data will be presented on the safety population of the parallel-arm period and of the single-arm period. Treatment-emergent adverse events (TEAEs), treatment-emergent SAEs, treatment-emergent AESIs, and TEAEs leading to treatment discontinuation, will be summarized based on the Medical Dictionary for Regulatory Activities (MedDRA) coding of verbatim terms reported by investigators (Section 9.2.5).

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

- The observation period to be used for the safety population is the TEAE period. The TEAE period is defined
  - For the parallel-arms period as the time from the first IMP injection to the day before the second IMP injection (for patients entering into the single arm period period) or to 70 days after the first IMP injection, whichever comes first
  - For the single-arm period as the time from the first IMP injection received in the single arm period to 70 days after the last IMP injection.

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

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

- Treatment period: the treatment period used for quantitative analysis is defined:
  - For the parallel-arms period as the time from the first IMP injection to 35 days after this injection or to the day before the second IMP injection (for patients entering into the single arm period period) whichever comes first.
  - For the single-arm period as the time from the first IMP injection received in the single arm period to 35 days after the last IMP injection.

11.4.4.1 Analysis of the adverse event data

The analyses of AEs will focus on TEAEs. Treatment-emergent AEs are defined as any AEs that are newly developed or worsened or that become serious during the TEAE period.

Treatment-emergent AE incidence tables will present the number (%) of patients experiencing at least 1 TEAE by system organ class (SOC) (sorted by internationally agreed order), high-level group term (HLGT), high-level term (HLT) and preferred term (PT) sorted in alphabetical order. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each auto-injector device group.

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

Death: The following summaries will be provided:

- Number (%) of patients who died by study period (TEAE, on-study) and reasons for death summarized on the safety population
- Death in nonrandomized patients or randomized and not treated patients
- TEAE leading to death (death as an outcome on the Adverse Event 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.

11.4.4.2 Analysis of the laboratory data

For laboratory data, including the incidence of PCSAs, actual values and change from baseline will be summarized by treatment group.

The number and percentage of patients with at least 1 PCSA at any time during the TEAE period will be summarized for each laboratory parameter. Shift tables showing changes with respect to the baseline status will be provided.

The summary statistics (including number, mean, median, standard deviation, minimum, and maximum) of all laboratory variables will be calculated for each visit (baseline, each post-baseline time point, endpoint) by auto-injector device group.

11.4.4.3 Summary of the vital sign data

The number and percentage of patients with at least 1 PCSA at any time during the TEAE period will be summarized for each vital signs variable. Shift tables showing changes with respect to the baseline status will be provided.

The summary statistics (including number, mean, median, standard deviation, minimum, and maximum) of all vital signs variables will be calculated over time.

11.4.5 Analyses of pharmacokinetic, pharmacodynamics and anti-alirocumab antibodies variables

Pharmacokinetic parameters (C_{max}, t_{max}, $AUC_{0\text{-}tau}$ and C_{trough}) will be summarized (mean, geometric mean, median, standard deviation, standard error of mean, coefficient of variation, minimum, and maximum) for each auto-injector device in the parallel-arms period and overall in the single-arm period (See Section 9.2.2).

For PK parameters log-transformed C_{max}, $AUC_{0\text{-}tau}$ and C_{trough}, estimates and 90% CI for the ratio of geometric means (SYDNEY/current AI) will be provided using a linear fixed effects model with baseline body weight as covariate.

Total and free PCSK9 concentrations will be summarized by visit using descriptive statistics.

Percent and absolute change from baseline in LDL-C will be summarized descriptively for each auto-injector device.

The anti-drug antibodies (ADA) status (positive/negative) and antibody titers will be summarized using descriptive statistics. Further details will be provided in SAP.

11.4.6 Analyses of efficacy variables

Lipid variables will be summarized (mean, median, standard deviation, minimum, and maximum) in percent and absolute change from baseline (See efficacy assessments - Section 9.2.4).

In addition, at Week 4 only, percent change from baseline in LDL-C will be analyzed using an ANCOVA model to determine the estimates and 95% confidence intervals for both SYDNEY and AI.

11.5 INTERIM ANALYSIS

Not applicable.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, and delegated Investigator staff and Sub investigator, in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, and the ICH guidelines for good clinical practice (GCP), all applicable laws, rules and regulations.

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

12.2 INFORMED CONSENT

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

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

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

12.3 HEALTH AUTHORITIES AND 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 health authorities (competent regulatory authority) and 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 with any addenda or labeling documents (summary of product characteristics, package insert), Investigator’s curriculum vitae, etc) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

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

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

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

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

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

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

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

13.2 RESPONSIBILITIES OF THE SPONSOR

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

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

13.3 SOURCE DOCUMENT REQUIREMENTS

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

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

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

Should a correction be made, the 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 trial master file.

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

14.4 PROPERTY RIGHTS

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

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

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

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

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

14.5 DATA PROTECTION

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

14.6 INSURANCE COMPENSATION

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

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

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

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

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

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

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

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

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

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

14.8.1 By the Sponsor

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

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

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

14.8.2 By the Investigator

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

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

14.9 CLINICAL TRIAL RESULTS

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

14.10 PUBLICATIONS AND COMMUNICATIONS

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

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

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

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

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

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

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

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

In case of substantial amendment to the clinical trial protocol, approval from the health authorities (competent regulatory authority) will be sought before implementation.

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

16 BIBLIOGRAPHIC REFERENCES

1. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J. 2012 Jul;33(13):1635-701.

2. 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. June 2009. 30 p.

3. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem.1972; 18(6): 499-502.

17 APPENDICES

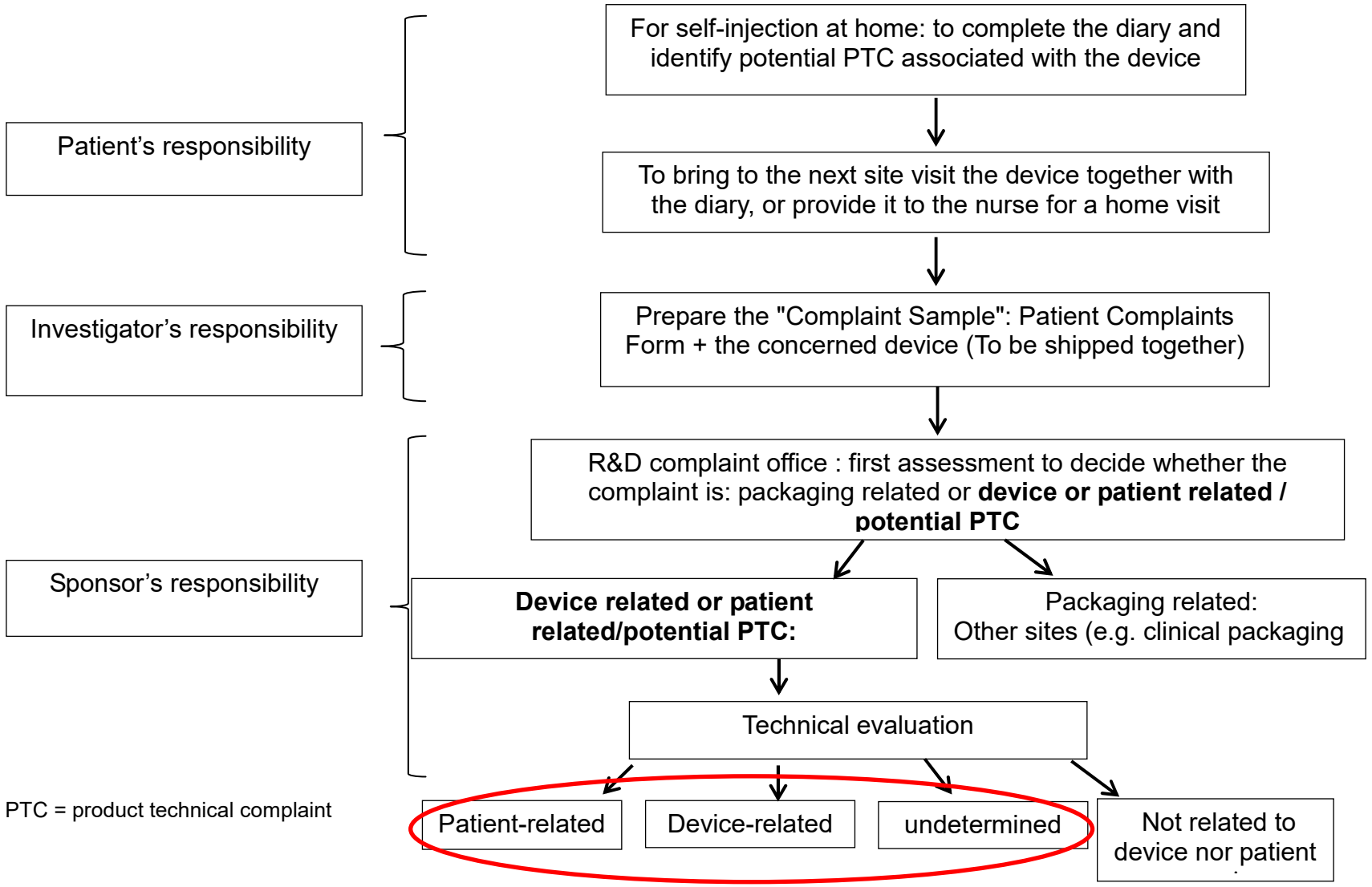
Appendix A Guidance on contraceptive methods

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. It is also recommended to continue using an effective contraceptive method for at least 4 weeks after the last injection of IMP.

Appendix B Procedures for handling patient complaints with identification of potential product technical complaints

PROCEDURE FOR IDENTIFICATION OF POTENTIAL PRODUCT TECHNICAL COMPLAINTS



PTC = product technical complaint

Appendix C Patient Related Questionnaires

1. Injection experience questionnaire

Patient Questions for Praluent/Sydney Take-Home Bridging Study

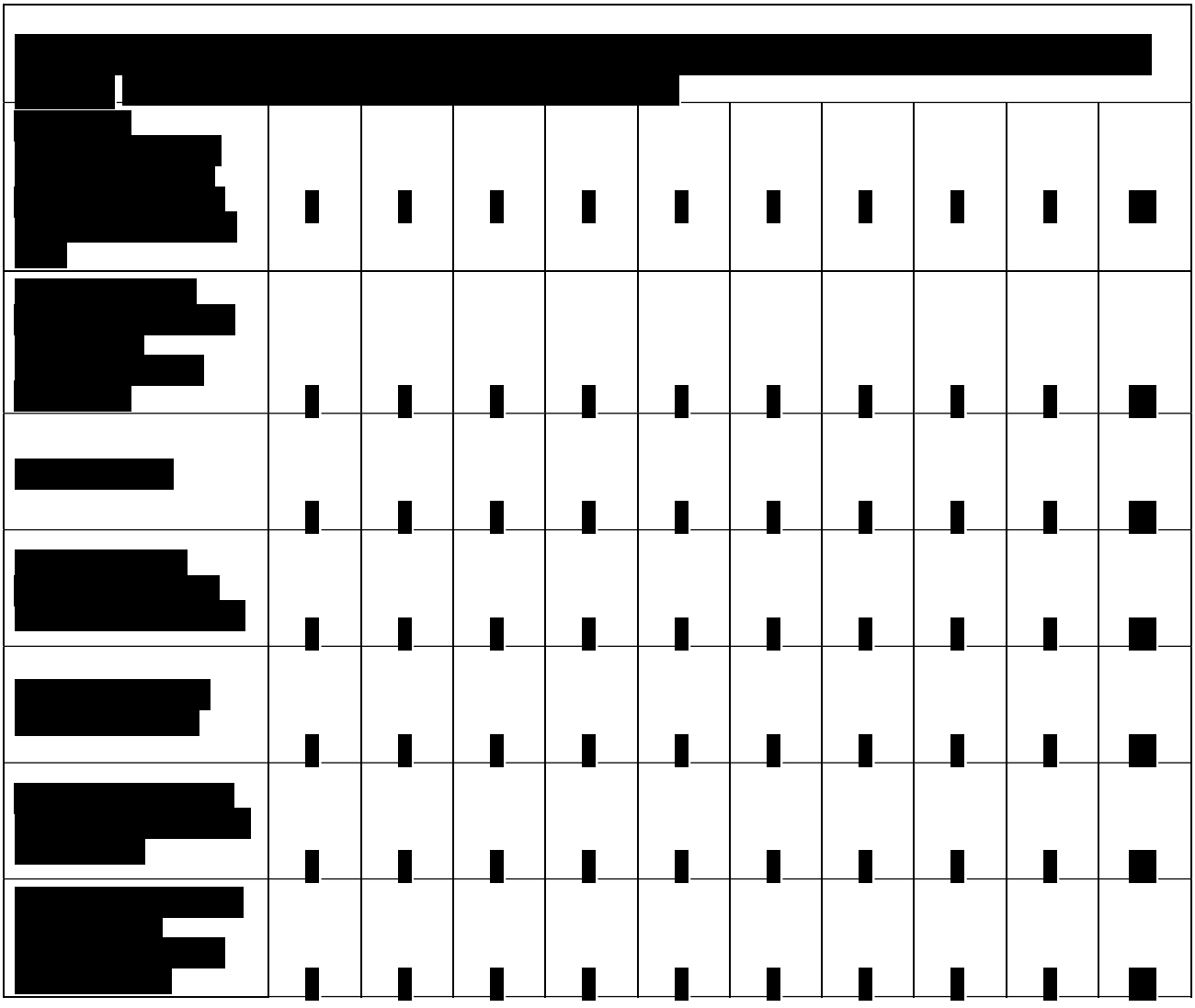
STUDY NUMBER: MSC14864

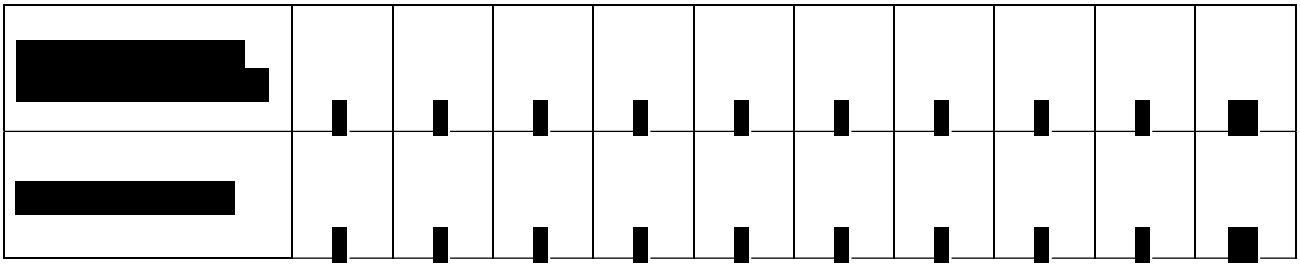
Injection Experience Questionnaire – Arm 1/Current AI device

(For Day 1 injection only)

To be completed after each injection

Please answer these questions immediately after you finish each injection.





Injection Experience Questionnaire – Arm 2 + Arm 1 after switch to modified device (SYDNEY)

To be completed after each injection

2. Patient Perspective Questionnaire

Patient Perspective Questionnaire

To be completed after your final injection

3. Injection – Treatment Acceptance Questionnaire (I-TAQ)

Injection – Treatment Acceptance Questionnaire (I-TAQ) version 1

Instructions

This questionnaire asks about how acceptable you find the study treatment which you take as an injection. **Please only think about the study treatment you take as an injection** when you answer each question and not any other treatments you may be taking. For each question, please mark the response that most closely corresponds to your own experiences. There are no right or wrong answers. If you are not sure about any of the questions, mark the response which you think is most appropriate. **Please think back over the past four weeks when answering every question.**

1 Over the past four weeks, how **confident** were you that the injection treatment **treated your condition**?

☐ Not at all confident | ☐ A little confident | ☐ Somewhat confident | ☐ Quite Confident | ☐ Very confident

2 Over the past four weeks, how **effective** was the injection treatment at treating your condition?

☐ Not at all effective | ☐ A little effective | ☐ Somewhat effective | ☐ Quite effective | ☐ Very effective

3 Over the past four weeks, did you experience any **side effects** including **injection site side effects (such as redness, bruising or swelling)** from the injection treatment?

☐ No — Please go to Question 8

☐ Yes — Please continue to question 4

4 Over the past four weeks, how acceptable or unacceptable did you find the **side effects** of the injection treatment?

☐ Very Unacceptable | ☐ Unacceptable | ☐ Neither acceptable nor unacceptable | ☐ Acceptable | ☐ Very acceptable

5 Over the past four weeks, did the side effects of the medication **interfere with your physical activity (e.g. lifting things, walking, jogging, etc.)**?

☐ No, not at all | ☐ Yes, a little | ☐ Yes, somewhat | ☐ Yes, quite a bit | ☐ Yes, very much

6 Over the past four weeks, did the side effects of the medication **interfere with your leisure and free time activities (e.g. gardening, reading, dancing, visiting friends, etc.)**?

☐ No, not at all | ☐ Yes, a little | ☐ Yes, somewhat | ☐ Yes, quite a bit | ☐ Yes, very much

7 Over the past four weeks, did the side effects of the medication **interfere with your daily activities (e.g. shopping, working, house work, yard work etc.)**?

☐ No, not at all | ☐ Yes, a little | ☐ Yes, somewhat | ☐ Yes, quite a bit | ☐ Yes, very much

8 Over the past four weeks, how **confident** did you feel in your ability to **give yourself the injection treatment**?

☐ Not at all confident | ☐ A little confident | ☐ Somewhat confident | ☐ Quite confident | ☐ Very confident

I-TAQ – US English – Version 1, 13 March 2015 – Regeneron Pharmaceuticals and Sanofi

Page 1 of 3

9 Over the past four weeks, how easy or difficult was it to **give yourself the injection treatment?**

☐ Very difficult ☐ Difficult ☐ Neither easy nor difficult ☐ Easy ☐ Very easy

10 Over the past four weeks, how acceptable or unacceptable did you find **giving yourself the injection treatment?**

☐ Very unacceptable ☐ Unacceptable ☐ Neither acceptable nor unacceptable ☐ Acceptable ☐ Very acceptable

11 Over the past four weeks, did you experience any **pain** when injecting your treatment?

☐ No **Please go to Question 13**

☐ Yes **Please continue to question 12**

12 Over the past four weeks, how acceptable or unacceptable did you find the **pain** you experienced when injecting your treatment?

☐ Very unacceptable ☐ Unacceptable ☐ Neither acceptable nor unacceptable ☐ Acceptable ☐ Very acceptable

13 Over the past four weeks, how acceptable or unacceptable did you find the **way you had to store the injection treatment?**

☐ Very unacceptable ☐ Unacceptable ☐ Neither acceptable nor unacceptable ☐ Acceptable ☐ Very acceptable

14 Over the past four weeks, how acceptable or unacceptable did you find **the time it took to prepare your injection treatment?**

☐ Very unacceptable ☐ Unacceptable ☐ Neither acceptable nor unacceptable ☐ Acceptable ☐ Very acceptable

15 Over the past four weeks, how acceptable or unacceptable did you find **the time it took to give yourself the injection treatment?**

☐ Very unacceptable ☐ Unacceptable ☐ Neither acceptable nor unacceptable ☐ Acceptable ☐ Very acceptable

16 Over the past four weeks, how acceptable or unacceptable did you find **the number of times** you had to give yourself the injection treatment?

☐ Very unacceptable ☐ Unacceptable ☐ Neither acceptable nor unacceptable ☐ Acceptable ☐ Very acceptable

I-TAQ – US English – Version 1, 13 March 2015 – Regeneron Pharmaceuticals and Sanofi

Page 2 of 3

17 Over the past four weeks, how easy or difficult was it to **remember** to **give yourself the injection treatment?**

☐	☐	☐	☐	☐
Very difficult	Difficult	Neither easy nor difficult	Easy	Very easy

18 Over the past four weeks, how easy or difficult was it **to fit in taking the injection into your daily life?**

☐	☐	☐	☐	☐
Very difficult	Difficult	Neither easy nor difficult	Easy	Very easy

19 Over the past four weeks, how **convenient or inconvenient** did you find taking the injection treatment?

☐	☐	☐	☐	☐
Very inconvenient	Inconvenient	Neither convenient nor inconvenient	Convenient	Very convenient

20 After this study, would you **choose to continue** using the injection treatment to treat your condition?

☐	☐	☐	☐	☐
Definitely not	Probably not	I don't know	Yes probably	Yes definitely

21 Thinking about all aspects of your injection treatment over the past four weeks, how **acceptable or unacceptable** did you find the treatment?

☐	☐	☐	☐	☐
Very unacceptable	Unacceptable	Neither acceptable nor unacceptable	Acceptable	Very acceptable

For the next question, please think about all treatments you are currently taking including the study injection and any tablets or pills.

Please mark the response that most closely corresponds to your own experiences. There are no right or wrong answers. If you are not sure about which response to choose, mark the one which you think is most appropriate.

22 Overall, over the past four weeks, how **acceptable or unacceptable** did you find taking **all of your treatments**, including the study injection and **any other pills or tablets?**

☐	☐	☐	☐	☐
Very unacceptable	Unacceptable	Neither acceptable nor unacceptable	Acceptable	Very acceptable

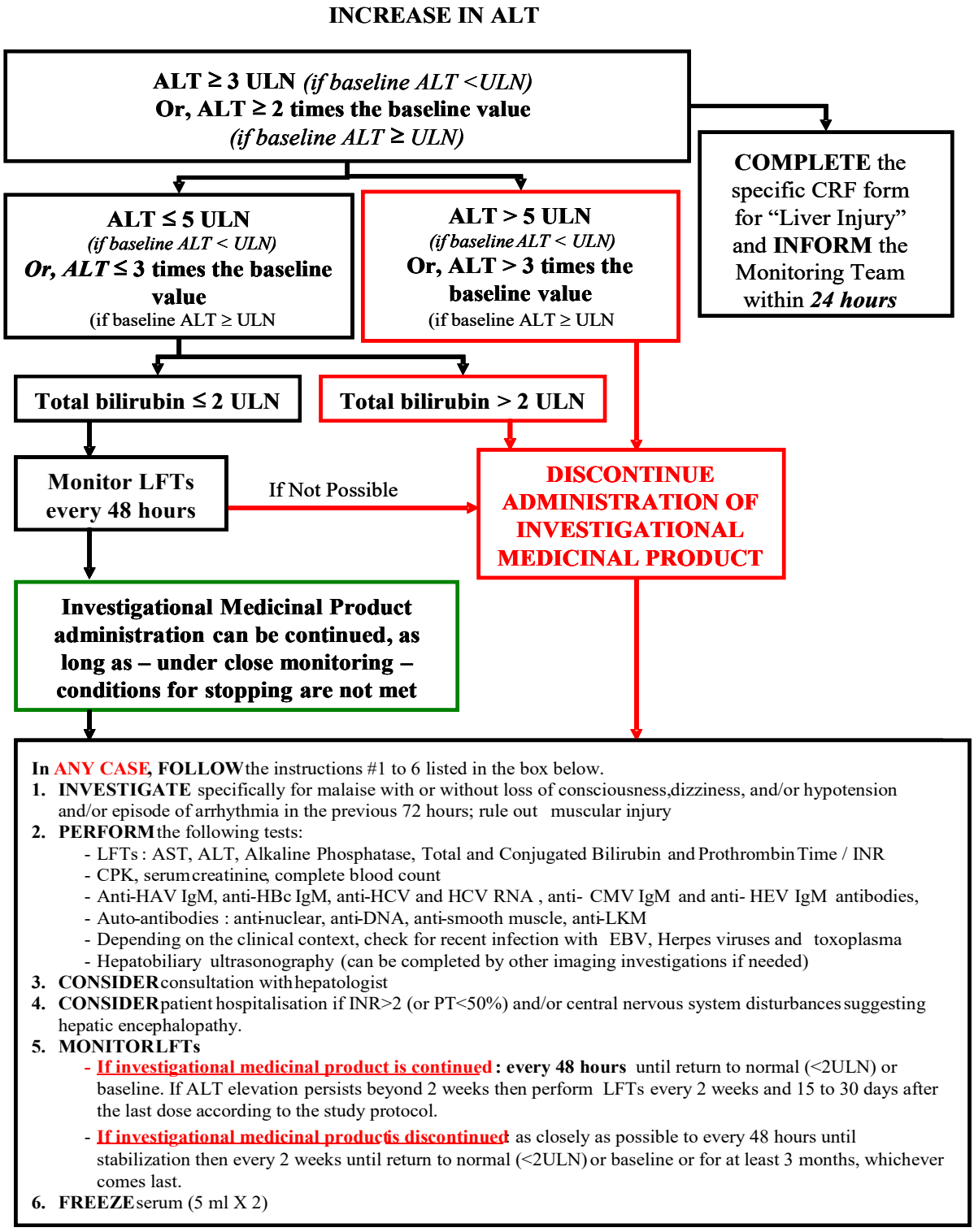
Appendix D Definition of Cardiovascular Disease Risk Categories

- **Very high CV risk** is defined as a history of documented CHD, ischemic stroke, transient ischemic attack, carotid artery occlusion >50% without symptoms, carotid endarterectomy or carotid artery stent procedure, peripheral arterial disease, abdominal aortic aneurysm, renal artery stenosis, renal artery stent procedure, type 1 or type 2 diabetes mellitus with target organ damage.

  A history of documented CHD includes 1 or more of the following:

  - Acute myocardial infarction.
  - Silent myocardial infarction.
  - Unstable angina.
  - Coronary revascularization procedure (eg, percutaneous coronary intervention or coronary artery bypass graft surgery).
  - Clinically significant CHD diagnosed by invasive or non-invasive testing (such as coronary angiography, stress test using treadmill, stress echocardiography or nuclear imaging).
- **High CV risk** is defined as a calculated 10-year fatal CVD risk SCORE ≥5% (1), moderate chronic kidney disease, type 1 or type 2 diabetes mellitus without target organ damage, or heFH.
- **Moderate CV risk** is defined as a calculated 10-year fatal CVD risk SCORE ≥1 and <5% (1).

Appendix E General guidance for the follow-up of ALT increase by Sanofi



Appendix F Procedure for collection, handling, storage and shipment of SAR236533, pharmacokinetic, and anti-SAR236553 antibody samples

1. SAMPLING SUPPLIES DESCRIPTION

Serum SAR236553 samples	**Collection material:** 5mL red-top vacutainer tubes (containing no additives or anti-coagulant, B-D Cat #367814; Vacutainer 5mL tubes) for **serum**
	Storage tube: Aliquot approximately equal volumes of serum into TWO separate 1.8 mL plastic 2D barcoded cryovials, one for the primary aliquot and one for the duplicate aliquot. Do not exceed 1.0 mL of serum into each cryovial. Use one of the approved cryovials listed below. • Nunc Item # 374502 • VWR: Catalog # 89233-708 • ThermoFisher/USA Scientific: Catalog # 12590007
Serum Anti-SAR236553 antibody (ADA) samples	**Collection material:** 5mL red-top vacutainer tubes (containing no additives or anti-coagulant, B-D Cat #367814; Vacutainer 5mL tubes) for **serum**
	Storage tube: Aliquot approximately equal volumes of serum into TWO separate 1.8 mL plastic 2D barcoded cryovials, one for the primary aliquot and one for the duplicate aliquot. Do not exceed 1.0 mL of serum into each cryovial. Use one of the approved cryovials listed below. • Nunc Item# 374502 • VWR: Catalog # 89233-708 • ThermoFisher/USA Scientific: Catalog # 12590007
Miscellaneous	Refrigerated centrifuge Collection material provided by Contract Research Organization (CRO)
	Specimen storage labels for SAR236553 provided by: CRO Specimen storage labels for anti- SAR236553 provided by: CRO Specimen storage tube labels for pharmacogenetic specimens provided by Covance, Indianapolis, IN
	Styrofoam shippers with boxes, shipping labels, Ziplock storage bag, and any other necessary packaging supplies in order to comply with IATA Dangerous Goods Regulations, Packing Instructions 650 for shipment below 0°C.

2. SERUM SAR236553 AND ANTI-SAR236553 ANTIBODY (ADA) SAMPLES

2. 1 Collection/Handling/Processing of Samples

Collection schedule

Per protocol

PK Serum Sample Collection and Preparation

- At intervals stated in the clinical study protocol, whole blood from subjects will be collected in 5-mL red-top vacutainer tubes (US B-D Cat #367814, European B-D Cat #369032) containing clot activator and no additional additives or anti-coagulant for **PK SERUM** sample preparation.
- Collect 5 mL blood directly into 5-mL red-top vacutainer tube and invert 5 times.
- Allow blood to clot for 30 minutes.
- Centrifuge at approximately 1200 x g for 15 minutes to separate clot from serum.
- Within 30 minutes after centrifugation, draw off serum very slowly with transfer pipette, approaching no closer than 0.5 cm of the buffy coat and taking great care not to disturb the buffy coat (any contamination may invalidate the assay).
- All cryovials must be properly labeled with labels provided by CRO as per the laboratory manual.
- Aliquot approximately equal volumes of serum into **TWO** separate 1.8-mL plastic 2D barcoded cryovials, one for the primary aliquot and one for the duplicate aliquot. Do not exceed 1 mL of serum into each cryovial. Use one of the approved cryovials listed below.
  - Nunc Item # 374502
  - VWR: Catalog # 89233-708
  - ThermoFisher/USA Scientific: Catalog # 12590007
- Freeze all cryovials immediately. All serum samples must be stored in a -20° C or colder freezer that does **NOT** auto-defrost until the next earliest shipment. For long-term storage, all serum samples should be stored in a -80° C freezer.
  - **Note: If the site does not have a -20°C or colder freezer that does NOT auto-defrost, ship the serum samples on dry ice on the day of collection to CRO.**
- Sites must ship the primary aliquot in a separate shipment from the duplicate aliquot.

ADA Serum Sample Collection and Preparation

- At intervals stated in the clinical study protocol, whole blood from subjects will be collected in 5-mL red-top vacutainer tubes (US BD Cat #367814, European B-D Cat #369032) containing clot activator and no additional additives or anti-coagulant for **ADA SERUM** sample preparation.
- Collect 5 mL blood directly into 5-mL red-top vacutainer tube and invert 5 times.
- Allow blood to clot for 30 minutes.
- Centrifuge at approximately 1200 x g for 15 minutes to separate clot from serum.
- Within 30 minutes after centrifugation, draw off serum very slowly with transfer pipette, approaching no closer than 0.5 cm of the buffy coat and taking great care not to disturb the buffy coat (any contamination may invalidate the assay).
- All cryovials must be properly labeled, with labels provided by CRO as per the laboratory manual.
- Aliquot approximately equal volumes of serum into **TWO** separate 1.8-mL plastic 2D barcoded cryovials, one for the primary aliquot and one for the duplicate aliquot. Do not exceed 1 mL of serum into each cryovial. Use one of the approved cryovials listed below.
  - Nunc Item# 374502
  - VWR: Catalog # 89233-708
  - ThermoFisher/USA Scientific: Catalog # 12590007
- Freeze all cryovials immediately. All serum samples must be stored in a -20° C or colder freezer that does **NOT** auto-defrost until the next earliest shipment. For long-term storage, all serum samples should be stored in a -80° C freezer.
  - **Note: If the site does not have a -20°C or colder freezer that does NOT auto-defrost, ship the serum samples on dry ice on the day of collection to PPD Central Labs.**
- Sites must ship the primary aliquots in a separate shipment from the duplicate aliquots.

2.2 Labeling of specimens

Additional instructions will be provided by the central lab vendor and/or the Sponsor.

Appendix G Local injection site reactions assessment

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

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

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

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

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

Appendix H Clinical diagnosis of heterozygous familial hypercholesterolemia (heFH)

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.			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.			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	>330	8
b LDL-cholesterol	6.5-8.4	250-329	5
c LDL-cholesterol	5.0-6.4	190-249	3
d LDL-cholesterol	4.0-4.9	155-189	1
(HDL-cholesterol and triglycerides are normal)			
DNA-analysis			
a Functional mutation low-density lipoprotein receptor gene present			8
Diagnosis of heFH is:			
Certain When		>8 points	
Probable When		6-8 points	
Possible When		3-5 points	

Simon Broome Register Diagnostic Criteria for Heterozygous Familial ypercholesterolemia

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 MI 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.

MSC14864 16.1.1 Protocol

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	Clinical Approval	21-Nov-2017 16:09 GMT+0100
[redacted]	Clinical Approval	21-Nov-2017 19:44 GMT+0100