AMENDED CLINICAL TRIAL PROTOCOL NO. 02

COMPOUND: alirocumab / SAR236553-REGN727

An Open-Label Study to Evaluate the Efficacy and Safety of Alirocumab in Children and Adolescents with Homozygous Familial Hypercholesterolemia

STUDY NUMBER: EFC14660

VERSION DATE / STATUS: 11-Sep-2018 / Approved

NCT03510715

Version Number:	1	EudraCT	2017-002297-39
		IND Number	105574
		WHO universal trial number	U1111-1200-2046
Date:	11-Sep-2018	Total number of pages:	112

NAMES AND ADDRESSES OF

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 02	All	11-Sep-2018, version 1 (electronic 2.0)
Amended Clinical Trial Protocol 01	All	20-Feb-2018, version 1 (electronic 1.0)
Original Protocol		21-Dec-2017, version 1 (electronic 1.0)

Amended protocol 02 (11-Sep-2018)

This amended protocol (amendment 02) is considered to be nonsubstantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical integrity of participants nor the scientific value of the study.

OVERALL RATIONALE FOR THE AMENDMENT

Requests have been received from the Norwegian and Argentinian regulatory agencies for monthly pregnancy tests on all female patients of childbearing potential throughout the entire study in accordance to the clinical trials facilitation group (CTFG) guideline on "Recommendations related to contraception and pregnancy testing in clinical trials". As a result, in these countries logistic aspects will be arranged to allow urine pregnancy tests to be performed by the patients at home in-between clinic visits.

In addition, parts of the protocol inadvertently state a separate informed consent form should be used for homozygous familial hypercholesterolemia (hoFH) genotyping. However, the consent for hoFH genotyping is actually part of the core study information and informed consent form (CSICF), therefore relevant sections in the protocol are being revised accordingly for clarification purpose.

Protocol amendment summary of changes table

Section# and Name	Description of Change	Brief Rationale
12.2 Informed consent	Specifying that the optional consent for genotyping is part of the main informed consent form.	Clarification that the homozygous familial hypercholesterolemia consent is not a separate document from the informed consent form.
17. Appendices- Appendix I. Country Specific Requirements and 1.2 Study flowchart-footnote "u"	Monthly urine pregnancy tests to be performed at home added as country specific changes.	Added as Appendix I for Norway and Argentina, in keeping with the clinical trials facilitation group (CTFG) guidelines.
Throughout	Minor editorial revisions to reflect the rationale stated above.	Minor, therefore have not been summarized.

CLINICAL TRIAL SUMMARY

COMPOUND: alirocumab	**STUDY No.: EFC14660**
TITLE	An Open-Label Study to Evaluate the Efficacy and Safety of Alirocumab in Children and Adolescents with Homozygous Familial Hypercholesterolemia
INVESTIGATOR/TRIAL LOCATION	Worldwide
PHASE OF DEVELOPMENT	Phase 3
STUDY OBJECTIVE(S)	**Primary objective:** • To evaluate the efficacy of alirocumab (75 or 150 mg depending on body weight [BW]), administered every 2 weeks (Q2W), on low-density lipoprotein cholesterol (LDL-C) levels at Week 12 of treatment in children with homozygous familial hypercholesterolemia (hoFH) 8 to 17 years of age on top of background treatments. **Secondary objectives:** • To evaluate the efficacy of alirocumab after 24 and 48 weeks of treatment on LDL-C levels. • To evaluate the effects of alirocumab on other lipid parameters (eg, apolipoprotein B [Apo B], non-high density lipoprotein cholesterol [non-HDL-C], total-cholesterol [total-C], high-density lipoprotein cholesterol [HDL-C], lipoprotein (a) [Lp (a)], triglycerides [TG], apolipoprotein A-1 [Apo A-1] levels) after 12, 24, and 48 weeks of treatment. • To evaluate the safety and tolerability of alirocumab up to 48 weeks of treatment. **Other objectives:** • To evaluate the development of anti-alirocumab antibodies (ADA) during 48 weeks of treatment. • To evaluate the pharmacokinetics (PK) of alirocumab.
STUDY DESIGN	This study is a multi-national, multi-center, open-label study with a treatment period of 48 weeks. Children and adolescents aged 8 to 17 years with hoFH confirmed by genetic testing and LDL-C ≥130 mg/dL (3.37 mmol/L) at screening visit, despite treatment with stable lipid modifying therapy (LMT)* at optimal doses**, will be selected to enter the screening period. *Stable LMTs are defined as stable optimal dose of statin ± other stable LMTs or stable dose of non-statin LMTs in statin-intolerant patients for at least 4 weeks prior to screening LDL-C being obtained. **The optimal dose of statin is defined as the dose prescribed based on local guidelines or practice, or is the dose that is maximally tolerated due to adverse effects of higher doses. For patients not receiving maximally tolerated statin, statin intensification should be carefully considered prior to entry in this study in order to ensure that the addition of a non-statin LDL-C lowering therapy (ie, alirocumab) would be the next appropriate step in the management of the patient's hypercholesterolemia. The highest dose of statin should not exceed the maximum labeled dose of statin for pediatric patients as per the local prescribing information.

	A statin-intolerant patient is defined as one with the documented inability to tolerate at least 2 statins: one statin at the lowest daily starting dose, and another statin at any dose, due to skeletal muscle-related symptoms, other than those due to strain or trauma, such as pain, aches, weakness, or cramping, that began or increased during statin therapy and stopped when statin therapy was discontinued. Patients not receiving a daily approved regimen of a statin (eg, 1 to 3 times weekly) are also considered as not able to tolerate a daily dose. The study will consist of a run-in period (as needed), a screening period, an open-label treatment period, and a follow-up period. **Run-in period (as needed, up to Week -6):** The run-in period will be up to 4 weeks (+2 days) in duration. Patients who consent to participate in the study, but who have not been on stable LMTs for at least 4 weeks or require statin intensification when initially seen, can participate in a run-in period until LMT dose(s) have been stable for at least 4 weeks. Patients eligible for the run-in period are expected to fulfill the LDL-C eligibility criterion at the end of the run-in period. Patients who require treatment with statin de novo are not allowed to enter the run-in period in order to avoid the potential for multiple titration steps. Patients, who have initiated apheresis procedure (every week or every other week) at least 6 months prior to giving informed consent to the study, can enter the run-in period. Another possible situation requiring the run-in period includes patients with suspected hoFH based on clinical criteria but without confirmation by previous genetic testing. Such patients will be asked to undergo centralized genetic testing during the run-in period. **Screening period:** For all patients regardless of their participation in a run-in period, the screening period will be up to 2 weeks (+5 days) in duration. The injection training will occur during the screening period after the eligibility criteria have been checked and it is confirmed that the patient is likely to be included. Patients aged ≥12 years (or another designated person such as parent, etc) will be trained to self-inject/inject with placebo for alirocumab. Patients 8 to 11 years old will be assigned a parent or another designated person who will be trained during the injection training visit or an alternative arrangement. In all cases, alternative arrangements for this required injection training may be allowed as needed, regardless of age. Please note that this visit (injection training visit) can take place at the same visit as D1 as per the site or patient preference. Prior to the injection, a local topical anesthetic may be utilized as per the Investigator's judgment. Investigators will have the option of providing a second placebo kit for alirocumab for patients/parents who require additional injection training prior to enrollment. Patients can be enrolled after the injection training visit and as soon as all inclusion and no exclusion criteria are met.

	Treatment period: The overall treatment period is 48 weeks in duration. All patients will receive subcutaneously (SC) either 75 or 150 mg alirocumab Q2W at entry depending on their BW, without any dose adjustment up to Week 12. After Week 12, the dose of alirocumab can be adjusted in case of weight change after baseline, such that the dose corresponds to the patient's BW: • 75 mg for BW <50 kg. • 150 mg for BW ≥50 kg. For patients treated with apheresis, the frequency will be fixed to the individual patient's established schedule up to Week 12. After Week 12, the frequency of apheresis can be adapted following Investigator judgment. The first investigational medicinal product (IMP) injection from the study treatment kit allocated by interactive response technology (IRT) will be administered at the site on the day of entry and as close as possible after their entry into the study. Patients will be monitored at the investigational site for at least 30 minutes after this first injection. The subsequent injections will be performed at a patient-preferred location (eg, home). All of the IMP injections can be performed by trained patient (self-injection if aged ≥12 years), parent, or another designated person, or alternative arrangements for injection administration will be allowed as needed (eg, return to the investigational site). Prior to any injection, a local topical anesthetic may be utilized as per the Investigator's judgment. Injection training: • Further injection training can be provided at the enrollment visit Week 0/Day 1 when the patient/parent or a trained designated person injects the first IMP. • Additional training can be offered at scheduled or unscheduled visits with the scheduled open-label treatment, as per patient/parent or Investigator's judgment. The laboratory measurement of lipid parameters will be performed by a central laboratory. The results will be communicated to the sites. Patients will be instructed to follow a diet to treat their hypercholesterolemia in accordance with local guidelines or treatment practice and they should be on this diet throughout the entire study duration. The Investigator will be responsible, based on his/her own judgment related to the patients' LDL-C levels and the safety profile, to continue or discontinue alirocumab throughout the study. The statin dose or other LMT should not be modified to adjust to the degree of LDL-C lowering before Week 12, unless otherwise indicated. Even if it is unlikely in this hoFH population, further recommendations for the management and monitoring of patients who will have achieved LDL-C level <50 mg/dL (1.30 mmol/L) on one or more occasion are provided in this protocol. **Follow-up period:** A follow-up call will be planned 10 weeks after the last IMP injection, ie, 8 weeks after the end of treatment (EOT) visit, for the patients who complete the study and for patients who discontinue early for any reason.

STUDY POPULATION **Main selection criteria**	**Inclusion criteria:** I 01. Male and female children and adolescents aged 8 to 17 years genetically diagnosed with homozygous familial hypercholesterolemia* inadequately controlled (see threshold mentioned in exclusion criterion E 02) despite treatment with optimal dose of statin** with or without other LMTs, or non-statin LMTs if statin-intolerant***, at stable dose(s) for at least 4 weeks. I 02. A signed informed consent indicating parental permission with or without patient assent, depending on capacity for understanding based on developmental maturity. In cases involving emancipated or mature minors with adequate decision-making capacity, or when otherwise permitted by law, a signed informed consent directly from patients. I 03. For patients on apheresis, currently undergoing stable LDL apheresis therapy for at least 4 weeks prior to the screening visit (Week -2) and have initiated apheresis treatment for at least 6 months (see Appendix A). * *Diagnosis of hoFH must be made either by previous genotyping (true homozygotes, compound heterozygotes, or double heterozygotes) or current genotyping performed after having been suspected by clinical criteria according to European Atherosclerosis Society (EAS) Consensus Panel recommendations for diagnosis of HoFH. Previous genotyping refers to documented results that are available from prior genotyping testing supporting a diagnosis of hoFH. Current centralized genotyping refers to patients electing to undergo genotyping during the run-in period with results supporting a diagnosis of hoFH (see Appendix B).* ** *The optimal dose of statin is defined as the stable daily dose prescribed based on local guidelines or practice, or is the dose that is maximally tolerated due to adverse effects of higher doses. For patients not receiving the maximally tolerated dose of statin, statin intensification should be carefully considered prior to inclusion in this study in order to ensure that the addition of a non-statin LDL-C lowering therapy (ie, alirocumab) would be the next appropriate step in the management of the patient's hypercholesterolemia. The highest dose of statin should not exceed the maximum labeled dose of statin for pediatric patients as per the local prescribing information.* *** *A statin-intolerant patient is defined as a patient with the documented inability to tolerate at least 2 statins: one statin at the lowest daily starting dose, AND another statin at any dose, due to skeletal muscle-related symptoms, other than those due to strain or trauma, such as pain, aches, weakness, or cramping that began or increased during statin therapy and stopped when statin therapy was discontinued. Patients not receiving a daily approved regimen of a statin (eg, 1 to 3 times weekly) will also be considered as not able to tolerate a daily dose.* **Exclusion criteria:** **Key Exclusion criteria (additional details are in Section 7.2):** E 01. Children and adolescents aged less than 8 years or more than 17 years at the time of informed consent signature, unless different local regulation applies (eg, for Russia only: patients aged less than 12 years or more than 17 years at the time of informed consent signature). *Note: Patients aged 8 to less than 10 years who have not had previous attempts to lower LDL-C by other means will be excluded.*

	E 02. Patients with LDL-C (pre-apheresis, if applicable) less than 130 mg/dL (3.37 mmol/L) obtained during the screening period after the patient has been on stable apheresis procedure or LMT (ie, stable optimal dose of statin ± other stable LMTs, or stable non-statin LMTs in statin-intolerant patients) treatment for at least 4 weeks. E 03. Patients with null low-density lipoprotein receptor (LDLR) mutations in both alleles. E 04. Patients with BW less than 25 kg. E 05. Patients aged 8 to 9 years not at Tanner Stage 1 and patients aged of 10 to 17 years not at least at Tanner Stage 2 in their development. E 06. Daily dose of statin that is above the maximum recommended dose for pediatric patients as per the local prescribing label. E 07. Patients who will receive statin de novo during the run-in period. E 08. Use of nutraceutical products or over-the-counter therapies that may affect lipids which have not been at a stable dose for at least 4 weeks prior to the screening visit. E 09. Patients not previously instructed on a cholesterol-lowering diet prior to the screening visit. E 10. Mipomersen in the last 5 months. E 11. Patients with uncontrolled (ie, HbA_{1c} >9% at the screening visit) Type 1 or 2 diabetes mellitus. E 12. Patients with known uncontrolled thyroid disease (ie, thyroid-stimulating hormone levels outside of the laboratory's reference range within the past 6 months, or with elevated free T3 or T4 and with clinical symptoms of hyperthyroidism). E 13. Patients who use systemic corticosteroids. E 14. Patients with uncontrolled (ie, systolic blood pressure or diastolic blood pressure above local guidelines or equivalent) hypertension. E 15. Fasting triglycerides >350 mg/dL (3.95 mmol/L) at the screening visit. E 16. Severe renal impairment (ie, estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2) at the screening visit. E 17. ALT (alanine aminotransferase) or AST (aspartate aminotransferase) >2 x upper limit of normal (ULN) (1 repeat laboratory allowed per patient) at the screening visit. E 18. CPK (creatine phosphokinase) >3 x ULN (1 repeat laboratory allowed per patient) at the screening visit.
Total expected number of patients:	Approximately 18 patients enrolled.
Expected number of sites:	Approximately 20 sites.
STUDY TREATMENT(s)	
Investigational medicinal product(s)	Alirocumab
Formulation:	Prefilled syringes (PFS) with finger grip, to be replaced by PFS with safety system (PFS-S) as soon as available: Alirocumab 75 or 150 mg/mL solution as described below: • BW <50 kg: 1.0 mL of alirocumab 75 mg/mL solution. • BW ≥50 kg: 1.0 mL of alirocumab 150 mg/mL solution.
Route(s) of administration:	Subcutaneous (SC) injections in the abdomen, thigh, or outer area of upper arm.

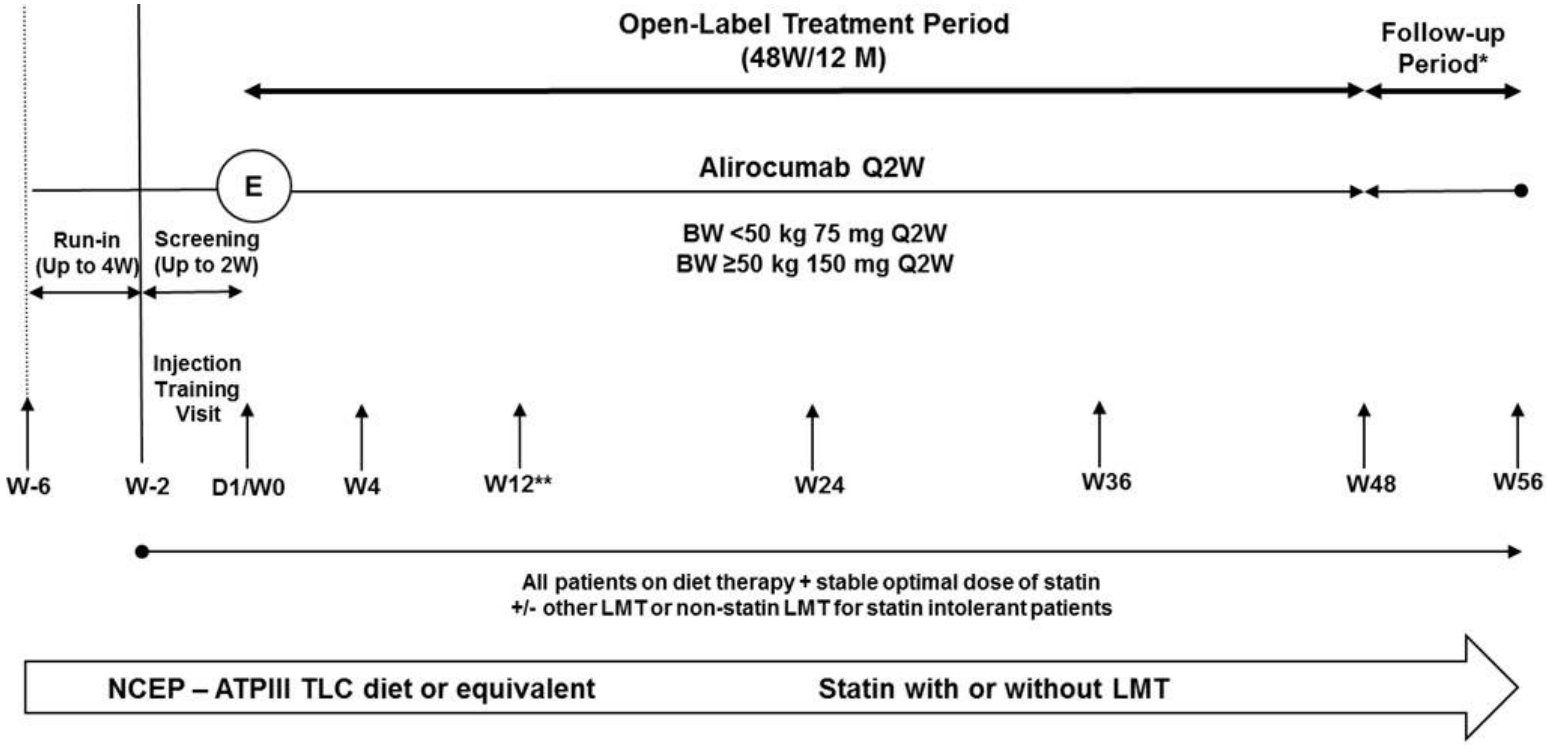
Dose regimen:	Alirocumab Q2W
Noninvestigational medicinal product(s)	The following classes of drugs (not all of which are indicated for pediatric use in all countries; for further information, Investigators should refer to their local prescribing information) are identified as noninvestigational medicinal product (NIMP) because the medication is a potential background therapy that will not be provided by the Sponsor: • Statins. • Cholesterol absorption inhibitors (ezetimibe). • Bile acid-binding sequestrants (such as cholestyramine, colestipol, colesevelam). • Nicotinic acid. • Fenofibrate. • Omega-3 fatty acids (≥1000 mg daily).
ENDPOINT(S)	**Primary endpoint:** • Percent change in LDL-C (pre-apheresis, if applicable) from baseline to Week 12 in the intent-to-treat (ITT) population, using all LDL-C values (pre-apheresis, if applicable) regardless of adherence to treatment (ITT estimand). **Secondary efficacy endpoints:** • Percent change in LDL-C (pre-apheresis, if applicable) from baseline to Week 12 in the ITT population, using all LDL-C values during the treatment period (on-treatment estimand). • Percent change in LDL-C (pre-apheresis, if applicable) from baseline to Weeks 24 and 48 (ITT and on-treatment estimands). • Percent change in Apo B, non-HDL-C, total-C, Lp (a), HDL-C, fasting TG, and Apo A-1 (pre-apheresis, if applicable) from baseline to Weeks 12, 24, and 48 (ITT and on-treatment estimands). • Proportion of patients with ≥15% reduction in LDL-C (pre-apheresis, if applicable) at Weeks 12, 24, and 48 (ITT and on-treatment estimands). • The absolute change in LDL-C from baseline to Weeks 12, 24, and 48 (ITT and on-treatment estimands).
	Safety endpoints: • Main safety parameters: adverse events (AEs), serious AEs (SAEs), and AEs of special interest (AESIs), assessed throughout the study. • Other safety parameters: laboratory data, vital signs, body weight, height, and Tanner stage, assessed throughout the study. **Other endpoints:** • Anti-alirocumab antibodies (ADA) assessed throughout the study. • Alirocumab and PCSK9 concentrations assessed throughout the study.

ASSESSMENT SCHEDULE	Run-in period (as needed): The run-in period will be up to 4 weeks (+2 days), with 1 visit. Patients can enter the screening period as soon as the criterion for stable LMT is met and/or centralized genotyping data (if no previous genotyping) is available. Screening period: The screening period will be up to 2 weeks (+5 days) in duration. The injection training will occur during the screening period after the eligibility criteria have been checked and it is confirmed that the patient is likely to be included. Patients aged ≥12 years (or another designated person such as parent, etc) will be trained to self-inject/inject with placebo for alirocumab. Patients 8 to 11 years old will be assigned a parent or another designated person who will be trained during the injection training visit or an alternative arrangement. In all cases, alternative arrangements for this required injection training may be allowed as needed, regardless of age. Patients can be enrolled after the injection training visit and as soon as eligibility is confirmed. Treatment period: The overall treatment period will be 48 weeks in duration. Visits will be scheduled as follows: enrollment visit (Day 1, Week 0), Weeks 4, 12, 24, 36, and 48 (end of the treatment period visit). Follow-up period: A follow-up call will be planned 10 weeks after the last IMP injection, ie, 8 weeks after the EOT visit, for the patients who will complete the study and for the patients who discontinue early for any reason.
STATISTICAL CONSIDERATIONS	**Sample size determination:** No sample size calculation was performed. Eighteen patients are planned to be enrolled to have at least 15 evaluable patients considering the recruitment constraints in this rare disease population. **Analysis population:** The primary efficacy analysis population will be the ITT population, defined as the patients receiving at least one dose or partial dose of IMP. Safety analyses will be performed on the safety population, which will consist of patients receiving at least one dose or partial dose of IMP. **Primary analysis:** The percent change from baseline in LDL-C at Week 12 will be analyzed in the ITT population using a mixed-effect model with repeated measures (MMRM) approach. All post-baseline data available within the Week 4 to Week 48 analysis windows will be used and missing data will be accounted for by the MMRM model. The model will include the fixed categorical effect of time point (Weeks 4, 12, 24, and 48), as well as the continuous fixed covariate of baseline LDL-C value. **Safety analysis:** Safety analyses (AEs, laboratory data, and vital signs) will be descriptive, based on the safety population.
DURATION OF STUDY PERIOD (per patient)	A study duration of up to 62 weeks (run-in period, as needed): up to 4 weeks, screening period: up to 2 weeks, treatment period: 48 weeks and follow-up of 8 weeks.

STUDY COMMITTEES	Steering committee: ☒ Yes ☐ No The independent Steering Committee will provide scientific and strategic direction for the trial and will have overall responsibility for its execution. The Steering Committee will provide guidance on producing and conducting a scientifically sound design and ensuring accurate reporting of the study. The Steering Committee will address and resolve scientific issues encountered during the study. The Steering Committee will also review the recommendations from the Data Monitoring Committee (DMC) throughout the study. Data monitoring committee: ☒ Yes ☐ No An independent DMC for pediatric studies will monitor patient safety by conducting reviews of accumulated safety data. The DMC will provide the Sponsor and the Steering Committee with appropriate recommendations on the conduct of the clinical trial to ensure the protection and safety of the patients enrolled in the study. In addition, the DMC will also institute any measures that may be required for ensuring the integrity of the study results during the study execution. Adjudication committee: ☐ Yes ☒ No

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



* Follow-up call to be performed 10 weeks after the last injection for the patients who complete the study and for the patients who discontinue early
** Primary efficacy endpoint at Week 12

ATPIII = Adult Treatment Panel III; D = Day; E = enrollment; LMT = lipid modifying therapy; NCEP = National Cholesterol Education Panel; TLC = Therapeutic Lifestyle Changes; W = Week

1.2 STUDY FLOW CHARTS

Study Flow chart	Run-in (as needed)[a]	Screening		Open-Label Treatment Period						Follow-up Phone call
VISIT	1	2	3	4	5	6	7	8	9	10
Week	Up to W-6	Up to W-2	Up to W-1[b]	W0/D1	W4	W12	W24	W36	W48[c]	W56
Visit Window (+/- days)	+2	+5	+/- 7		+/- 7	+/- 3	+/- 7	+/- 7	+/- 3	+/- 7
Informed consent	X[d]									
hoFH Genotyping Informed Consent (if needed)[e f]	X									
Inclusion criteria	X	X		X						
Exclusion criteria	X	X		X						
Patient demography	X[f]									
Medical/surgical/family medical history	X[f]									
Alcohol/smoking habits	X[f]									
Prior medication history	X[f, g]									
Physical examination	X[f]					X	X		X	
Measured body weight	X[f]			X	X	X	X	X	X	
Measured height	X[f]			X	X	X	X		X	
Tanner stage[h]	X[f]					X	X		X	
IRT contact	X	X	X	X		X	X	X	X	X
Inclusion				X						
Treatment:										
Injection training			X[i, j]	X[j, k]						
IMP administration Q2W regimen[j, l]				←----------	----------	----------	----------	----------	----------→	
Open-label IMP kit dispensation[m]				X		X	X	X		
Compliance check of IMP and data collection on IMP administration					X	X	X	X	X	
Concomitant medication recording				X	X	X	X	X	X	X

Study Flow chart	Run-in (as needed)[a]	Screening		Open-Label Treatment Period						Follow-up Phone call
VISIT	1	2	3	4	5	6	7	8	9	10
Week	Up to W-6	Up to W-2	Up to W-1[b]	W0/D1	W4	W12	W24	W36	W48[c]	W56
Visit Window (+/- days)	+2	+5	+/- 7		+/- 7	+/- 3	+/- 7	+/- 7	+/- 3	+/- 7
Check of stability of background LMT, including apheresis frequency, if applicable	X	X	X	X	X	X	X	X	X	
Review of diet[n]	X[f]			X	X	X	X	X	X	
Efficacy:										
Total-C, LDL-C, HDL-C, TG, non-HDL-C[o, p]		X		X	X	X	X		X	
Apo B, Apo A-1, ratio Apo B/Apo A-1, and Lp (a)[o, p]				X		X	X		X	
Safety:										
AE/SAE recording	X	X	X	X	X	X	X	X	X	X
Vital signs[q]	X			X	X	X	X	X	X	
Laboratory testing:										
hoFH genotyping[e, o]	X									
Hematology and chemistry[r, o]		X		X	X	X	X		X	
HbA_{1c} [o]		X				X	X		X	
CPK-MB and cardiac troponin[s, o]				X		X				
Creatine phosphokinase (CPK)[o]		X		X		X	X		X	
Liver panel[t, o]		X		X	X	X	X		X	
Pregnancy test[u, o]		X		X		X	X	X	X	
Anti-alirocumab antibodies (ADA)[v, o]				X		X	X		X	
Serum alirocumab concentration (pharmacokinetics) and PCSK9 concentrations[w, o]				X		X	X		X	

AE = adverse event; Apo A-1 = apolipoprotein A 1; Apo B = apolipoprotein B; CPK-MB = creatine phosphokinase-MB; HDL-C = high-density lipoprotein cholesterol; hoFH = homozygous familial hypercholesterolemia; IMP = investigational medicinal product; IRT = interactive response technology; IVRS = Interactive Voice Response System; LDL-C = low-density lipoprotein cholesterol; LMT = lipid modifying therapy; Lp (a) = lipoprotein (a); non-HDL-C = non-high density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9; Q2W = every 2 weeks; SAE = serious adverse event; total-C = total cholesterol; TG = triglycerides

a Patients who have not been on stable LMT for at least 4 weeks or require statin intensification when initially seen can participate in a run-in period until LMT dose(s) have been stable for at least 4 weeks. Patients with suspected hoFH but without confirmation by previous genetic testing can undergo centralized genetic testing during the run-in period.
b The W-1 visit (injection training visit) can take place at the same visit as D1 as per the site or patient preference.
c End-of-treatment period visit.
d Informed consent should be obtained only once. If the patient enters the run-in period then informed consent will be obtained prior to entry into the run-in period. If the patient does not require a run-in period, then informed consent will be obtained prior to entry into the screening period.
e Genotyping for hoFH will be conducted from a specimen of whole blood, saliva, or buccal swab in patients consenting to undergo genotyping testing. This test will be recommended for all patients, but will be mandatory only for patients without previously documented genotyping. For non-mandatory genotyping, the sample should preferably be taken during the screening period, but can be done at any visit during the treatment period.
f The corresponding assessment should be obtained only once. If the patient enters the run-in period then the corresponding assessment will be obtained during the run-in period. If the patient does not require a run-in period, then the corresponding assessment will be obtained during the screening period.
g Document prior medication history within the previous 12 weeks, especially for lipid modifying therapy (including statins) and nutraceutical products that may affect lipids (eg, omega-3 fatty acids, plant stanols such as those found in Benecol, flax seed oil, and psyllium).
h See Appendix C for Tanner stage evaluation.
i Injection training at screening period visit Week -1 is performed with placebo for alirocumab. Investigators will have the option of providing a second placebo kit for alirocumab for patients/parents who require additional injection training prior to enrollment.
j Prior to the injection, a local topical anesthetic may be utilized as per the Investigator's judgment.
k Further injection training can be provided at the enrollment visit Week 0/Day 1 when the patient/parent or a trained designated person injects the first dose of IMP from the open-label study treatment kit allocated by IVRS. Additional training can be offered at scheduled or unscheduled visits with the scheduled open-label treatment, as per patient/parent or Investigator's judgment.
l The first IMP injection during the treatment period will be done at the site on the day of enrollment and as close as possible after enrollment in the study. Subsequent injections will be done at a patient-preferred location (eg, home). These injections can be performed by a trained patient (self-injection) for patients ≥12 years old or parent, or another designated person, or alternative arrangements for injection administration will be allowed as needed for all patients whatever their age. It is suggested that patients ≥12 years old, who are trained to self-inject, do so with parental (or another designated person) supervision; however, this is not mandatory. The Investigator may evaluate the sustained reliability of this practice on a case by case basis given the variable adolescent ages, maturity levels, availability of the caregiver, or other relevant considerations, with the patient. The final decision as to whether supervision is appropriate for self-injection of alirocumab for patients ≥12 years old is per Investigator discretion.
m Along with kit dispensation, the treatment administration package (see Section 8.5) should be given as well as the patient diary and injection instruction manual, as needed.
n Patients/parents will be instructed to follow a diet to treat their hypercholesterolemia in accordance with local guidelines or treatment practice.
o Prior to any laboratory testing, the site may utilize a local topical anesthetic as per the Investigator's judgment. In case only a limited amount of blood can be drawn, specific tests performed for each sample obtained will be prioritized (estimated total blood volume of 91 mL for the entire study; 124 mL for patients on apheresis); see Section 10. Lipid panel 1 (Total-C, LDL-C, HDL-C, TG, and non-HDL-C) should take highest priority, followed by safety parameters, and then other parameters.
p The lipid levels will be communicated to the Investigator during the treatment period.
q Vital signs include: heart rate, systolic and diastolic BP in a sitting position.
r Hematology includes: complete blood cell count (CBC) including hematocrit, hemoglobin, red blood cell count, white blood cell count with differential count, and platelets. Chemistry includes: glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, uric acid, lactate dehydrogenase (LDH), total protein, albumin, and gamma-glutamyl transferase (γGT).
s CPK-MB and troponin levels will be assayed at baseline and at Week 12 and in case of any clinically relevant cardiovascular effect observed in patients.
t Liver panel: ALT, AST, alkaline phosphatase (ALP), and total bilirubin.
u Pregnancy test should be done on females of childbearing potential who are sexually active or females who have experienced menarche (they must have a confirmed test at screening). Pregnancy tests may be performed more frequently in some countries due to local legislations related to women of childbearing potential enrolled in clinical trials. See Appendix I. The screening (Week -2) pregnancy test should be a blood test. All other pregnancy tests will be with a local urine pregnancy test.
v Patient who prematurely discontinue alirocumab injections or who complete the study but have a titer at or above 240 for ADA at their last visit will have additional ADA samples taken at 6 to 12 months after the last alirocumab administration and thereafter, at about every 3 to 6 months until the titer returns to below 240.
w Blood samples should be collected before IMP injection and apheresis, if applicable. The PK samples will also be used for free and total PCSK9 analyses.

2 TABLE OF CONTENTS

2.1 LIST OF TABLES

3 LIST OF ABBREVIATIONS

ADA: anti-alirocumab (drug) antibodies
ADR: adverse drug reaction
AE: adverse event
ALP: alkaline phosphatase
Apo A-1: apolipoprotein A-1
Apo B: apolipoprotein B
AST: aspartate aminotransferase
BP: blood pressure
BW: body weight
CI: confidence interval
CPK: creatine phosphokinase
CPK-MB: creatine phosphokinase-MB
CRF: case report form
CVD: cardiovascular disease
DBP: diastolic blood pressure
DMC: Data Monitoring Committee
DRF: discrepancy resolution form
DTP: direct-to-patient
EAS: European Atherosclerosis Society
eCRF: electronic case report form
eGFR: estimated glomerular filtration rate
ELISA: enzyme-linked immunosorbent assay
EOT: end of treatment
ER: emergency room
FH: familial hypercholesterolemia
FSH: follicle stimulating hormone, follicle stimulating hormone
GCP: Good Clinical Practice
HbA_{1c}: hemoglobin A_{1c}
HDL-C: high-density lipoprotein cholesterol
heFH: heterozygous familial hypercholesterolemia
hoFH: homozygous familial hypercholesterolemia
HRT: hormone replacement therapy
IEC: independent ethics committee
IMP: investigational medicinal product
IRB: institutional review board
IRT: interactive response technology
ITT: intent-to-treat
IVRS: interactive voice response system
IWRS: interactive web response system
LDL-C: low-density lipoprotein cholesterol
LDLR: low-density lipoprotein receptor

LDLRAP1:	LDL receptor adaptor protein 1
LLQ:	lower limit of qualification
LMT:	lipid modifying therapy
Lp (a):	lipoprotein (a)
LS:	least-square
MedDRA:	medical dictionary for regulatory activities
MMRM:	mixed-effect model with repeated measures
NIMP:	noninvestigational medicinal product
non-HDL-C:	non-high density lipoprotein cholesterol
PCSA:	potentially clinically significant abnormality
PCSK9:	proprotein convertase subtilisin/kexin type 9
PFS:	pre-filled syringes
PFS-S:	PFS with safety system
PK:	pharmacokinetic(s)
PT:	preferred term
Q2W:	every 2 weeks
Q4W:	every 4 weeks
SAE:	serious adverse event(s)
SAP:	statistical analysis plan
SBP:	systolic blood pressure
SC:	subcutaneous
SD:	standard deviation
SE:	standard error
SOC:	system organ class
TG:	triglyceride
Total-C:	total cholesterol
ULN:	upper limit of normal
WOCBP:	women of childbearing potential
γGT:	gamma-gutamyl transferase

4 INTRODUCTION AND RATIONALE

Familial hypercholesterolemia (FH) is an inherited disorder of lipid metabolism, characterized by severely elevated levels of low-density lipoprotein cholesterol (LDL-C) that lead to premature atherosclerosis and cardiovascular disease (CVD) (1). It can be either an autosomal dominant or an autosomal recessive disease that results from mutations in the low-density lipoprotein receptor (LDLR), apolipoprotein B (Apo B), proprotein convertase subtilisin/kexin type 9 (PCSK9), or in the LDL receptor adaptor protein 1 (LDLRAP1). The latter is a rare mutation in LDLRAP1, a protein which interacts with the LDL receptor or signal transducing adaptor family member 1 (STAP1) gene with a recessive mode of transmission, since carrier parents have normal lipid profiles. In all cases, these result in an accumulation of LDL-C in the plasma from birth, and subsequent development of tendon xanthomas, xanthelasmas, atheromata, and CVD (2).

Homozygous familial hypercholesterolemia (hoFH) is a rare, serious condition genetically defined to include individuals with the same mutation(s) in either LDLR, Apo B, or PCSK9 alleles (true homozygotes) or defined to include individuals with different mutations in each allele (compound heterozygotes). Rarely, hoFH patients may have mutations in 2 different FH-causing genes, one within the LDLR gene and one in another gene (double heterozygotes). Historically thought to affect 1 in a million people, new research indicates that hoFH prevalence is likely to be higher, with as many as 1 in 160 000 to 300 000 people affected (2). Phenotypically, the severity of hoFH depends on the amount of residual LDLR activity, historically categorized as either receptor-negative (<2% of normal LDLR activity) or receptor-defective (2% to 25% of normal LDLR activity) based on the amount of activity in skin fibroblasts. The genetic definition used in the current study will include all individuals considered to be either true homozygotes or compound heterozygotes. However, those individuals with null LDLR mutations in both alleles will be excluded because it is expected that alirocumab will not be efficacious in those patients, as already shown with another PCSK9 inhibitor, evolocumab (3, 4).

Homozygous FH is characterized by drastically increased levels of LDL-C from early childhood onwards. Patients with hoFH have severe hypercholesterolemia (500 to 1000 mg/dL, 12.95 to 25.9 mmol/L), resulting in lifelong exposure to high levels of plasma LDL-C and increased risk of developing atherosclerosis at a highly accelerated rate, often manifesting within the first 2 decades of life. In children, the only clinical symptom is xanthoma tuberosum, typically occurs predominantly on the knees, elbows, and Achilles tendon. If left untreated, it is common that affected subjects die at an early age, due to CVDs (5).

Familial hypercholesterolemia including both heterozygous and homozygous forms may be suspected in a child, adolescent, or young adult (<20 years of age) if he/she has an untreated fasting LDL-C level ≥160 mg/dL (or non-high density lipoprotein cholesterol [non-HDL-C], ≥190 mg/dL) (6). Because of the high risk of progression to premature clinical CVD associated with these findings, pediatric guidelines recommend LDL-C lowering intervention and specific lipid targets for children and adolescents with heterozygous familial hypercholesterolemia (heFH). An LDL-C level of <130 mg/dL (3.4 mmol/L) is considered acceptable and <110 mg/dL (2.85 mmol/L) ideal for children with heFH (6), or the achievement of ≥50% reduction in LDL-C. Since LDL-C levels are only indicative of hoFH, especially in children, and do not exclude hoFH diagnosis, a similar LDL-C threshold to that used for heFH will be used to trigger a

genotyping determination. Thus, the protocol will include patients with a screening LDL-C ≥130 mg/dL (3.4 mmol/L) despite being treated with stable lipid modifying therapy (LMT). The LDL-C targets recommended in the European Atherosclerosis Society (EAS) Consensus Panel statement related to hoFH were <2.5 mmol/L (<100 mg/dL), <3.5 mmol/L (<135 mg/dL) in children, or <1.8 mmol/L (<70 mg/dL) in adults with clinical CVD (2). These targets are similar to those for patients at high cardiovascular risk; however, it is well recognized that these targets are ambitious because they are very difficult to achieve with current lipid modifying treatments.

After initiation of diet (including dietary adjuncts of plant sterols/stanols and soluble fiber), statins are the preferred initial pharmacologic treatment in children with FH. Consideration should be given to starting medical treatment at the age of 8 years or older. In special cases, such as those with homozygous FH, treatment might need to be initiated at earlier ages, including mechanical removal of LDL-C by lipoprotein apheresis (7), which is an important adjunct treatment in hoFH that can help in LDL-C goal attainment. Ideally, treatment should be started by the age of 5 and not later than 8 years, although the Panel recognizes that practical feasibility and cost also influence decisions regarding treatment (2, 8).

Six statins (rosuvastatin, atorvastatin, simvastatin, pravastatin, lovastatin, and fluvastatin) are FDA approved as an adjunct to diet to lower markedly elevated LDL-C levels in children 10 years of age and older (ages 8 years and older for pravastatin) (6). In general, statins reduce LDL-C levels in children with FH by 23% to 50% (9, 10, 11, 12). Adverse event (AE) profiles for statins in children are similar to those reported in adult studies and include rare instances of myopathy and hepatic enzyme elevation. Despite severely reduced LDLR level/activity in hoFH patients, high doses of statins may be somewhat effective in lowering LDL-C concentrations. Limited data are available for the combination of ezetimibe and simvastatin (13) and are consistent with studies conducted in adults, showing an incremental decrease of approximately 15% in LDL-C levels compared with administration of simvastatin alone. Taken together, this information supports the age of patients included in this study as well as the definition of stable LMTs as provided in the inclusion criteria of the protocol and its mandatory use as background therapy. Stable LMTs include stable optimal doses of statin based on pediatric guidelines, which will be followed by the site (14).

Novel therapeutic approaches in hoFH, including the recently licensed treatments lomitapide (adults only) and mipomersen (from 12 years old), as well as high dose PCSK9 monoclonal antibody therapy, offer the potential for further substantial LDL-C lowering by 25% to 50% on top of current standards of care, including maximal statin therapy (2). Another PCSK9 inhibitor, evolocumab, was evaluated at a dose of 420 mg every 4 weeks (Q4W) in a hoFH population, including patients from 12 years old (4). In the open-label TAUSSIG trial, evolocumab 420 mg Q4W demonstrated a favorable benefit/risk profile in all 106 patients, including 14 adolescents aged from 12 to less than 18 years old. Mean reductions in LDL-C were -24% for LDLR defective, -6% for LDLR negative/negative,-51% for PCSK9 gain of function/LDLR negative and -43% for Autosomal Recessive Hypercholesterolemia (ARH) (15). Owing to the potential risk for hepatic toxicity, lomitapide and mipomersen have been approved for restricted use and will not be authorized in this study.

Alirocumab is a fully human monoclonal antibody that targets PCSK9 (16) approved in adults but not yet approved in the pediatric population. A clinical development program is ongoing in the pediatric population, including a Phase 2 study conducted in heFH children and adolescents from 8 to 17 years old (NCT02890992) which will be followed by a Phase 3 study in the same heFH pediatric population. Since in the adult clinical development program body weight (BW) was identified as a significant covariate affecting alirocumab exposure and pharmacokinetics (PK) with however a limited impact on alirocumab PK, the dose to be used in the pediatric population was defined according to BW categories, ie, BW <50 kg or BW ≥50 kg. The Phase 2 DFI14223 study, conducted in 31 pediatric heFH patients in 3 cohorts, evaluated a fixed dosage according to BW categories, with staggered doses of 30 mg every 2 weeks (Q2W) (Cohort 1), and 40 mg Q2W (Cohort 2), or 75 mg Q4W (Cohort 3), for children with a BW below 50 kg (ie, lower BW category), and doses of 50 mg Q2W (Cohort 1), and 75 mg Q2W (Cohort 2), or 150 mg Q4W (Cohort 3) for children with a BW ≥50 kg (ie, higher BW category). Staggered doses were employed as a cautious approach in the first introduction of alirocumab in the pediatric population, where it was expected that 40 mg Q2W for BW <50 kg and 75 mg Q2W for BW ≥50 kg would be the efficacious dose. The effect on LDL-C and safety were analyzed. The primary efficacy endpoint, as measured by the percent change from baseline in LDL-C at Week 8, demonstrated a greater reduction in LDL-C, overall, in Cohort 2 using the Q2W dosing regimen (least-square [LS] mean change from baseline in LDL-C -46.1%), with a mean reduction observed in both BW categories (-40.4% with 40 mg Q2W in the lower BW category, and -49.8% with 75 mg Q2W in the higher BW category), compared with Cohort 1, which also used a Q2W dosing regimen (LS mean change from baseline in LDL-C -21.2%, with a mean reduction not consistent across the 2 doses: -41.2% with the 30 mg Q2W dose in the lower BW category versus -7.9% with the 50 mg Q2W dose in the higher BW category). For Cohort 3, the overall LS mean change from baseline in LDL-C was -7.7%, with a mean reduction of -17.5% with the 75 mg Q4W dose in the lower BW category and a mean increase of +4.0% with the 150 mg Q4W dose in the higher BW category. Similarly At Week 8, the largest proportion of patients in the 2 BW categories reaching both the target of LDL-C <130 mg/dL (3.37 mmol/L) and LDL-C <110 mg/dL (2.85 mmol/L) was observed with the 2 alirocumab doses (40 mg Q2W/75 mg Q2W) as per BW category (<50 kg/≥50 kg) used Cohort 2. Overall, for the combined doses, the proportion of patients who achieved a LDL-C value <110 mg/dL (2.85 mmol/L) was 76.4%. There were no patients with treatment-emergent serious adverse events, treatment-emergent adverse events (TEAEs) leading to death, or TEAEs leading to permanent treatment discontinuation. There were no adverse events of special interest (AESIs) including, neurological events, neurocognitive events, increase in alanine aminotransferase (ALT), allergic drug reactions, or local injection site reactions for all of the 6 dose groups. Alirocumab was well tolerated with a favorable safety profile in all cohorts and dose groups.

In addition to the pediatric program, the efficacy and safety of the alirocumab dose of 150 mg Q2W is currently being investigated in the ongoing study R727-CL-1628 (NCT03156621), conducted in hoFH adult patients. Based on the totality of this information, the doses for the EFC14660 study were established for hoFH children and adolescents. In this study, conducted in even more severe patients with confirmed hoFH genotyping, the alirocumab doses of 75 mg Q2W for BW <50 kg and 150 mg Q2W for BW ≥50 kg were selected to allow the greatest benefit associated with a good safety profile in hoFH patients known to have a very high baseline LDL-C despite optimal treatment with LMTs, including statins, and other LMTs.

Very little information is available on statin intolerance in the pediatric population but this cannot be ruled out. This is acknowledged by the NICE guidance that recommends healthcare professionals consider offering non-statin LMT for lowering LDL-C levels in children and young people with FH who are intolerant of statins (17). Presently available non-statin LMTs commonly prescribed in the pediatric population, in particular ezetimibe and colesevelam, appear less effective than statins in lowering LDL-C, and therefore similar issues are met with regard to achieving treatment goals. It is recognized that there is no consensus definition for statin intolerance. The protocol provides a definition of statin intolerance that was utilized in the adult alirocumab program. This strict definition has been discussed and agreed upon by the Pediatric Steering Committee.

This study is designed to evaluate the efficacy and safety of alirocumab 75 mg Q2W for BW <50 kg and 150 mg Q2W for BW ≥50 kg in a pediatric population with hoFH. It is a 48 week uncontrolled, open-label treatment period study. The assessment of the primary endpoint of LDL-C at Week 12 represents the time point at which stable efficacy should be achieved based on the data from the large adult alirocumab program and should provide a reasonable duration of efficacy in this rare disease patient population who are expected to ultimately derive a potential benefit from the drug. It should be noted that all patients will be on an optimal dose of statin with or without other LMT (or non-statin LMT only if statin intolerant according to a strict definition) and that this should continue throughout the study. Patients who have initiated apheresis treatment for at least 6 months prior to screening and are currently undergoing stable LDL apheresis therapy as described in Appendix A are also eligible for the study.

Conclusion on the benefit risk assessment with alirocumab

Based on the clinical data available to date in the adult population, treatment with alirocumab has demonstrated a significant LDL-C lowering effect in a population of patients with non-FH or with heFH. The LDL-C lowering efficacy was associated with consistent decreases in total cholesterol (Total-C), Apo B, non-HDL-C, a decrease in lipoprotein (a) [Lp (a)], and a favorable trend for high-density lipoprotein cholesterol (HDL-C), and triglycerides. Maximum efficacy was observed as early as 4 weeks after the initial dose, and efficacy was well sustained up to 2 years. In the DFI14223 pediatric study, treatment with alirocumab over 8 weeks demonstrated a significant and sustained LDL-C lowering effect in Cohort 2.

Alirocumab administration to date in clinical trials has been associated with a favorable safety and tolerability profile.

Immunogenicity and systemic hypersensitivity are considered as important identified risks.

The following safety information is based on the adult clinical trials. Injection site reactions (including erythema/redness, itching, swelling, pain, and tenderness), upper respiratory tract signs and symptoms (including mainly oropharyngeal pain, rhinorrhea, and sneezing), pruritus, hypersensitivity, eczema nummular, urticaria, and hypersensitivity vasculitis are identified as adverse drug reactions (ADRs) for alirocumab. The ADRs include AEs for which there is some basis to believe that there is a causal relationship between the drug and the occurrence of the AE.

Monitoring of these AEs will be continued in all studies conducted in adult and pediatric patients.

In addition, in adults, there was no safety signal observed with neurologic events, ALT increase and hepatic disorders, adjudicated cardiovascular events, diabetes mellitus, skeletal muscle-related disorders, and ophthalmologic disorders in the alirocumab-treated group overall, but more cataracts (2.6%) were noted in patients treated with alirocumab who achieved 2 consecutive LDL-C values <25 mg/dL (0.65 mmol/L) compared with 0.8% of alirocumab-treated patients who did not achieve such low levels. Although the limitations of this postrandomization comparison have to be considered, and there were no statistically significant differences in the incidence of cataracts in this subgroup of patients when compared to control groups, cataracts in patients with very low LDL-C levels are considered as a potential risk, and the Sponsor will continue to monitor this potential risk. There was no safety signal observed for neurocognitive disorders; however, the Sponsor will monitor this potential risk as an AESI in this study.

Monitoring for, and collection of, all AEs will occur in this study conducted in pediatric patients.

In the DFI14223 pediatric study, treatment with alirocumab over 8 weeks and during the open-label extension showed that alirocumab was well tolerated with a favorable safety profile in all cohorts and dose groups. No new clinically significant safety findings were noted in patients treated with alirocumab.

An independent Data Monitoring Committee (DMC) dedicated to the pediatric clinical program conducted with alirocumab will meet periodically to review the safety data collected in this study.

This specific study is undertaken to demonstrate the efficacy and safety of alirocumab in the hoFH pediatric population. Due to the rapid clinical progression of atherosclerotic disease in children and adults with FH, pediatric guidelines (14, 15, 16, 17, 18, 19) recommend LDL-C lowering intervention starting with statins. However, in this particular population with very high LDL-C levels, and where achieving target LDL-C reductions with currently available LMTs appears very ambitious, adding alirocumab to the LDL-C lowering therapies can improve the condition of this hoFH population.

5 STUDY OBJECTIVES

5.1 PRIMARY

To evaluate the efficacy of alirocumab (75 or 150 mg depending on BW), administered every 2 weeks (Q2W), on low-density lipoprotein cholesterol (LDL-C) levels at Week 12 of treatment in children with homozygous familial hypercholesterolemia (hoFH) 8 to 17 years of age on top of background treatments.

5.2 SECONDARY

- To evaluate the efficacy of alirocumab after 24 and 48 weeks of treatment on LDL-C levels.
- To evaluate the effects of alirocumab on other lipid parameters (eg, Apo B, non-HDL-C, total-C, HDL-C, Lp (a), triglycerides [TG], apolipoprotein A-1 [Apo A-1] levels) after 12, 24, and 48 weeks of treatment.
- To evaluate the safety and tolerability of alirocumab up to 48 weeks of treatment.

5.3 OTHER

- To evaluate the development of anti-alirocumab antibodies (ADA) during 48 weeks of treatment.
- To evaluate the pharmacokinetics (PK) of alirocumab.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

This study is a Phase 3, multi-national, multi-center, open-label study with a treatment period of 48 weeks.

Children and adolescents aged 8 to 17 years with hoFH confirmed by genetic testing and LDL-C ≥130 mg/dL (3.37 mmol/L) at the screening visit, despite treatment with stable LMTs at optimal doses, will be selected to enter the screening period. All efforts will be made to achieve adequate representation across age groups.

Stable LMTs are defined as stable optimal dose of statin ± other stable LMTs or stable dose of non-statin LMTs in statin-intolerant patients for at least 4 weeks prior to screening LDL-C being obtained. The optimal dose of statin is defined as the dose prescribed based on local guidelines or practice, or is the dose that is maximally tolerated due to adverse effects of higher doses.
For patients not receiving maximally tolerated statin, statin intensification should be carefully considered prior to entry in this study in order to ensure that the addition of a non-statin LDL-C lowering therapy (ie, alirocumab) would be the next appropriate step in the management of the patient's hypercholesterolemia. The highest dose of statin should not exceed the maximum labeled dose of statin for pediatric patients as per the local prescribing information.
A statin-intolerant patient is defined as one with the documented inability to tolerate at least 2 statins: one statin at the lowest daily starting dose, and another statin at any dose, due to skeletal muscle-related symptoms, other than those due to strain or trauma, such as pain, aches, weakness, or cramping, that began or increased during statin therapy and stopped when statin therapy was discontinued. Patients not receiving a daily approved regimen of a statin (eg, 1 to 3 times weekly) are also considered as not able to tolerate a daily dose.

Patients who have been on a stable apheresis[1] schedule prior to the screening visit (Week -2), and stable background medical LMT for at least 4 weeks prior to the screening visit (Week -2), will enter a 2-week screening period.

Genotyping for hoFH will be conducted from a specimen of whole blood, saliva, or buccal swab in patients consenting to undergo genotyping testing. This test will be recommended for all patients but will be mandatory only for patients without previously documented genotyping.
For non-mandatory genotyping, the sample should preferably be taken during the screening period, but can be done at any visit during the treatment period.

The study will consist of a run-in period (as needed), a screening period, an open-label treatment period, and a follow-up period.

[1] Stable apheresis is defined as 4 apheresis procedures performed during a 4 week period, approximately 1 week apart, or 4 apheresis procedures performed during an 8 week period, approximately 2 weeks apart (see Appendix A).

The initial dose of alirocumab will be based on BW (75 mg Q2W for patient <50 kg, 150 mg Q2W for patients ≥50 kg). After Week 12, if there is a change in BW, the dose of alirocumab can be adjusted such that the dose corresponds to the patient's BW.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

The study comprises 4 periods as described below (please see the graphical study design and study flowchart in Section 1.1 and Section 1.2, respectively):

- A run-in period (if needed) up to 4 weeks (+2 days) in duration.
- A screening period up to 2 weeks (+5 days) in duration.
- A 48-week open-label treatment period.
- A follow-up of 8 weeks (±3 days).

The total duration of the study will be up to 62 weeks for each patient.

A detailed description of the assessments performed in each study period is provided in Section 10.1.

6.2.2 Determination of end of clinical trial (all patients)

The end of the study is defined as the last patient last visit planned per protocol.

6.3 INTERIM ANALYSIS

No formal interim analysis is planned.

Interim analyses might be performed if requested by Health Authorities or if needed for the purpose of scientific communication.

6.4 STUDY COMMITTEES

6.4.1 Steering Committee

The Steering Committee is composed of university-based physicians (experts in pediatric lipids field, and/or pediatric cardiology) with clinical and methodological expertise, working in collaboration with the Sponsor. The independent Steering Committee will provide scientific and strategic direction for the trial and will have overall responsibility for its execution. The Steering Committee will provide guidance on producing and conducting a scientifically sound design and ensuring accurate reporting of the study. The Steering Committee will address and resolve scientific issues encountered during the study. The Steering Committee will also review the recommendations from the DMC throughout the study.

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

6.4.2 Data Monitoring Committee

An independent DMC for pediatric studies will monitor patient safety by conducting reviews of accumulated safety data. The DMC will provide the Sponsor and the Steering Committee with appropriate recommendations on the conduct of the clinical trial to ensure the protection and safety of the patients enrolled in the study. In addition, the DMC will institute any measures that may be required for ensuring the integrity of the study results during the study execution.

The DMC will be charged with reviewing the safety of patients with LDL-C <50 mg/dL (1.30 mmol/L) and more particularly, will review AE potentially associated with LDL-C <50 mg/dL (1.30 mmol/L) (see Section 10.6.3) in conjunction with the independent physician.

Detailed activities and responsibilities of the DMC are described in the DMC charter.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

I 01. Male and female children and adolescents aged 8 to 17 years genetically diagnosed with homozygous familial hypercholesterolemia[2] inadequately controlled (see threshold mentioned in exclusion criterion E 02) despite treatment with optimal dose of statin[3] with or without other LMTs, or non-statin LMTs if statin-intolerant[4], at stable dose(s) for at least 4 weeks.

I 02. A signed informed consent indicating parental permission with or without patient assent, depending on capacity for understanding based on developmental maturity. In cases involving emancipated or mature minors with adequate decision-making capacity, or when otherwise permitted by law, a signed informed consent directly from patients.

I 03. For patients on apheresis, currently undergoing stable LDL apheresis therapy for at least 4 weeks prior to the screening visit (Week -2) and have initiated apheresis treatment for at least 6 months (see Appendix A).

[2] *Diagnosis of hoFH must be made either by previous genotyping (true homozygotes, compound heterozygotes, or double heterozygotes) or current genotyping performed after having been suspected by clinical criteria according to EAS Consensus Panel recommendations for diagnosis of HoFH. Previous genotyping refers to documented results that are available from prior genotyping testing supporting a diagnosis of hoFH. Current centralized genotyping refers to patients electing to undergo genotyping during the run-in period with results supporting a diagnosis of hoFH (see Appendix B).*

[3] *The optimal dose of statin is defined as the stable daily dose prescribed based on local guidelines or practice, or is the dose that is maximally tolerated due to adverse effects of higher doses. For patients not receiving the maximally tolerated dose of statin, statin intensification should be carefully considered prior to inclusion in this study in order to ensure that the addition of a non-statin LDL-C lowering therapy (ie, alirocumab) would be the next appropriate step in the management of the patient's hypercholesterolemia. The highest dose of statin should not exceed the maximum labeled dose of statin for pediatric patients as per the local prescribing information.*

[4] *A statin-intolerant patient is defined as a patient with the documented inability to tolerate at least 2 statins: one statin at the lowest daily starting dose, AND another statin at any dose, due to skeletal muscle-related symptoms, other than those due to strain or trauma, such as pain, aches, weakness, or cramping, that began or increased during statin therapy and stopped when statin therapy was discontinued. Patients not receiving a daily approved regimen of a statin (eg, 1 to 3 times weekly) will also be considered as not able to tolerate a daily dose.*

7.2 EXCLUSION CRITERIA

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

7.2.1 Exclusion criteria related to study methodology

E 01. Children and adolescents aged less than 8 years or more than 17 years at the time of informed consent signature, unless different local regulation applies (eg, for Russia only: patients aged less than 12 years or more than 17 years at the time of informed consent signature).

Note: Patients aged 8 to less than 10 years who have not had previous attempts to lower LDL-C by other means will be excluded.

E 02. Patients with LDL-C (pre-apheresis, if applicable) less than 130 mg/dL (3.37 mmol/L) obtained during the screening period after the patient has been on stable apheresis procedure or LMT (ie, stable optimal dose of statin ± other stable LMTs, or stable non-statin LMTs in statin-intolerant patients) treatment for at least 4 weeks.

E 03. Patients with null LDLR mutations in both alleles.

E 04. Patients with BW less than 25 kg.

E 05. Patients aged 8 to 9 years not at Tanner Stage 1 and patients aged of 10 to 17 years not at least at Tanner Stage 2 in their development (See Appendix C).

E 06. Daily dose of statin that is above the maximum recommended dose for pediatric patients as per the local prescribing label.

E 07. Patients who will receive statin de novo during the run-in period.

E 08. Use of nutraceutical products or over-the-counter therapies that may affect lipids which have not been at a stable dose for at least 4 weeks prior to the screening visit.

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

E 10. Mipomersen in the last 5 months.

E 11. Patients with uncontrolled (ie, hemoglobin A_{1c} [HbA_{1c}] >9% at the screening visit) Type 1 or 2 diabetes mellitus.

E 12. Patients with known uncontrolled thyroid disease (ie, thyroid-stimulating hormone levels outside of the laboratory's reference range within the past 6 months, or with elevated free T3 or T4 and with clinical symptoms of hyperthyroidism).

E 13. Patients who use systemic corticosteroids.

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

E 14. Patients with uncontrolled (ie, systolic blood pressure [SBP] or diastolic blood pressure [DBP] above local guidelines or equivalent) hypertension.

E 15. Fasting triglycerides >350 mg/dL (3.95 mmol/L) at the screening visit.

E 16. Severe renal impairment (ie, estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2) at the screening visit.

E 17. ALT or aspartate aminotransferase (AST) >2 x upper limit of normal (ULN) (1 repeat laboratory allowed per patient) at the screening visit.

E 18. Creatine phosphokinase (CPK) >3 x ULN (1 repeat laboratory allowed per patient) at the screening visit.

Note: If any of the above liver function tests or CPK are out of range, a test can be repeated once, using the central laboratory services.

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

E 20. Conditions/situations or laboratory findings such as:

- Any clinically significant abnormality identified at the time of screening that in the judgment of the Investigator or any Subinvestigator would preclude safe completion of the study or constrain endpoints assessment such as major systemic diseases.
- Patients considered by the Investigator or any Subinvestigator as inappropriate for this study for any reason, eg:
  - Those deemed unable to meet specific protocol requirements, such as scheduled visits.
  - Those deemed unable to administer or tolerate long-term injections as per the patient/parent or the Investigator.
  - 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.
  - Uncooperative or any condition that could make the patient potentially non-compliant to the study procedures.

E 21. Known or suspected alcohol and/or drug abuse.

E 22. Patients who have previously received evolocumab.

E 23. Treatment with any investigational medicinal product (IMP) within 8 weeks or 5 half-lives prior to the screening period, whichever is longer.

Note: If half-life is not known, then 8 weeks should be applied for non-biological IMP and 6 months for biological IMP.

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

E 24. All contraindications to the background statins or other LMTs (as applicable) 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 sanofi compound

E 25. Hypersensitivity to alirocumab or to any of the ingredients of alirocumab injections.

E 26. Females who have experienced menarche who are unwilling or unable to be tested for pregnancy.

Note: Females who have experienced menarche must have a confirmed negative pregnancy test at screening and other study visits. Pregnancy tests may be performed more frequently in some countries due to local legislation related to women of childbearing potential (WOCBP) randomized in clinical trials. See Appendix I for further details.

E 27. Positive pregnancy test in females who have experienced menarche.

E 28. Females who are breast-feeding.

E 29. Females of childbearing potential not protected by highly effective method(s) of birth control (see contraceptive guidance in Appendix D).

Note: Females of childbearing potential must use an effective contraceptive method throughout the entire duration of study treatment and for at least 10 weeks after the last injection.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

IMP: alirocumab

Formulation: Prefilled syringes (PFS) with finger grip, to be replaced by PFS with safety system (PFS-S) as soon as available: alirocumab 75 or 150 mg/mL solution as described below:

- BW <50 kg: 1.0 mL of alirocumab 75 mg/mL solution.
- BW ≥50 kg: 1.0 mL of alirocumab 150 mg/mL solution.

Route of administration: Subcutaneous (SC) injections in the abdomen, thigh, or outer area of upper arm.

Dose regimen: Alirocumab Q2W: 75 mg for BW <50 kg or 150 mg for BW ≥50 kg.

After Week 12, the dose of alirocumab can be adjusted in case of weight change after baseline, such that the dose corresponds to the patient's BW.

A manual for IMP administration (injection instruction manual) will be provided to patients containing detailed instructions on use. The IMP could be administered by self-injection (only patients with age ≥12 will be able to self-inject) or by another designated person (such as a parent, nurse, etc). The used PFS will be discarded in a sharps container which will be provided to patients. Patients will be asked to store the IMP in a refrigerator. Prior to administration, the IMP should be put in a safe location at room temperature for about 30 to 40 minutes. Thereafter, the IMP should be administered as soon as possible. If LDL apheresis coincides with study drug administration, study drug will be administered immediately after completion of the LDL apheresis procedure.

During the treatment period, alirocumab will be administered Q2W SC, starting at Week 0 and continuing up to the end of the open-label treatment period (last injection on Week 46).

Administration of IMP will start as soon as possible after the treatment kit numbers have been provided by the Interactive Response Technology (IRT). If at all possible, the first injection will be done at the investigational site by the patient or another designated person (such as parent, nurse, etc) under direct site staff supervision. Patients will be monitored at the investigational site for at least 30 minutes after this first injection. The IMP should ideally be administered Q2W SC at approximately the same time of the day; however, it is acceptable to have a window period of ±3 days. The time of the day is based on patient's preference. If, by mistake or due to other circumstances, an injection is delayed by more than 7 days or completely missed, then the patient should return to the original schedule of study treatment administration without administering delayed injections. On the other hand, if the delay is less than or equal to 7 days from the missed date, then the patient should administer the delayed injection and then resume the original schedule of study treatment administration.

All of the IMP injections can be performed by trained patient ≥12 years (self-injection) or parent, or another designated person, or alternative arrangements for injection administration will be allowed as needed (eg, if the patient, or caregiver[s] do not develop the comfort to inject the investigational drug at home, or the Investigator determines that patient [or caregiver] injection at home is not appropriate, injections can be performed at the site by way of unscheduled visits). It is suggested that patients ≥12 years old, who are trained to self-inject, do so with parental (or another designated person) supervision; however, this is not mandatory. The Investigator may evaluate the sustained reliability of this practice on a case by case basis given the variable adolescent ages, maturity levels, availability of the caregiver, or other relevant considerations, with the patient. The final decision as to whether supervision is appropriate for self-injection of alirocumab for patients ≥12 years old is per Investigator discretion. Prior to any injection, a local topical anesthetic may be utilized as per the Investigator's judgment.

Provision of IMP:

In exceptional cases, patients will have the option, where available, to receive the IMP at home using a Direct-To-Patient (DTP) service provider on appropriate visits. Patient identification remains confidential and will not be disclosed to the study Sponsor. For this reason, the IMP delivery will be managed by the service provider. The clinical site will instruct the patient, as appropriate, on how the DTP process operates before it starts.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCT(S)

The following classes of drugs (not all of which are indicated for pediatric use in all countries; for further information, Investigators should refer to their local prescribing information) are identified as noninvestigational medicinal product (NIMP) because the medication is a potential background therapy that will not be provided by the Sponsor:

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

8.3 BLINDING PROCEDURES

8.3.1 Methods of blinding

Not applicable – this is an open-label study.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

This is an open-label study and every patient will receive alirocumab.

The lists of treatment kit numbers will be generated centrally by sanofi. The IMPs will be packaged in accordance with those lists.

The Trial Supply Operations Manager (TSOM) will provide the list of treatment kit numbers. Then, this centralized treatment allocation system provider will generate the patient list and allocate the treatment kits to the patients.

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

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

8.5 INVESTIGATIONAL MEDICINAL PRODUCT PACKAGING AND LABELING

Each kit will contain PFS of alirocumab as described in Section 8.1.

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

The IMP will be stored in a refrigerator between +2°C and +8°C (36°F to 46°F) by the site. The temperature of the site refrigerator should be checked daily and recorded on a log sheet. Any temperature excursion during transportation to the site or during storage at site should be promptly reported to the Sponsor who will assess the suitability for use of the IMPs.

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

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

After the supply of IMP kits to patients at the study site visits, appropriate provisions will be in place for transportation of the IMP kits from the study site to the patient's refrigerator in case of self-injections or injections administered by parent or designated person.

NOTE: Exceptionally, after discussion between Investigational Site and Sponsor (eg, patient unable to attend an Investigational Site visit due to special circumstances) some IMP kits could be supplied, when feasible, directly from site to patient via a Sponsor-approved courier company. This process (which requires maintenance of the cold chain) would be implemented only at

selected sites/countries (where certain conditions would be fulfilled, and where permitted locally) and for selected patients (who could handle and would consent to such a process). This DTP process will be described in detail in a separate document and will be implemented after appropriate training of Monitoring Teams and Investigational Sites.

8.7 RESPONSIBILITIES

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

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

Any quality issue noticed with the receipt or use of an IMP/NIMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 10.4.7).

A potential defect in the quality of IMP/NIMP 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/NIMP and eliminate potential hazards.

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

8.7.1 Treatment accountability and compliance

The IMP administration data will be recorded by the Investigator on the electronic case report form (eCRF) and by patients/parents on a patient's diary. 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 accountability at site is to be performed at IMP kit re-supply visits only (see Section 10.1). The used and unused kit(s) should be brought back to such visits for accountability purposes.
- The Investigator or designee will complete the corresponding Treatment Log Form from the patient's diary.
- The Investigator or designee will enter data in the appropriate eCRF pages, according to data recorded in the Treatment Log Form.

- The monitor will check the data consistency between eCRF pages, Treatment Log Forms using the patient's diary, and returned unused syringes of a corresponding kit.

For any background LMT that is supplied by the sponsor (eg, via a local warehouse), tracking and reconciliation will be conducted in accordance with the Sponsor's directives.

8.7.2 Return and/or destruction of treatments

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

If the site is not able to destroy or destruction not allowed in the country, all treatments kits will be retrieved by the Sponsor.

For background LMT (statin or other LMT) not provided by the Sponsor, tracking has to be achieved by the Investigator according to the system proposed by the Sponsor.

8.8 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient concomitantly with any IMP(s). Concomitant medications will not be provided by sanofi.

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 (other than those that are prohibited during the study) may be given at the discretion of the Investigator, with a stable dose (statin ± other LMT). 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 eCRF and source data.

Nutraceutical products or over-the-counter therapies (with the exception of prohibited medications, see Section 8.8.3) that may affect lipids are allowed only if they have been used at a stable dose for at least 4 weeks prior to screening visit, and during the screening period. During the treatment period, modification to these nutraceutical products or over-the-counter therapies is allowed but in general should be avoided. Examples of such nutraceutical products or over-the-counter therapies include omega-3 fatty acids, plant stanols such as those found in Benecol, flax seed oil, and psyllium.

Any adjustment will be documented in the eCRF.

8.8.1 Management of background lipid modifying therapy

Patients must have been on stable LMTs, defined as stable optimal dose of statin ± other stable LMTs or stable dose of non-statin LMTs in statin-intolerant patients, for at least 4 weeks prior to screening LDL-C being obtained.

During the treatment period, lipid levels will be communicated to the Investigator.

Patients will be instructed to follow a diet to treat their hypercholesterolemia in accordance with local guidelines or treatment practice, and they should be on this diet throughout the entire study duration.

The Investigator will be responsible, based on his/her own judgment related to the patients' LDL-C levels and the safety profile, to continue or discontinue alirocumab throughout the study. The statin dose or other LMT should not be modified to adjust for the degree of LDL-C lowering before Week 12, unless otherwise indicated.

8.8.2 Contraception

Females of childbearing potential must use an effective contraceptive method throughout the entire duration of the study treatment and for at least 10 weeks after the last IMP injection (see Appendix D).

8.8.3 Prohibited concomitant medications

Prohibited concomitant medications from the initial screening visit until the end of treatment (EOT) period visit include the following:

- Oral and injectable corticosteroids.
- Fibrates (except fenofibrate).
- Mipomersen.
- Immunosuppressants.
- Other PCSK9 inhibitor, evolocumab.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 PRIMARY ENDPOINT

9.1.1 Primary efficacy endpoint

Percent change in LDL-C (pre-apheresis, if applicable) from baseline to Week 12 in the intent-to-treat (ITT) population, using all LDL-C values (pre-apheresis, if applicable) regardless of adherence to treatment (ITT estimand).

The LDL-C at Week 12 will be the LDL-C level obtained within the Week 12 analysis window. All calculated and measured LDL-C values (scheduled or unscheduled, fasting or not fasting) may be used to provide a value for the primary efficacy endpoint if appropriate according to the above definition. In case both calculated and measured LDL-C are provided for the same sampling, the measured LDL-C will be considered. For patients undergoing apheresis, pre-apheresis values will be considered. The analysis window used to allocate a time point to a measurement will be defined in the statistical analysis plan (SAP).

9.2 SECONDARY ENDPOINTS

9.2.1 Secondary efficacy endpoints

- Percent change in LDL-C (pre-apheresis, if applicable) from baseline to Week 12 in the ITT population, using all LDL-C values during the treatment period (on-treatment estimand).
- Percent change in LDL-C (pre-apheresis, if applicable) from baseline to Weeks 24 and 48 (ITT and on-treatment estimands).
- Percent change in Apo B, non-HDL-C, Total-C, Lp (a), HDL-C, fasting TG and Apo A-1 (pre-apheresis, if applicable) from baseline to Weeks 12, 24, and 48 (ITT and on-treatment estimands).
- Proportion of patients with ≥15% reduction in LDL-C (pre-apheresis, if applicable) at Weeks 12, 24, and 48 (ITT and on-treatment estimands).
- The absolute change in LDL-C from baseline to Weeks 12, 24, and 48 (ITT and on-treatment estimands).

9.2.2 Efficacy assessment method

9.2.2.1 Lipid parameters

Total-C, HDL-C, TG, Apo B, Apo A-1, and Lp (a) will be directly measured by the central laboratory as per the schedule in Section 1.2. LDL-C will be calculated using the Friedewald formula by the central laboratory as per the schedule in Section 1.2. If TG values exceed 400 mg/dL (4.52 mmol/L), then the central laboratory will reflexively measure (via the beta quantification method) the LDL-C rather than calculating it. Non-HDL-C will be calculated by subtracting HDL-C from the Total-C. Ratio Apo B/Apo A-1 will be calculated. Detailed procedures of sample preparation, storage, and shipment will be described in the specific laboratory manual which will be provided to sites. Information on the processing, methodology and other relevant information will be available upon request, in the Reference Laboratory Manual.

Efficacy endpoints will not be considered as AEs, such as those involving abnormalities in lipid levels, unless meeting the criteria in Section 10.4.

9.2.3 Safety endpoints

Main safety parameters: AEs, serious AEs (SAE), and AESIs, assessed throughout the study.

Other safety parameters: laboratory data, vital signs, body weight, height, and Tanner stage, assessed throughout the study.

The AESIs are defined in Section 10.4.1.3.

9.2.3.1 Observation period

The observation of safety data will be as follows:

- Pre-treatment period: The pre-treatment observation period is defined from the signed informed consent up to the first dose of IMP.
- TEAE period: The TEAE observation period is defined as the time from the first dose of IMP to the last dose of IMP + 70 days (10 weeks).
- Post-treatment period: The post-treatment observation period is defined as the time starting the day after the end of the TEAE period up to the end of the study for each patient.

9.2.3.2 Adverse events

Refer to Section 10.4 to Section 10.7 for details.

All AEs reported by the Investigator, will be described.

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

Groupings of AEs may include the following:

- General allergic events (AESIs or not, see Section 10.4.1.3).
- Local injection site reactions (AESIs or not, see Section 10.4.1.3).
- Neurologic AEs (AESIs or not, see Section 10.4.1.3).
- Neurocognitive events.
- Symptomatic overdose with IMP:
  - An overdose (accidental or intentional) is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic injection counts) and defined as at least twice of the intended dose within the intended therapeutic interval (ie, 2 or more injections from the treatment kit are administered in <7 calendar days to be reported using the corresponding screens in the eCRF using the term "symptomatic overdose (accidental or intentional)". The patient should be monitored and appropriate symptomatic treatment instituted, if needed.
- Pregnancy of female patient (including male patient's partner).
- ALT increase.

Adverse event observation period:

- The AE observations are per the observation periods defined above.

Death observation period:

The death observations are per the observation period defined above. In addition, "poststudy" death includes all deaths reported after the end of the study (see definition of end of study period per patient in Section 6.2.2).

9.2.3.3 Laboratory safety variables

The clinical laboratory data consist of blood analysis (including hematology and clinical chemistry). Clinical laboratory values will be analyzed after conversion into standard international units. International units will be used in all listings and tables.

9.2.3.4 Vital signs

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

9.2.3.5 Tanner stages measurement

The Tanner stages will be measured (see Appendix C) throughout the study according to the schedule in Section 1.2. The Tanner stages assessment for each patient at each site should be performed, if possible by the same Investigator/designee trained to assess pubertal development.

9.3 OTHER ENDPOINTS

9.3.1 Pharmacokinetics

Total serum alirocumab concentrations, as well as total and free PCSK9 concentrations will be measured from the same PK sample.

9.3.1.1 Sampling time

Serum samples for total alirocumab concentration will be collected before IMP (pre-dose) (pre-apheresis and post-apheresis, if applicable) at Weeks 0, 12, 24, and 48 per the study flowchart (see Section 1.2).

Exact date and time of last IMP administration and PK sampling are to be recorded. Pharmacokinetics handling for alirocumab are presented in Table 1.

9.3.1.2 Pharmacokinetics handling procedure

Table 1 - Pharmacokinetics handling for alirocumab

Sample type	Alirocumab
Matrix	Serum
Blood sample volume	3 mL
Anticoagulant	none
Blood handling procedures	See laboratory manual
Storage conditions	-20°C (-4 F°) (-80°C [-112 F°] preferred)

9.3.1.3 Bioanalytical method

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

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

9.3.2 Anti-alirocumab antibody assessments

Anti-alirocumab antibodies include the antibody status (positive/negative), antibody titers, and neutralizing activity for positive ADA. Samples should be collected pre-apheresis, if applicable.

9.3.2.1 Sampling time

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

9.3.2.2 Sampling procedure

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

9.3.2.3 Bioanalytical method

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

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

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

9.3.3 Pharmacogenetic assessment

For the purposes of verifying participant eligibility, patients with suspected hoFH based on clinical criteria, but without confirmation by previous genetic testing, will be asked to undergo centralized hoFH genotyping.

No other pharmacogenetic testing will be done in this study.

9.3.4 Pharmacodynamic variables

The pharmacodynamic effect of alirocumab corresponding to the effect on LDL-C is described in the efficacy section (see Section 9.1.1 and Section 9.2.1).

9.3.5 Creatine phosphokinase-MB and cardiac troponin

Creatine phosphokinase-MB (CPK-MB) and cardiac troponin levels will be assessed at baseline and at Week 12 and in case of any clinically relevant cardiovascular effect observed in patients.

9.4 FUTURE USE OF SAMPLES

Not applicable.

9.5 APPROPRIATENESS OF MEASUREMENTS

See Section 4.

10 STUDY PROCEDURES

For all visits after Day 1/Week 0 (enrollment visit), a timeframe of a certain number of days will be allowed. The window period for the visits at Weeks 4, 24, 36, and 56 is ±7 days, and the window period for the visits at Weeks 12 and 48 is ±3 days.

For all visits after Day 1/Week 0, if one visit date is changed, then the next visit should take place according to the original schedule as outlined in Section 1.2.

Blood sampling:

The blood sampling for determination of lipid parameters (ie, Total-C, LDL-C, HDL-C, TG, non-HDL-C, Apo B, Apo A-1, ratio Apo B/Apo A-1, and Lp (a)) should be performed in the morning, in fasting condition (ie, overnight, at least 8 hours fast and refrain from smoking) for all site visits throughout the study. Alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the blood sampling are discouraged.

Of note, appropriate visits at patient's home may occur, if nursing services are available.

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

In case only a limited amount of blood can be drawn, specific tests performed for each sample obtained will be prioritized (the total maximum blood volume of 38.0 mL/day or 50.9 mL/month [20, 21, 22]). Lipid panel 1 (Total-C, LDL-C, HDL-C, TG, and non-HDL-C) should take highest priority, followed by safety parameters, and then other parameters.

Laboratory tests:

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

- Hematology - complete blood cell count including hematocrit, hemoglobin, red blood cell count, white blood cell count with differential count, and platelets.
- Chemistry - glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorus, urea nitrogen, creatinine, uric acid, lactate dehydrogenase, total protein, albumin, and gamma-glutamyl transferase (γGT).

Note: eGFR and creatinine clearance will be calculated at screening; creatinine clearance will be calculated for all subsequent visits where chemistry laboratory testing is performed. The formula for calculating eGFR and creatinine clearance is provided in Appendix E.

- Lipid panel 1: Total-C, calculated LDL-C, HDL-C, TG, and non-HDL-C.
- Lipid panel 2: Apo B, Apo A-1, ratio Apo B/Apo A-1, and Lp (a).

- Liver panel: ALT, AST, alkaline phosphatase (ALP), and total bilirubin (in case of total bilirubin values above the normal range, differentiation into conjugated and non-conjugated bilirubin will occur automatically).
- CPK.
- $HbA_{1c.}$
- CPK-MB and cardiac troponin.
- Pregnancy test: pregnancy test should be done on females of childbearing potential or females who have experienced menarche. The screening (Week -2) pregnancy test should be a blood test. All other pregnancy tests will be with a local urine pregnancy test. Refer to Appendix I for further details.

Notes: Any clinically relevant abnormal laboratory value should be immediately rechecked (whenever possible using the central laboratory) for confirmation before making any decision for the concerned patient. It should be documented as an AE/SAE as applicable. Please also refer to Section 10.4.

Instructions for the central laboratory will be given in a specific manual provided to each Investigator.

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

Pharmacogenetic samples:

Blood samples for hoFH genotyping will be obtained during the run-in period for patients with suspected hoFH not confirmed by previous genetic testing.

Pharmacokinetic samples:

Serum samples for assessment of alirocumab concentration will be obtained periodically throughout the study as per schedule note in study flowchart of Section 1.2. Blood samples should be collected before IMP injection. The PK samples will also be used for free and total PCSK9 analysis.

Physical examination:

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

Blood pressure/heart rate:

Blood pressure should be measured in sitting position under standardized conditions, approximately at the same time of the day, on the same arm, with the same apparatus if possible (after the patient has rested comfortably in sitting position for at least 5 minutes). The use of calibrated apparatus with age related cuff size is mandatory. Values are to be recorded in the eCRF; both SBP and DBP should be recorded. At the first screening visit, BP should be measured in both arms. The arm with the highest DBP will be determined at this visit, and BP should be measured on this arm throughout the study. This highest value will be recorded in the eCRF.

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

Tanner stages:

The Tanner stages (18, 19) should be measured by the Investigator at the time points indicated in the study schedule flowchart Section 1.2. Tanner stages are provided in Appendix C. The Tanner stages assessment for each patient at each site should be performed, if possible by the same Investigator/designee trained to assess pubertal development.

Body weight and height:

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

The use of calibrated balance scales is mandatory. Self-reported weights are not acceptable; patients must not read the scales themselves. Height needs to be measured as self-reported heights are not acceptable.

Training for new device:

If a new device is introduced during the course of the study, training will be scheduled accordingly at the next planned visit prior to the first administration.

10.1 VISIT SCHEDULE

The visit schedule and procedures/assessments are listed in the study flow chart in Section 1.2.

The aim of this section is to provide details on how some of the procedures/assessments have to be performed. The study consists of 8 or 9 on-site visits and 1 telephonic visit (follow-up).

If patients are treated with LDL apheresis, the visits from Day 1/Week 0, Week 4 and Week 12 must coincide with an LDL apheresis procedure as well as with study drug administration; study drug will be administered immediately after completion of the LDL apheresis procedure. After Week 12, it is strongly recommended to conduct further visits Week 24 and Week 48 the same day as an LDL apheresis procedure, if these procedures are maintained.

Only patients who meet/are likely to meet the inclusion criteria as noted in Section 7.1 should be screened.

10.1.1 Run-in period (as needed, up to Week -6)

Patients who consent to participate in the study, but who have not been on stable LMTs for at least 4 weeks or require statin intensification when initially seen, can participate in a run-in period until LMT dose(s) have been stable for at least 4 weeks. Patients eligible for the run-in period are expected to fulfill the LDL-C eligibility criterion at the end of the run-in period. Patients who require treatment with statin de novo are not allowed to enter the run-in period in order to avoid the potential for multiple titration steps. Patients who have initiated apheresis procedure (every week or every other week) at least 6 months prior to giving informed consent to the study, can enter the run-in period.

Another possible situation requiring the run-in period includes patients with suspected hoFH based on clinical criteria but without confirmation by previous genetic testing. Such patients will be asked to undergo centralized genotyping testing during the run-in period.

The run-in period is up to 4 weeks (+2 days) in duration, with 1 visit.

Patients can enter the screening period as soon as the criterion for stable LMT is met and/or centralized genotyping data (if no previous genotyping) are available.

10.1.1.1 Visit 1 (Week -6, Run-in)

- Obtaining the informed consent:
  - The patient will receive verbal information concerning the aims and methods of the study, its constraints and risks, and the study duration. Written information will be provided to the patient. Written informed consent must be signed by the patient and Investigator prior to any investigations.
- Obtaining the hoFH Genotyping Informed Consent from the dedicated section in the main ICF (if needed, ie, if no previous result of genotyping is available).
- Assessment of inclusion/exclusion criteria.
- Collection of demographic data (age, gender, race, and ethnic origin).
- Medical/surgical/family medical history.
- Record habits: alcohol habits (during the last 12 months), smoking status.
- Document prior medication history within the previous 12 weeks, especially for LMT (including statin) and nutraceutical products that may affect lipids (eg, omega-3 fatty acids, plant stanols such as those found in Benecol, flax seed oil, and psyllium).
- Check of stability of background LMT, including apheresis schedule (see Appendix A).
- Review of diet.
- Physical examination including vital signs (heart rate, SBP and DBP in sitting position) in both arms.
- Body weight measurement.

- Height without shoes.
- Tanner stage.
- Collect AEs from this point onward:
  - All AEs and SAEs will be collected from the time of informed consent signature and throughout the study.
- Sampling for hoFH genotyping (if needed).
- IRT will be contacted for notification of screening and for patient number allocation.

10.1.2 Screening period

For all patients regardless of their participation in a run-in period, the screening period is up to 2 weeks (+5 days) in duration.

The injection training will occur during the screening period after the eligibility criteria have been checked and it is confirmed that the patient is likely to be included. Patients aged ≥12 years (or another designated person such as parent, etc) will be trained to self-inject/inject with placebo for alirocumab. Patients 8 to 11 years old will be assigned a parent or another designated person who will be trained during the injection training visit or an alternative arrangement. In all cases, alternative arrangements for this required injection training may be allowed as needed, regardless of age. Please note that this visit (injection training visit) can take place at the same visit as D1 as per the site or patient preference. Prior to the injection, a local topical anesthetic may be utilized as per the Investigator's judgment. Investigators will have the option of providing a second placebo kit for alirocumab for patients/parents who require additional injection training prior to enrollment.

All laboratory tests measured at the central laboratory needed for checking the exclusion criteria of the patients will be performed during the screening period.

The screening period may include more than one site visit for patients for whom not all screening procedures can be done at the first visit. The sample for lipid testing must be obtained only after the patient has been on a stable LMT therapy (optimal statin dose ± other LMT, including apheresis) for at least 4 weeks.

Patients can be enrolled after the injection training visit and as soon as all inclusion and no exclusion criteria are met.

Patients will be instructed to follow a diet to treat their hypercholesterolemia in accordance with local guidelines or treatment practice and they should be on this diet throughout the entire study duration.

10.1.2.1 Visit 2 (Up to Week -2, Screening visit)

For the complete list and contents of procedures/assessments scheduled for the screening period, please refer to the Study Flow Chart in Section 1.2 and for detailed description of assessments Section 9 and Section 10.6.

The following procedures/assessments will be performed at the Screening visit:

- Obtaining the informed consent (if the patient did not have a run-in period):
  - The patient will receive verbal information concerning the aims and methods of the study, its constraints and risks and the study duration. Written information will be provided to the patient. Written informed consent must be signed by the patient and Investigator prior to any investigations.
- IRT will be notified (allocation of patient number, registration of screening, collection of demographic information). The patient number is composed of a 12-digit number containing the 3-digit country code, the 4-digit center code and the 5-digit patient chronological number (which is 00001 for the first patient screened in a center, 00002 for the second patient screened in the same center, etc).
- Assessment of inclusion/exclusion criteria.
- Check of stability of background LMT, including apheresis schedule (if applicable)
- If not collected before:
  - Collection of demographic data (age, gender, race, and ethnic origin).
  - Collection of genotyping results.
  - Medical/surgical/family medical history.
  - Record habits: alcohol habits (during the last 12 months), smoking status.
  - Document prior medication history within the previous 12 weeks, especially for LMT (including statin) and nutraceutical products that may affect lipids (eg, omega-3 fatty acids, plant stanols such as those found in Benecol, flax seed oil, and psyllium).
  - Review of diet.
  - Physical examination including vital signs (heart rate, SBP and DBP in sitting position) in both arms.
  - Body weight measurement.
  - Height without shoes.
  - Tanner stage.
- Collect AEs.
- Fasting blood sampling for:
  - Total-C, LDL-C, HDL-C, TG, and non-HDL-C (pre-apheresis and post-apheresis, if applicable).
  - Hematology and chemistry.
  - $HbA_{1c.}$
  - CPK.
  - Liver panel.
  - Pregnancy test.

10.1.2.2 Visit 3 (Week -1, Injection training)

The injection training will occur during the screening period after the eligibility criteria have been checked and it is confirmed that the patient is likely to be included. Patients aged ≥12 years (or another designated person such as parent, etc) will be trained to self-inject/inject with placebo for alirocumab. Patients 8 to 11 years old will be assigned a parent or another designated person who will be trained during the injection training visit or an alternative arrangement. In all cases, alternative arrangements for this required injection training may be allowed as needed, regardless of age.

Prior to the injection, a local topical anesthetic may be utilized as per the Investigator's judgment. Investigators will have the option of providing a second placebo kit for patients/parents who require additional injection training prior to enrollment.

Patients can be enrolled after the injection training visit and as soon as eligibility is confirmed.

The injection training visit at Week -1 can take place at the same visit as D1 as per the site or patient preference.

The following additional procedures/assessments will be performed at the injection training visit:

- IRT contact.
- Check of stability of background LMT, including apheresis schedule (if applicable).
- Collect AEs.

10.1.3 Treatment period

The overall treatment period is 48 weeks in duration.

All patients will receive subcutaneously (SC) either 75 or 150 mg alirocumab Q2W at entry, depending on their BW, without any dose adjustment up to Week 12. After Week 12, the dose of alirocumab can be adjusted in case of weight change after baseline, such that the dose corresponds to the patient's BW:

- 75 mg for BW <50 kg.
- 150 mg for BW ≥50 kg.

For patients treated with apheresis, the frequency will be fixed to the individual patient's established schedule up to Week 12. After Week 12, the frequency of apheresis can be adapted following Investigator judgment.

For dosing and timing of injection details, see Section 8.1.

The first IMP injection from the study treatment kit allocated by IRT will be administered at the site on the day of entry and as close as possible after their entry into the study. Patients will be monitored at the investigational site for at least 30 minutes after this first injection. Subsequent injections will be performed at a patient-preferred location (eg, home). All of the IMP injections

can be performed by a trained patient (self-injection if aged ≥12 years), parent, or another designated person, or alternative arrangements for injection administration will be allowed as needed (eg, return to the investigational site). It is suggested that patients ≥12 years old, who are trained to self-inject, do so with parental (or another designated person) supervision; however, this is not mandatory. The Investigator may evaluate the sustained reliability of this practice on a case by case basis given the variable adolescent ages, maturity levels, availability of the caregiver, or other relevant considerations, with the patient. The final decision as to whether supervision is appropriate for self-injection of alirocumab for patients ≥12 years old is per Investigator discretion. Prior to any injection, a local topical anesthetic may be utilized as per the Investigator's recommendation.

The laboratory measurement of lipid parameters will be performed by a central laboratory. The results will be communicated to the sites.

Statin and other LMT, including apheresis, (if applicable) should be stable during the treatment period barring exceptional circumstances whereby overriding concerns (including but not limited to triglyceride alert posted by the central laboratory) warrant such changes, as per the Investigator's judgment.

10.1.3.1 Visit 4 (Day 1, Week 0, Enrollment visit)

The following procedures/assessments will be performed:

- Assessment of inclusion/exclusion criteria.
- Concomitant medication recording.
- Check of stability of background LMT, including apheresis (if applicable).
- Review of diet.
- Vital signs.
- Body weight.
- Body height.
- IRT contact.
- Inclusion in study.
- Collect AEs.
- Fasting blood sampling for:
  - Total-C, LDL-C, HDL-C, TG, and non-HDL-C (pre-apheresis and post-apheresis, if applicable).
  - Apo B, Apo A-1, ratio Apo B/Apo A-1, and Lp (a) (pre-apheresis, if applicable).
  - Hematology and chemistry.
  - CPK-MB and cardiac troponin.
  - CPK.
  - Liver panel.

- Anti-alirocumab antibodies (ADA) (pre-apheresis, if applicable).
- Serum alirocumab concentration (PK) and PCSK9 concentrations (pre-apheresis and post-apheresis, if applicable).

- Pregnancy test (urine).
- IMP administration; patients will remain under observation at the site for 30 minutes post-injection.
- IMP kit dispensation (including treatment administration package, patient diary, and injection instruction manual, as needed).

Injection training: Further injection training can be provided at the enrollment visit Week 0/Day 1 when the patient/parent or a trained designated person injects the first dose of IMP allocated by IRT. Additional training can be offered at scheduled or unscheduled visits within the scheduled treatment period, as per patient/parent or Investigator's judgment.

It is suggested that patients ≥12 years old, who are trained to self-inject, do so with parental (or another designated person) supervision; however, this is not mandatory. The Investigator may evaluate the sustained reliability of this practice on a case by case basis given the variable adolescent ages, maturity levels, availability of the caregiver, or other relevant considerations, with the patient. The final decision as to whether supervision is appropriate for self-injection of alirocumab for patients ≥12 years old is per Investigator discretion.

10.1.3.2 Visit 5 (Week 4)

The following procedures/assessments will be performed:

- Compliance check of IMP and data collection on IMP administration.
- Concomitant medication recording.
- Check of stability of background LMT, including apheresis (if applicable).
- Review of diet.
- Collect AEs.
- Vital signs.
- Body weight.
- Body height.
- Fasting blood sampling for:
  - Total-C, LDL-C, HDL-C, TG, and non-HDL-C (pre-apheresis and post-apheresis, if applicable).
  - Hematology and chemistry.
  - Liver panel.
- IMP administration.

10.1.3.3 Visit 6 (Week 12)

The following procedures/assessments will be performed:

- Compliance check of IMP and data collection on IMP administration
- Concomitant medication recording.
- Check of stability of background LMT, including apheresis (if applicable).
- Review of diet.
- Collect AEs.
- Vital signs.
- Physical examination.
- Body weight.
- Body height.
- IRT contact.
- Tanner stage.
- Fasting blood sampling for:
  - Total-C, LDL-C, HDL-C, TG, and non-HDL-C (pre-apheresis and post-apheresis, if applicable).
  - Apo B, Apo A-1, ratio Apo B/Apo A-1, and Lp (a) (pre-apheresis, if applicable).
  - Hematology and chemistry.
  - $HbA_{1c.}$
  - CPK-MB and cardiac troponin.
  - CPK.
  - Liver panel.
  - Anti-alirocumab antibodies (ADA) (pre-apheresis, if applicable).
  - Serum alirocumab concentration (PK) and PCSK9 concentrations (pre-apheresis and post-apheresis, if applicable).
- Pregnancy test (urine).
- IMP kit dispensation (including treatment administration package, patient diary, and injection instruction manual, as needed).
- IMP administration.

10.1.3.4 Visit 7 (Week 24)

The following procedures/assessments will be performed:

- Compliance check of IMP and data collection on IMP administration.
- Concomitant medication recording.
- Check of stability of background LMT, including apheresis (if applicable).
- Review of diet.
- Collect AEs.
- Vital signs.
- Physical examination.
- Body weight.
- Body height.
- Tanner stage.
- IRT contact.
- Fasting blood sampling for:
  - Total-C, LDL-C, HDL-C, TG, and non-HDL-C (pre-apheresis and post-apheresis, if applicable).
  - Apo B, Apo A-1, ratio Apo B/Apo A-1, and Lp (a) (pre-apheresis, if applicable).
  - Hematology and chemistry.
  - $HbA_{1c.}$
  - CPK.
  - Liver panel.
  - Anti-alirocumab antibodies (ADA) (pre-apheresis, if applicable).
  - Serum alirocumab concentration (PK) and PCSK9 concentrations (pre-apheresis and post-apheresis, if applicable).
- Pregnancy test (urine).
- IMP kit dispensation (including treatment administration package, patient diary, and injection instruction manual, as needed).
- IMP administration.

10.1.3.5 Visit 8 (Week 36)

The following procedures/assessments will be performed:

- Compliance check of IMP and data collection on IMP administration.
- Concomitant medication recording.
- Check of stability of background LMT, including apheresis (if applicable).
- Review of diet.
- Collect AEs.
- Vital signs.
- Body weight.
- IRT contact.
- Pregnancy test (urine).
- IMP kit dispensation (including treatment administration package, patient diary, and injection instruction manual, as needed).
- IMP administration.

10.1.3.6 Visit 9 (Week 48, end of the treatment period visit)

The following procedures/assessments will be performed:

- Compliance check of IMP and data collection on IMP administration.
- Concomitant medication recording.
- Check of stability of background LMT.
- Review of diet.
- Collect AEs.
- Vital signs.
- Physical examination.
- Body weight.
- Body height.
- Tanner stage.
- IRT contact.
- Fasting blood sampling for:
  - Total-C, LDL-C, HDL-C, TG, and non-HDL-C (pre-apheresis and post-apheresis, if applicable).
  - Apo B, Apo A-1, ratio Apo B/Apo A-1, and Lp (a) (pre-apheresis, if applicable).

- Hematology and chemistry.
- HbA_{1c}.
- CPK.
- Liver panel.
- Anti-alirocumab antibodies (ADA) (pre-apheresis, if applicable).
- Serum alirocumab concentration (PK) and PCSK9 concentrations (pre-apheresis and post-apheresis, if applicable).

- Pregnancy test (urine).

10.1.4 Follow-up

A follow-up call will be planned 10 weeks after the last IMP injection, ie. 8 weeks after the EOT visit, for the patients who complete the study and for the patients who discontinue early for any reason.

The following procedures/assessments will be performed remotely:

- Concomitant medication recording.
- Collect AEs.
- IRT contact.

10.2 DEFINITION OF SOURCE DATA

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

- Agreement, date, and signature of informed consent mentioning the study identification.
- Patient identification, last participation in a clinical trial, medical history, associated diseases, and data related to the studied pathology.
- Genotyping result, if available.
- Contraception methods for females of childbearing potential who are sexually active.
- Previous and concomitant medication (including LMT).
- Study identification.
- Treatment number and dates of administration.
- Dates of visits and assessments including the examination report.
- Vital signs, height, BW, and Tanner stage.
- Faxed central laboratory reports (dated and signed by the Investigator or Subinvestigator)

- IRT confirmation fax (screening, screen failure, discontinuation, EOT period, end of follow-up period, and end of study).
- Adverse events and follow-up:
  - In case of SAE, the site should file in the source document at least copies of the hospitalization reports and any relevant examination reports documenting the follow-up of the SAE.
- Date of premature study discontinuation (if any) and reason.

Source documentation may be found in the following:

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

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

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 must be fully documented in the eCRF. In any case, the patient should remain in the study as long as possible.

Pregnancy will lead to definitive treatment discontinuation in all cases.

10.3.1 Temporary treatment discontinuation with investigational medicinal product(s)

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

For all temporary treatment discontinuations, duration must be recorded by the Investigator in the appropriate pages of the eCRF.

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

10.3.2 Permanent treatment discontinuation with investigational medicinal product(s)

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator not to re-expose the patient to the IMP at any time during the study, or from the patient not to be re-exposed to the IMP whatever the reason.

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 reason(s) for treatment discontinuation and this should be documented in the eCRF.

Patients should discontinue the IMP for the following reasons:

- Pregnancy, intention for pregnancy, or no longer using an effective contraceptive method of birth control (females of childbearing potential who are sexually active only).
- Acute injection reaction of clinical concern.
- Serious adverse event (or non-serious but severe in intensity) of allergic reaction considered related to alirocumab.
- At patient/parents request (ie, withdrawal of the consent for treatment).
- If, in the Investigator's opinion, continuation with the administration of the IMP would be detrimental to the patient's well-being.
- Intercurrent condition that requires discontinuation of the IMP.
- At the specific request of the Sponsor.

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

All cases of permanent treatment discontinuation must be recorded by the Investigator in the appropriate pages of the eCRF when considered as confirmed.

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.

Patients who prematurely discontinue study treatment (regardless of the reason) should undergo the following visits:

- At the time of treatment discontinuation, the patient should have, as soon as possible, an unscheduled visit with assessments normally planned at the EOT period visit.
- Week 12 and Week 48 visits, as described in Section 1.2, should be performed regardless of the timing of the last alirocumab injection.

In case of permanent treatment discontinuation, the recommendation is to limit data collection to critical data, ie, primary endpoint/main secondary endpoint and safety endpoints. All cases of permanent treatment discontinuation must be recorded by the Investigator in the appropriate pages of the eCRF when considered as confirmed.

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.

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 from the study treatment should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented.

All study withdrawals must be recorded by the Investigator in the appropriate screens of the eCRF and in the patient's medical records. In the medical record, at least the date of the withdrawal and the reason should be documented.

In addition, a patient may withdraw his/her consent to stop participating in the study. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-patient contact follow-up, eg, medical record checks. The site should document any case of withdrawal of consent.

For patients who fail to return to the site, unless the patient withdraws consent for follow-up, the Investigator must 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 reallocated (treated) 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.
- ALT >3 x ULN + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN.
- Suicide attempt or any event suggestive of suicidality.
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling).
- Bullous cutaneous eruptions.
- Cancers diagnosed during the study.
- Chronic neurodegenerative diseases (newly diagnosed).
- Suspected transmission of an infectious agent.

10.4.1.3 Adverse event of special interest

An AESI is an AE (serious or non-serious) 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. The AESIs may be added, modified, or removed during a study by protocol amendment.

The AESI are AEs (serious or nonserious) that need to be monitored, documented, and managed in a prespecified manner described in the protocol. Please see Appendix G for additional information.

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 eCRF.

AESIs in this study will include:

- 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 F of the protocol).
- 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 or as per Section 10.6.2, should be reported as an AESI.
  - All general allergic events require completion of the specific eCRF screen (see Section 10.6.2).
- 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 or as per Section 10.6.2, should be reported as an AESI.
  - All local injection site reactions require completion of the specific eCRF screen (see Section 10.6.2).
- 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.
- Pregnancy of a female subject entered in a study as well as pregnancy occurring in a female partner of a male subject entered in a study with IMP/NIMP;
  - 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 (ie, 2 or more injections from the treatment kit are administered in <7 calendar days) to be reported using the corresponding screens in the eCRF using the term "symptomatic overdose (accidental [or intentional])". The patient should be monitored and appropriate symptomatic treatment instituted if needed.
  - The circumstances of the overdose should be clearly specified in the verbatim.

  Of note, asymptomatic overdose has to be reported as a standard AE.

10.4.1.4 Local injection site reactions

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. Special eCRF screens will need to be completed. If such an AE was to occur, then do not report the individual components of the reaction but rather the term "local injection site reaction", the individual components being described in the specific eCRF screen.

If a local topical anesthetic is used before alirocumab injection, the time of local anesthetic administration, the time of alirocumab administration, and the time of AE will be recorded in the eCRF.

10.4.2 Serious adverse events waived from expedited regulatory reporting to regulatory authorities

Not applicable.

10.4.3 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 eCRF.

- 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. At the prespecified study end-date, patients who experience an ongoing SAE or an AESI should be followed until resolution, stabilization, or death and related data will be collected.
- When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.
- Laboratory or 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 2.

10.4.4 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 eCRF; the system will automatically send a notification to the monitoring team after approval of the Investigator within the eCRF 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 e-mail 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 eCRF, as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status, etc) should be sent (by fax or e-mail) to 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 case report form [CRF] process) is available and should be used when the eCRF system does not work.

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

10.4.5 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 10.4.4, even if not fulfilling a seriousness criterion, using the corresponding pages of the CRF (to be sent) or screens in the eCRF.

Instructions for AE reporting are summarized in Table 2 and Appendix G.

10.4.6 Guidelines for management of specific laboratory abnormalities

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

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

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

Table 2 - 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)	Allergic events meeting AESI criteria	Yes	Yes	No
		LISR meeting AESI criteria	Yes	Yes	Yes
		Pregnancy	Yes	Yes	Yes
		Symptomatic overdose	Yes	Yes	No
		ALT >3 x ULN (if baseline ALT < ULN), or ALT ≥2 times the baseline value (if baseline ALT ≥ ULN)	Yes	Yes	Yes
		Neurologic events meeting AESI criteria	Yes	Yes	No
		Neurocognitive events	Yes	Yes	No

10.4.7 Guidelines for reporting product complaints (IMP/NIMP)

Any defect in the IMP/NIMP must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Noninvestigational medicinal products include rescue medication, challenge agents, products use to assess endpoints in the clinical trial, concomitant products systematically prescribed to the study patients, and background treatment.

Appropriate information (eg, samples, labels, or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. 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 (suspected unexpected serious adverse reaction [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.
- The following AESIs to those regulatory authorities who require such reporting:
  - ALT >3 x ULN (if baseline ALT < ULN), or ALT ≥2 times the baseline value (if baseline ALT ≥ ULN).
  - Allergic events that require consultation with another physician.
  - Local injection site reactions that require consultation with another physician.
  - Pregnancy.
  - Symptomatic overdose with IMP alirocumab.
  - Neurologic events that require additional examinations/procedures and/or referral to a specialist.
  - Neurocognitive events.
  - Any other AE not listed as an expected event in the Investigator's Brochure or in this protocol will be considered as unexpected.

Adverse events that are considered expected will be specified by the reference safety information.

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/parent recognizes any signs of local intolerability, then this should be treated and followed up as per the Investigator's medical judgment.

10.6.2 Allergic adverse events

Specific eCRF screens are to be filled in to assess allergic AEs or allergic-like AEs 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 documented on the General Allergic AE and/or Local Injection Site Reaction Complementary Form.

All local injection site reactions should be recorded on the Local Injection Site Reaction Complementary Form. However, injection site reactions which progress/expand/worsen/etc, should be evaluated as recommended in Section 10.6.2.1 and the specific General Allergic AE and/or Local Injection Site Reaction Complementary Form should be completed.

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

10.6.2.1 Allergic adverse event with cutaneous involvement

Adverse events with cutaneous involvement which are obviously of allergic origin or injection site reactions which progress/expand/worsen/etc should be evaluated by a dermatologist as soon as possible, and preferably within 1 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 central laboratory assessment for hematology, chemistry, liver panel, PK, and ADA should be obtained. If it is possible, the site will take pictures of the skin lesions in order to provide the patient with them for the dermatologist's visit. If the photos are obtained, then copies should be kept as source documents which may later be collected by the Sponsor. The Investigator will provide a summary of the patient's case, reason for consultation, and information being requested to the consulting dermatologist.

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

10.6.2.2 Acute allergic injection reactions

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

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

10.6.3 Recommendations for managing and monitoring patients reaching LDL-C levels (ie, LDL-C <50 mg/dL [1.30 mmol/L]) during the treatment period

If a patient achieves a low LDL-C level (ie, LDL-C <50 mg/dL [1.30 mmol/L] on one or more occasion) during the treatment period, then the Investigator will:

- Call the patient/parent as soon as possible to inquire about interval occurrence of AEs.
- Decide whether the patient should be requested to rapidly have an unscheduled site visit, or assessment could be done at the next scheduled visit.
- At the site visit, plan for the following, based on Investigator's medical judgment:
  - Assess the need to have blood drawn from the patient for a repeat lipid assessment in order to confirm the observation of very low LDL-C.
  - Assess the need for conducting clinical investigations, arranging specialist consultation(s) as needed, including with an eye specialist in case of visual problems, as needed, and any relevant additional work-up.
  - Assess the need for alirocumab treatment temporary or permanent discontinuation.

10.7 ADVERSE EVENTS MONITORING

All AEs 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 sample size calculation was performed. Eighteen patients are planned to be enrolled to have at least 15 evaluable patients considering the recruitment constraints in this rare disease population.

11.2 DISPOSITION OF PATIENTS

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

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

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy population

The efficacy analysis population will be the ITT population defined as the patients receiving at least one dose or partial dose of IMP.

11.3.2 Safety population

Safety analyses will be performed on the safety population, which will consist of patients receiving at least one dose or partial dose of IMP.

In addition:

- Patients for whom it is unclear whether they took the study medication will be included in the safety population.

11.3.3 Other analysis populations

The ADA analysis will be performed on all treated patients (safety population) with a blood sample on Week 0 (baseline) and at least one evaluable blood sample for antibodies post first IMP injection.

The PK analysis will be performed on all treated patients (safety population) with at least one available PK sample post first IMP injection.

11.4 STATISTICAL METHODS

11.4.1 Extent of study treatment exposure and compliance

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

11.4.1.1 Extent of investigational medicinal product exposure

The total exposure will be assessed by:

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

11.4.1.2 Compliance

Compliance will be assessed using the following parameters:

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

This parameter will be summarized descriptively (N, mean, standard deviation [SD], median, minimum [Min] and maximum [Max]).

11.4.2 Analyses of efficacy endpoints

Efficacy endpoints analyzed with the ITT and on-treatment estimands will be analyzed in the ITT population.

11.4.2.1 Analysis of primary efficacy endpoint(s)

The percent change from baseline in LDL-C at Week 12 (see Section 9.1.1) will be analyzed in the ITT population using a mixed-effect model with repeated measures (MMRM) approach. All post-baseline data available within the Week 4 to Week 48 analysis windows will be used and missing data will be accounted for by the MMRM model. The model will include the fixed categorical effect of time point (Weeks 4, 12, 24, and 48), as well as the continuous fixed covariate of baseline LDL-C value.

This model will be run using SAS mixed procedure with an unstructured correlation matrix to model the within-patient errors. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Denominator degrees of freedom will be estimated using Satterthwaite's approximation. Throughout the MMRM model, LS mean and standard error (SE) at Week 12 will be provided with the SE and 95% confidence interval (CI).

Robustness of this statistical method will be assessed via sensitivity analysis detailed in the SAP, applying different imputations for missing LDL-C values during the treatment period and missing LDL-C values during the post-treatment period (ie, pattern mixture model).

11.4.2.2 Analyses of secondary efficacy endpoints

Multiple types of measurements are planned to be analyzed (see Section 9.2) during differing time points in the trial, specifically continuous measurements expected to have a normal distribution (eg, percent change in LDL-C), continuous measurements expected to have a non-normal distribution (eg, TG), and binary measurements (eg, proportion of patients with ≥15% reduction in LDL-C).

Continuous endpoints anticipated to have a normal distribution

Continuous secondary efficacy endpoints analyzed with the ITT estimand and anticipated to have a normal distribution (ie, lipids other than TG and Lp (a)) will be analyzed using the same MMRM model as for the primary endpoint with the corresponding baseline and post-baseline values.

Continuous secondary efficacy endpoints analyzed with the on-treatment estimand and anticipated to have a normal distribution will be analyzed using the same MMRM model but only including on-treatment values. The treatment period is defined as the time period from the first IMP injection up to the day of last injection + 21 days.

Continuous endpoints anticipated to have a non-normal distribution

Continuous secondary efficacy endpoints analyzed with the ITT estimand and anticipated to have a non-normal distribution (ie, TG and Lp (a)), will be analyzed using a robust regression model (ie, ROBUSTREG SAS procedure with M-estimation option) with baseline value as effect. Missing values will be addressed using a multiple imputation approach, which will be described in the SAP. The combined means will be provided with respective SE estimates and 95% CI.

Continuous secondary efficacy endpoints analyzed with the on-treatment estimand and anticipated to have a non-normal distribution will be analyzed using the same imputation and analysis models but only including on-treatment values in these models.

Binary endpoints

Binary secondary efficacy endpoints analyzed with the ITT estimand will be analyzed with multiple imputation approach for handling of missing values, which will be described in the SAP. Combined proportions will be provided with corresponding 95% CI.

Binary secondary efficacy endpoints analyzed with the on-treatment estimand will be analyzed using the same imputation model, but only including on-treatment values in this model.

11.4.2.3 Multiplicity considerations

Not applicable.

11.4.3 Analyses of safety data

The summary of safety results (see Section 9.2.3) will be presented by dose and overall. No formal inferential testing will be performed. Summaries will be descriptive in nature.

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

- The baseline value is defined as the last available value before first 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.
- The PCSA criteria will determine which patients had at least 1 PCSA during the TEAE period, taking into account all evaluations performed during the TEAE period, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the PCSA percentage.
- Treatment period: the treatment period used for quantitative analysis is defined as the time from first dose of IMP injection to the last dose of IMP injection +21 days.

Adverse event definition:

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

Drug-induced liver injury

Liver function tests, namely ALT, AST, ALP, and total bilirubin, are used to assess possible drug-induced liver toxicity. The proportion of patients with PCSA values at any post-baseline visit by baseline status will be displayed for each parameter. A graph of distribution of peak values of ALT versus peak values of total bilirubin will also be presented. Note that the ALT and total bilirubin values are presented on a logarithmic scale. The graph will be divided into 4 quadrants with a vertical line corresponding to 3 x ULN for ALT and a horizontal line corresponding to 2 x ULN for total bilirubin.

The incidence of liver-related AEs will be summarized. The selection of PT will be based on standardized MedDRA query (SMQ) hepatic disorder.

11.4.3.1 Adverse events

Adverse event incidence tables will present the number (n) and percentage (%) of patients experiencing an AE by SOC (sorted by internationally agreed order), HLGT, HLT, and 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.

Adverse event incidence table will be provided for all types of TEAEs: all TEAEs, all treatment-emergent AESI and grouping of terms (prespecified grouping, eg, allergic events, LISR), all treatment-emergent SAEs, and all TEAEs leading to permanent treatment discontinuation.

Deaths:

The following deaths summaries will be generated:

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

11.4.3.2 Laboratory data and vital signs

The summary statistics (including mean, median, Q1, Q3, standard error, minimum, and maximum) of all laboratory variables, all vital signs parameters (raw data and changes from baseline) will be calculated for each visit, last and worst value assessed during the treatment period.

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

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

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

11.4.4 Other endpoints

For definitions see Section 9.3.

11.4.4.1 Pharmacokinetics

Serum total alirocumab concentrations, and total and free PCSK9 concentrations will be summarized by visit using descriptive statistics by dose and overall. Serum concentration time profiles will be provided by dose and overall. Further details will be provided in the SAP.

Serum total alirocumab concentrations might be used for population PK modeling if considered necessary and the results of population PK modeling will be reported separately from the study report.

11.4.4.2 Anti-alirocumab antibody assessments

The antibody status (positive/negative) and antibody titers will be summarized by visit using descriptive statistics by dose and overall.

11.4.4.3 LDL-C less than 50 mg/dL (1.30 mmol/L)

The number and percentage of patients with 2 consecutives results, spaced out by at least 21 days, of calculated LDL-C <50 mg/dL (1.30 mmol/L), calculated LDL-C <25 mg/dL (0.65 mmol/L), calculated LDL-C <15 mg/dL (0.39 mmol/L), and the time to the first LDL-C <50 mg/dL (<25 mg/dL, <15 mg/dL respectively), will be provided by dose and overall.

11.4.4.4 Creatine phosphokinase-MB and cardiac troponin

Creatine phosphokinase-MB and cardiac troponin (value and percent change from baseline) at Week 12 will be summarized on the safety population using number of available data, mean, SD, median, Q1, Q3, minimum, and maximum for each dose and overall. In addition, the incidence of PCSA at any time during the TEAE period will be summarized by dose and overall using descriptive statistics.

11.5 INTERIM ANALYSIS

No interim analysis is planned (see Section 6.3).

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 Subinvestigator, 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, should fully inform the patient (and the parent[s] or guardian[s]) of all pertinent aspects of the clinical trial including the written information given approval/favorable opinion by the ethics committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study in language and terms they are able to understand.

Prior to a patient's participation in the clinical trial, the informed consent form should be signed, name filled in, and personally dated by the patient's parent(s) or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. Local law must be observed in deciding whether 1 or both parents/guardians consent is required. If only 1 parent or guardian signs the consent form, the Investigator must document the reason for only 1 parent or guardian's signature.

In addition, participants will assent as detailed below or will follow the IRB/IEC approved standard practice for pediatric participants at each participating center (age of assent to be determined by the IRBs/IECs or be consistent with the local requirements):

Participants who can read the assent form will do so before writing their name and signing and dating the form.

Participants who can write but cannot read will have the assent form read to them before writing their name on the form.

Participants who can understand but who can neither write nor read will have the assent form read to them in presence of an impartial witness, who will sign and date the assent form to confirm that assent was given.

The informed consent form and the assent 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.

In relation with the population of patients exposed in the trial, ie, pediatric/minor patients, the IRB/IEC should ensure proper advice from specialist with pediatrics expertise (competent in the area of clinical, ethical, and psychosocial problems in the field of pediatrics) according to national regulations. This should be documented.

Prior to collection of blood for genotyping for hoFH and/or for use of previous documented genotyping, the optional informed consent section within the main informed consent form (written) should be signed, name filled in, and personally dated by the patient or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written optional informed consent form will be provided to the subject.

The informed consent form and the optional genotyping informed consent obtained 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.

A copy of the signed and dated written informed consent form(s) will be provided to the patient or legal representative.

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, etc], Investigator's curriculum vitae), 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 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 eCRF, Discrepancy Resolution Form [DRF], or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

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

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

13.2 RESPONSIBILITIES OF THE SPONSOR

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

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

It is the responsibility of the Investigator to maintain adequate and accurate eCRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All 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 eCRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the Sponsor as soon as they are entered in the eCRF.

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

13.5 USE OF COMPUTERIZED SYSTEMS

The complete list of computerized systems used for the study is provided in a separate document which is maintained in the Sponsor's 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 and delegated Investigator staff/Subinvestigator shall not mention any information or the Product in any application for a patent or for any other intellectual property rights.

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

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

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

14.5 DATA PROTECTION

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

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

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

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

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

14.6 INSURANCE COMPENSATION

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

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, 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/she 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. Goldstein JL, Hobbs HH, Brown MS. Familial hypercholesterolemia. In: Scriver CR, Beaudet AL, Valle D, Sly WS, editors. The Metabolic and Molecular Bases of Inherited Disease. 8 ed. New York, NY: McGraw-Hill. 2001:2863-913.

2. Cuchel M, Bruckert E, Ginsberg HN, Raal FJ, Santos RD, Hegele RA, et al. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. Eur Heart J. 2014;35(32):2146-57.

3. Stein EA, Honarpour N, Wasserman SM, Xu F, Scott R, Raal FJ. Effect of the proprotein convertase subtilisin/kexin 9 monoclonal antibody, AMG 145, in homozygous familial hypercholesterolemia. Circulation. 2013;128(19):2113-20.

4. Raal FJ, Honarpour N, Blom DJ, Hovingh GK, Xu F, Scott R, et al. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial. Lancet. 2015;385:341-50.

5. Widhalm K, Benke IM, Fritz M, Geiger H, Helk O, Fritsch M, et al. Homozygous familial hypercholesterolemia: Summarized case reports. Atherosclerosis. 2017;257:86-9.

6. Daniels SR, Gidding SS, de Ferranti SD, National Lipid Association Expert Panel on Familial Hypercholesterolemia. Pediatric Aspects of Familial Hypercholesterolemias: recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol; 2011;5:30-7.

7. Goldberg AC, Hopkins PN, Toth PP, Ballantyne CM, Rader DJ, Robinson JG, et al. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol. 2011;5:133-40.

8. Stock J. EAS Consensus Panel statement on homozygous FH. Atherosclerosis. 2015 ;242(1):323-6.

9. McCrindle BW, Urbina EM, Dennison BA, Jacobson MS, Steinberger J, Rocchini AP, et al. Drug therapy of high-risk lipid abnormalities in children and adolescents: a scientific statement from the American Heart Association atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Disease in the Young, with the Council on Cardiovascular Nursing. Circulation. 2007;115(14):1948–67.

10. McCrindle BW, Ose L, Marais AD. Efficacy and safety of atorvastatin in children and adolescents with familial hypercholesterolemia or severe hyperlipidemia: a multicenter, randomized, placebo-controlled trial. J Pediatr. 2003;143:74–80.

11. De Jongh S, Ose L, Szamosi T, Gagné C, Lambert M, Scott R, et al. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized, double-blind, placebo-controlled trial with simvastatin. Circulation. 2002;106:2231–7.

12. Avis HJ, Hutten BA, Gagne C, Langslet G, McCrindle BW, Wiegman A, et al. Efficacy and safety of rosuvastatin therapy for children with familial hypercholesterolemia. J Am Coll Cardiol. 2010;55(11):1121–6.

13. Van der Graaf A, Cuffie-Jackson C, Vissers MN, Gagné C, Shi G, Veltri E, et al. Efficacy and safety of coadministration of ezetimibe and simvastatin in adolescents with heterozygous familial hypercholesterolemia. J Am Coll Cardiol. 2008;52(17):1421-9.

14. Eiland LS, Luttrell PK. Use of statins for dyslipidemia in the pediatric population. J Pediatr Pharmacol Ther. 2010;15(3):160-72.

15. Raal FJ, Hovingh GK, Blom D, Santos RD, Harada-Shiba M, Bruckert E, and al. Long-term treatment with evolocumab added to conventional drug therapy, with or without apheresis, in patients with homozygous familial hypercholesterolaemia: an interim subset analysis of the open-label TAUSSIG study. Lancet Diabetes Endocrinol. 2017;5(4):280-90.

16. Stein AE, Mellis S, Yancopoulos GD, Stahl N, Logan D, Smith WB, et al. Effect of a Monoclonal Antibody to PCSK9 on LDL Cholesterol. N Engl J Med. 2012;366:1108-18.

17. NICE clinical guideline. Identification and management of familial hypercholesterolemia. London: National Institute for Health and Clinical Excellence, 2008.

18. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Arch Dis Child. 1970;45(239):13–23.

19. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Arch Dis Child. 1969;44(235):291–303.

20. hhs.gov. OHRP Expedited Review Categories (1998) [Internet]. HHS.gov. 2016.

21. WHO | Blood sample volumes in child health research: review of safe limits [Internet].

22. European Union. Ethical considerations for clinical trials on medicinal products conducted with the paediatric population. Eur J Health Law. 2008;15(2):223–50.

17 APPENDICES

Appendix A. Management of patients treated with LDL apheresis therapy in the EFC14660 study

Introduction

Despite effective available treatments that can also be used in combination, many high-risk patients fail to reach their guideline target LDL-C level. For these patients who are still unable to achieve guideline target level for LDL-C, despite available lipid modifying therapy (LMT), mechanical removal of LDL-C by LDL apheresis is an option.

However, LDL apheresis is a costly procedure that is invasive and burdensome for patients, especially in children. Because of the sparsity of apheresis centers, many patients must travel a significant distance for this procedure, which is administered over 3 hours and must be given every week to every 4 weeks, depending on the patient's LDL-C level and cardiovascular risk. Low-density lipoprotein apheresis is generally well tolerated, but may result in hypotension, hypocalcemia, allergic reactions, and an acute decrease in serum protein levels.

An average reduction of the LDL-C value ranges from 30% to 75% depending on the technique and duration of apheresis (1). With weekly or bi-weekly treatment, the LDL-C levels can be reduced by 40% to 50%. The LDL-C levels rise towards baseline after each apheresis procedure, but do not reach the original levels; with repeated weekly or bi-weekly apheresis, the baseline levels continue to fall until a plateau is reached (2). Alirocumab may offer a significant therapeutic advancement for patients with HoFH who require LDL apheresis by decreasing the frequency or removing the need for apheresis procedures.

Screening and inclusion in EFC14660

Patients diagnosed with hoFH confirmed by genotyping, who are undergoing stable[5] LDL apheresis therapy every 1 or 2 weeks, are allowed to be enrolled in this study, and their background treatment with LMT will be maintained throughout the study.

Screening

Patients who have been on a stable apheresis schedule prior to the screening visit (Week -2) and stable background medical LMT for at least 4 weeks prior to the screening visit (Week -2) will enter a 2-week screening period.

[5] Stable apheresis is defined as 4 apheresis procedures performed during a 4 week period, approximately 1 week apart, or 4 apheresis procedures performed during an 8 week period, approximately 2 weeks apart.

Note: Acceptable apheresis techniques are: double membrane filtration, immunoadsorption, heparin-induced LDL precipitation, direct adsorption of lipids, dextran sulfate adsorption (plasma), dextran sulfate adsorption (whole blood).

Inclusion criteria

For patients on apheresis, currently undergoing stable LDL apheresis[6] therapy prior to the screening visit (Week -2) and have initiated apheresis treatment for at least 6 months.

Exclusion criteria

LDL apheresis schedule/apheresis settings that have not been stable for at least 4 weeks prior to the screening visit (Week -2) for patients undergoing apheresis weekly, and at least 8 weeks prior to the screening visit (Week -2) for patients undergoing apheresis bi-weekly.

During the course of the study

If patients are treated with LDL apheresis, the visits from Day 1/Week 0, Week 4 and Week 12 **must** coincide with an LDL apheresis procedure as well as with study drug administration; study drug will be administered immediately after completion of the LDL apheresis procedure.

Treatment injections during the treatment period will be administered at the site, starting on the day of enrollment (Week 0 [Day 1]/Visit 3). The patient will be monitored at the clinical site for 30 minutes after the first dose after this first injection. For this visit as well as visits Week 4 and Week 12, LDL apheresis must coincide with study visit; study drug will be administered immediately after completion of the LDL apheresis procedure.

From Day 1 to Week 12, the apheresis frequency will be fixed to the individual patient's established schedule.

After Week 12, at the Investigator's discretion, patients may continue to undergo apheresis procedures, as needed and the frequency of apheresis procedures can be adapted to their needs. If these procedures are maintained, it is strongly recommended to conduct the visits Week 24 and Week 48 the same day as an LDL apheresis procedure, in order to collect appropriately the investigational blood samples.

Blood sample collection and overall study assessment throughout the study

All samples for clinical laboratory (lipid and specialty lipid panels) and PK evaluations **must** be obtained immediately prior to and immediately after the LDL apheresis procedure, therefore LDL apheresis has to be administered at that visit and before study drug administration.

- Lipid panel 1 (Total-C, calculated LDL-C, HDL-C, TG, and non-HDL-C): samples should be drawn immediately prior to and immediately following the apheresis procedure.

[6] Stable apheresis is defined as 4 apheresis procedures performed during a 4 week period, approximately 1 week apart, or 4 apheresis procedures performed during an 8 week period, approximately 2 weeks apart.

Note: Acceptable apheresis techniques are: double membrane filtration, immunoadsorption, heparin-induced LDL precipitation, direct adsorption of lipids, dextran sulfate adsorption (plasma), dextran sulfate adsorption (whole blood).

- Alirocumab, and free and total PCSK9 levels: PK samples should be drawn immediately prior to and immediately following the apheresis procedure.
- Specialty lipid panel (lipid panel 2: Apo B, Apo A-1, and Lp (a)): samples should be drawn immediately prior to apheresis (where applicable).
- ADA assessment: samples should be drawn prior to apheresis (where applicable).

Study assessments such as vital signs, BP etc, have to be done before apheresis, and alirocumab is to be administered after apheresis.

REFERENCES

1. Bambauer R, Bambauer C, Lehmann B, et al. LDL Apheresis: Technical and Clinical Aspects. Scientific World Journal 2012;2012:1-19.

2. Thompsen J, Thompson PD. A systematic review of LDL apheresis in the treatment of cardiovascular disease. Atherosclerosis 2006;189:31-38.

Appendix B. Criteria for the diagnosis of homozygous familial Hypercholesterolaemia - EAS Consensus Panel recommendations for diagnosis of hoFH

- Genetic confirmation of 2 mutant alleles at the LDLR, APO B, PCSK9, or LDLRAP1 gene locus.

OR

- An untreated LDL-C >13 mmol/L (500 mg/dL) or treated LDL-C 7.8 mmol/L (300 mg/dL)* together with either:
  - Cutaneous or tendon xanthoma before age 10 years or,
  - Untreated elevated LDL-C levels consistent with heterozygous FH in both parents.

* These LDL-C levels are only indicative, and lower levels, especially in children or in treated patients, do not exclude HoFH.

Appendix C. Tanner stage

The Tanner stages (1, 2) assessment for each patient at each site should be performed, if possible by the same Investigator/designee trained to assess pubertal development.

Boys - development of external genitalia

Stage 1: Pre-adolescent. Testes, scrotum, and penis are of about the same size and proportion as in early childhood.

Stage 2: The scrotum and testes have enlarged and there is a change in the texture of the scrotal skin. There is also some reddening of the scrotal skin.

Stage 3: Growth of the penis has occurred, at first mainly in length but with some increase in breadth. There has been further growth of testes and scrotum.

Stage 4: Penis further enlarged in length and breadth with development of glans. Testes and scrotum further enlarged. There is also further darkening of the scrotal skin.

Stage 5: Genitalia adult in size and shape. No further enlargement takes place after Stage 5 is reached.

Girls - breast development

Stage 1: Pre-adolescent; elevation of papilla only.

Stage 2: Breast bud stage; elevation of breast and papilla as a small mound, enlargement of areola diameter.

Stage 3: Further enlargement of breast and areola, with no separation of their contours.

Stage 4: Projection of areola and papilla to form a secondary mound above the level of the breast.

Stage 5: Mature stage; projection of papilla only, due to recession of the areola to the general contour of the breast.

Boys/Girls - pubic hair

Stage 1: Pre-adolescent; the vellus over the pubes is not further developed than that over the anterior abdominal wall, ie, no pubic hair.

Stage 2: Sparse growth of long, slightly pigmented, downy hair, straight or only slightly curled, appearing chiefly at the base of the penis (boys) or along the labia (girls).

Stage 3: Considerably darker, coarser, and more curled. The hair spreads sparsely over the junction of the pubes.

Stage 4: Hair is now adult in type, but the area covered by it is still considerably smaller than in most adults. There is no spread to the medial surface of the thighs.

Stage 5: Adult in quantity and type, distributed as an inverse triangle of the classically feminine pattern (girls). Spread to the medial surface of the thighs, but not up the linea alba or elsewhere above the base of the inverse triangle.

BIBLIOGRAPHIC REFERENCES

1. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Arch Dis Child. 1970;45:13-23.

2. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Arch Dis Child. 1970;45:13-23.

Appendix D. Contraceptive guidance and collection of pregnancy information

DEFINITIONS

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

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

CONTRACEPTION GUIDANCE

Sexual counseling should be provided to patients when indicated.

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 3 – Highly effective contraceptive methods.

Table 3 - Highly effective contraceptive methods

Highly Effective Contraceptive Methods That Are User Dependent[a]

Failure rate of <1% per year when used consistently and correctly

- 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
  - Oral.
  - Injectable.

Highly Effective Methods That Are User Independent[a]

- Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b]
  - Intrauterine device (IUD).
  - Intrauterine hormone-releasing system (IUS).
- Bilateral tubal occlusion.

Vasectomized partner

A vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

Sexual abstinence

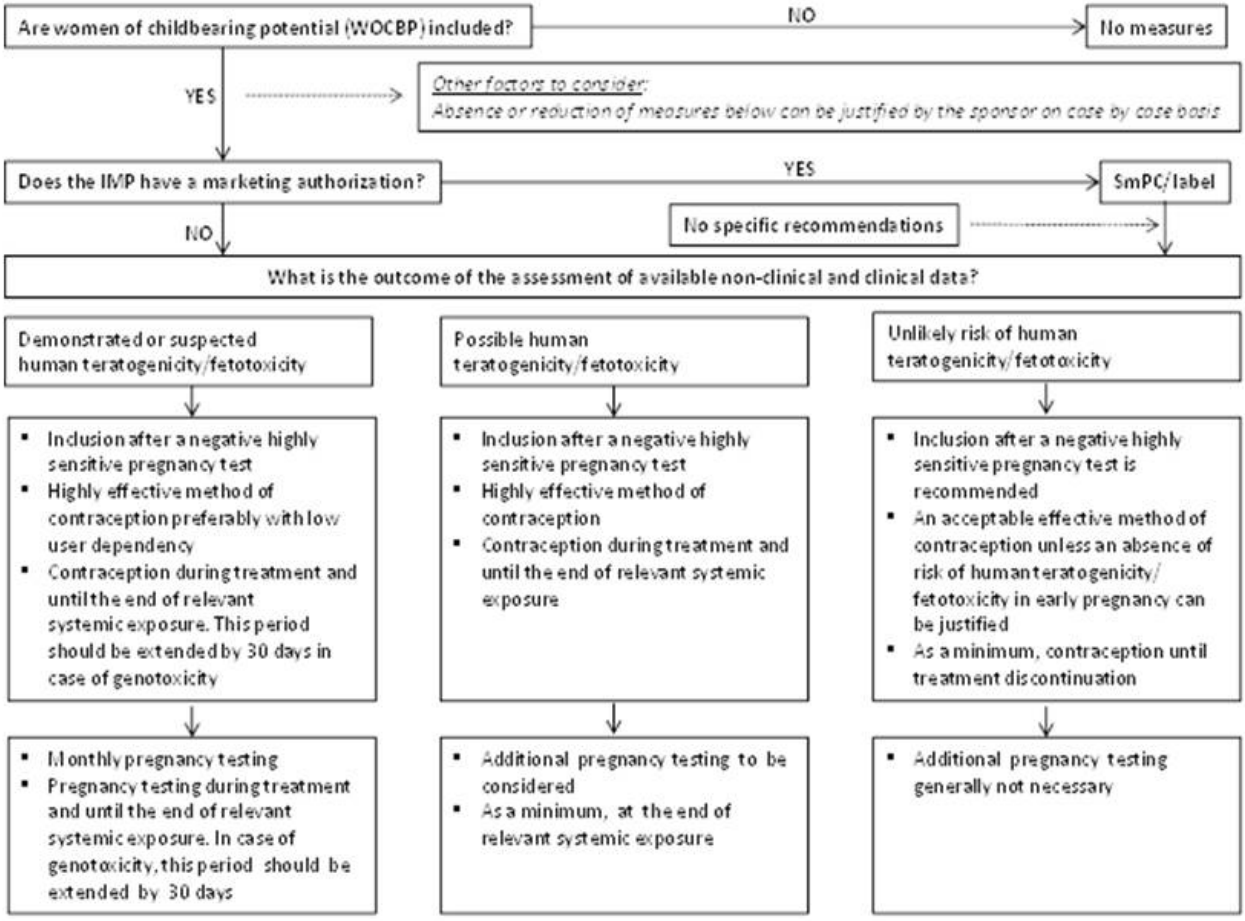
Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

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 participants participating in clinical studies.

b Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case TWO highly effective methods of contraception should be utilized during the treatment period and for at least 10 weeks after the last dose of study treatment.

See guidance below:



Clinical Facilitation Group (September 2014) - Recommendations related to contraception and pregnancy testing in clinical trials

COLLECTION OF PREGNANCY INFORMATION

Male participants with partners who become pregnant

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

Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

  Any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any poststudy pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor as described in Section 10.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study treatment.

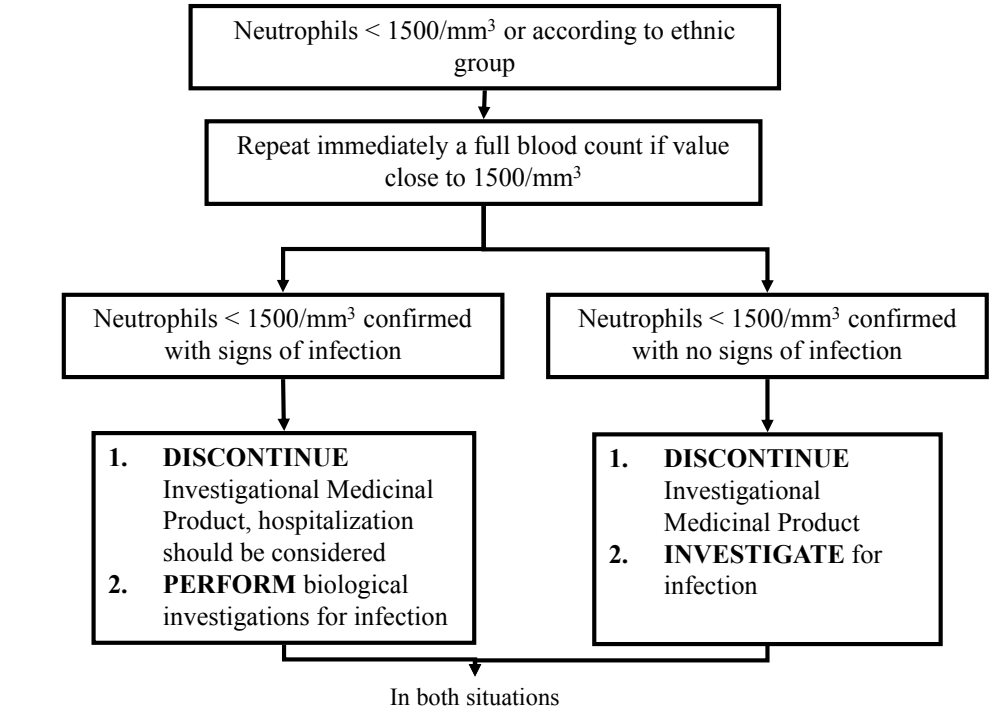
Appendix E. Pediatric formulae for eGFR and creatinine clearance

Calculation Name:	GFR SCHWARTZ	
Formula	**Units**	**Decimal Places**
Conventional: 0.413 * (Height (cm)/Serum Creatinine (mg/dL))	mL/min/1.73m^2	0
SI: *Convert creatinine into mg/dL:* Serum Creatinine (umol/L) x 0.01131 *GFR Formula:* 0.413 * (Height (cm)/Serum Creatinine (mg/dL))	mL/min/1.73m^2	0

Calculation Name:	Creat Clear Ped Schwartz 21	
Formula	**Units**	**Decimal Places**
Conventional: **<1 years:** (0.45 x Height (cm))/serum creatinine (mg/dL) **1-13 years:** (0.55 x Height (cm))/serum creatinine (mg/dL) **Females 13-21 years:** (0.55 x Height (cm))/serum creatinine (mg/dL) **Males 13-21 years:** (0.70 x Height (cm))/serum creatinine (mg/dL)	mL/min/1.73m^2	0
SI: **<1 years:** (0.45 x Height (cm))/serum creatinine (umol/L) x (0.01131) **1-13 years:** (0.55 x Height (cm))/(serum creatinine (umol/L) x (0.01131) **Females 13-21 years:** (0.55 x Height (cm))/serum creatinine (umol/L) x (0.01131) **Males 13-21 years:** (0.70 x Height (cm))/serum creatinine (umol/L) x (0.01131)	mL/min/1.73m^2	0

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

NEUTROPENIA

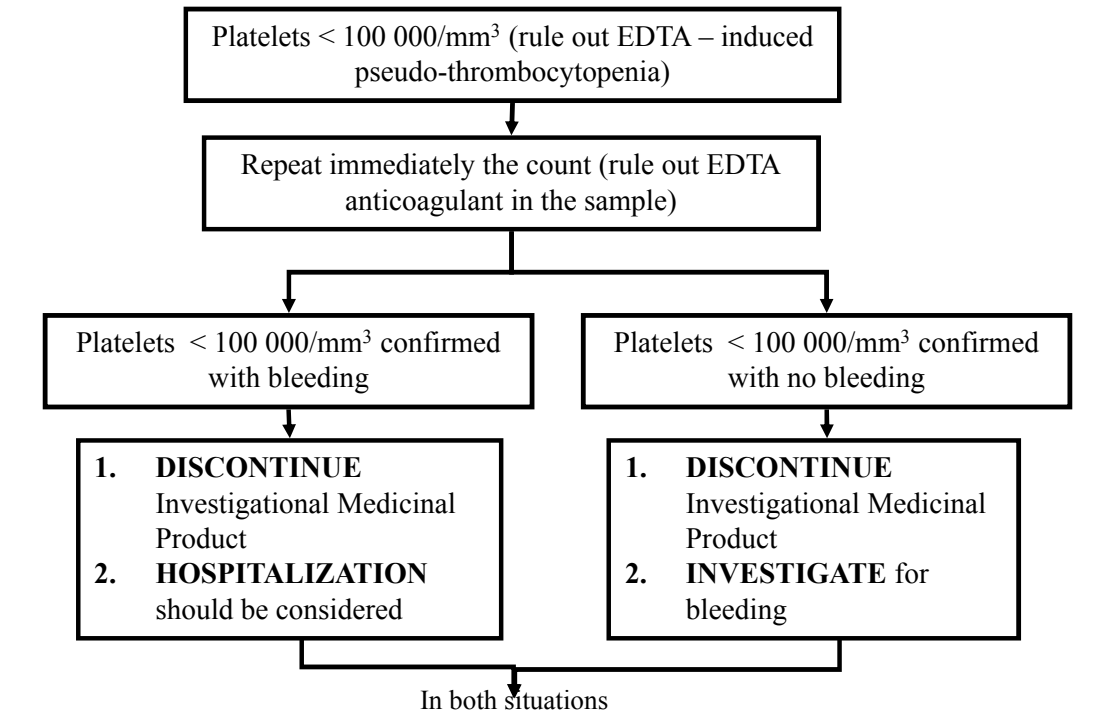


3. **INFORM** the local monitor
4. **INVESTIGATE** previous treatments particularly long-term, even a long time ago, exposure to toxic agents, e.g., benzene, X-rays, etc.
5. **PERFORM** and collect the following investigations (results):
   - RBC and platelet counts
   - Serology: EBV, (HIV), mumps,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

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

Neutropenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Section 10.4.3 is met.

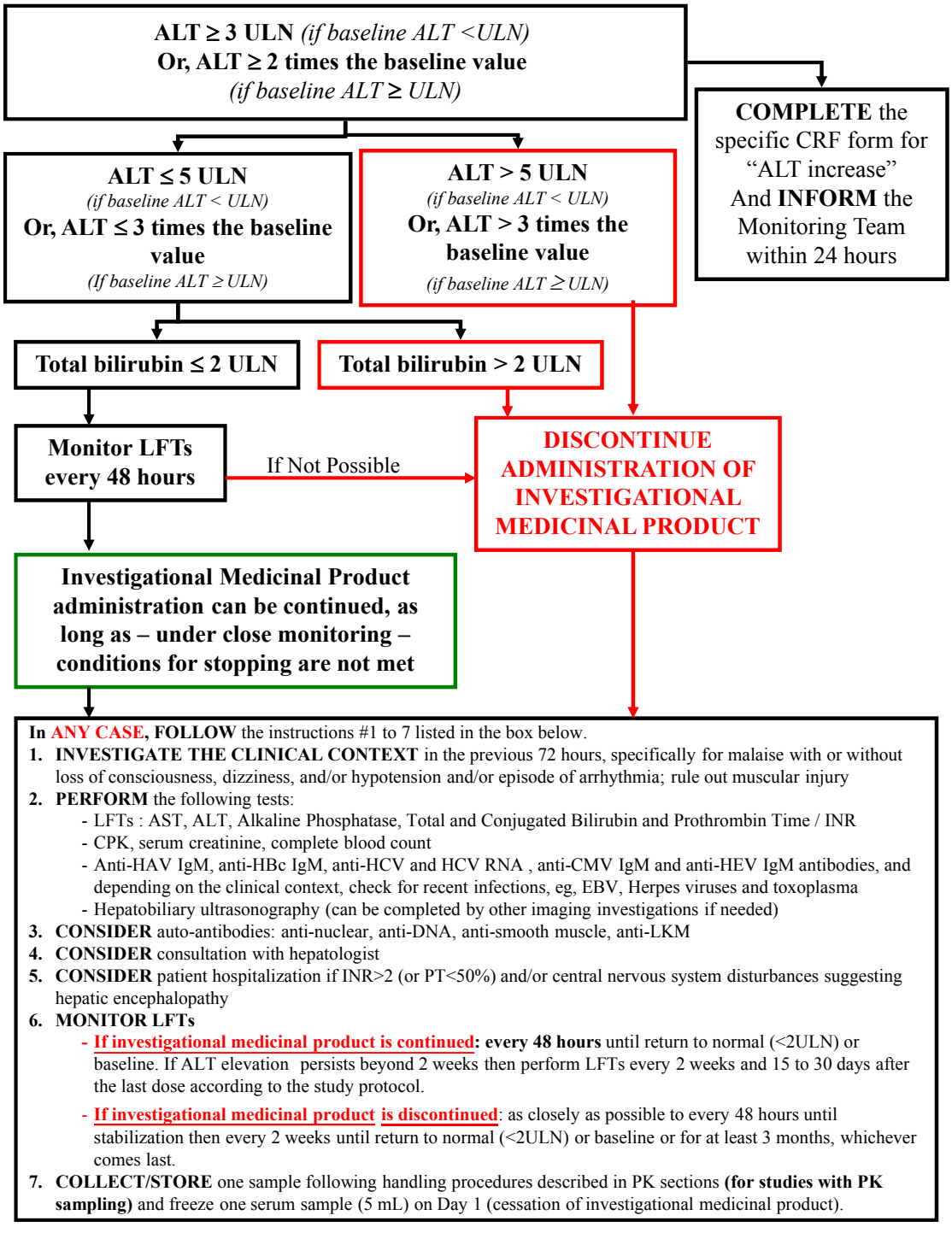
THROMBOCYTOPENIA



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

Thrombocytopenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Section 10.4.3 is met.

INCREASE IN ALT

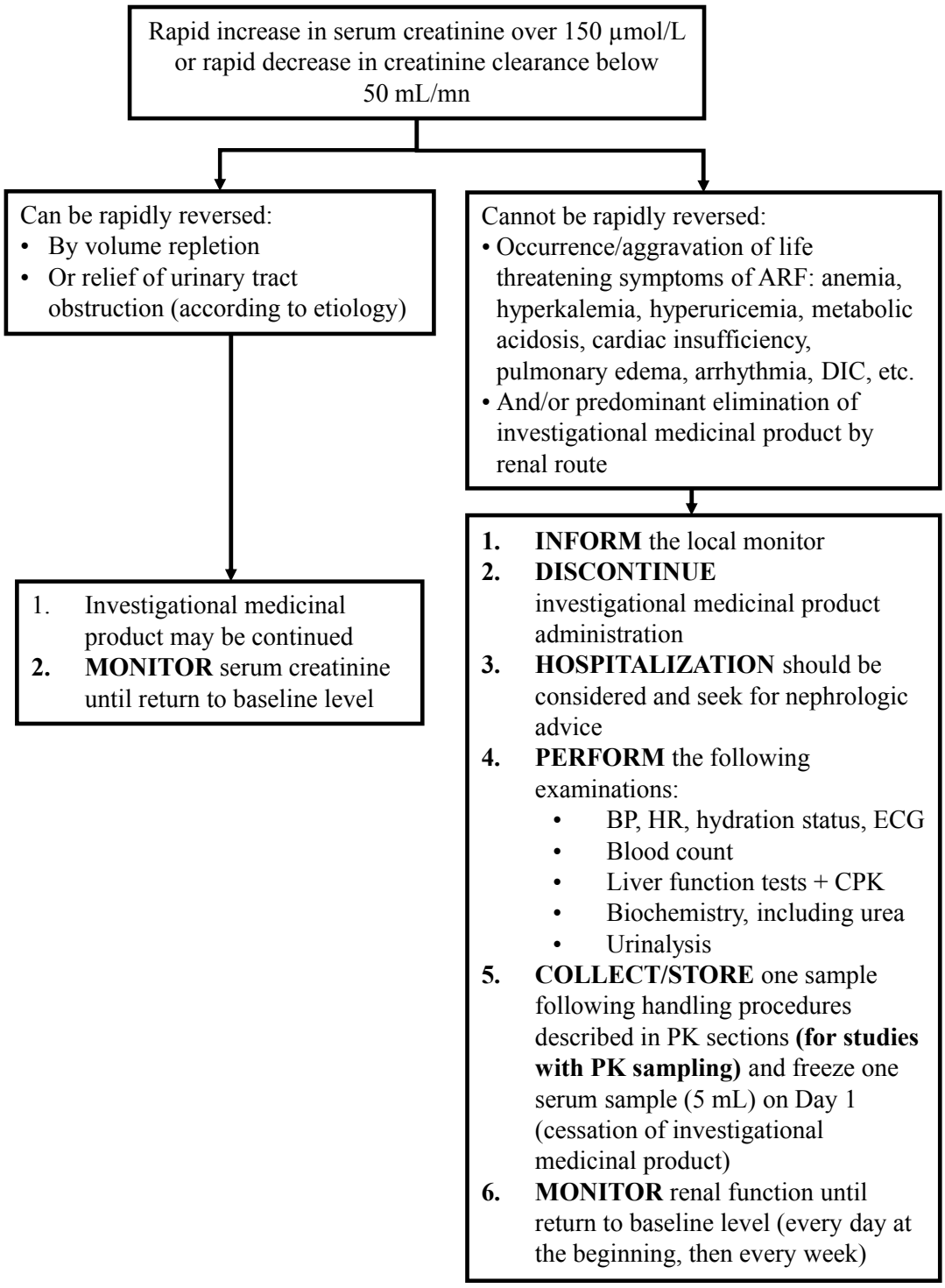


In ANY CASE, FOLLOW the instructions #1 to 7 listed in the box below.

1. **INVESTIGATE THE CLINICAL CONTEXT** in the previous 72 hours, specifically for malaise with or without loss of consciousness, dizziness, and/or hypotension and/or episode of arrhythmia; rule out muscular injury
2. **PERFORM** the following tests:
   - LFTs : AST, ALT, Alkaline Phosphatase, Total and Conjugated Bilirubin and Prothrombin Time / INR
   - CPK, serum creatinine, complete blood count
   - Anti-HAV IgM, anti-HBc IgM, anti-HCV and HCV RNA , anti-CMV IgM and anti-HEV IgM antibodies, and depending on the clinical context, check for recent infections, eg, EBV, Herpes viruses and toxoplasma
   - Hepatobiliary ultrasonography (can be completed by other imaging investigations if needed)
3. **CONSIDER** auto-antibodies: anti-nuclear, anti-DNA, anti-smooth muscle, anti-LKM
4. **CONSIDER** consultation with hepatologist
5. **CONSIDER** patient hospitalization if INR>2 (or PT<50%) and/or central nervous system disturbances suggesting hepatic encephalopathy
6. **MONITOR LFTs**
   - **If investigational medicinal product is continued: every 48 hours** until return to normal (<2ULN) or baseline. If ALT elevation persists beyond 2 weeks then perform LFTs every 2 weeks and 15 to 30 days after the last dose according to the study protocol.
   - **If investigational medicinal product is discontinued**: as closely as possible to every 48 hours until stabilization then every 2 weeks until return to normal (<2ULN) or baseline or for at least 3 months, whichever comes last.
7. **COLLECT/STORE** one sample following handling procedures described in PK sections **(for studies with PK sampling)** and freeze one serum sample (5 mL) on Day 1 (cessation of investigational medicinal product).

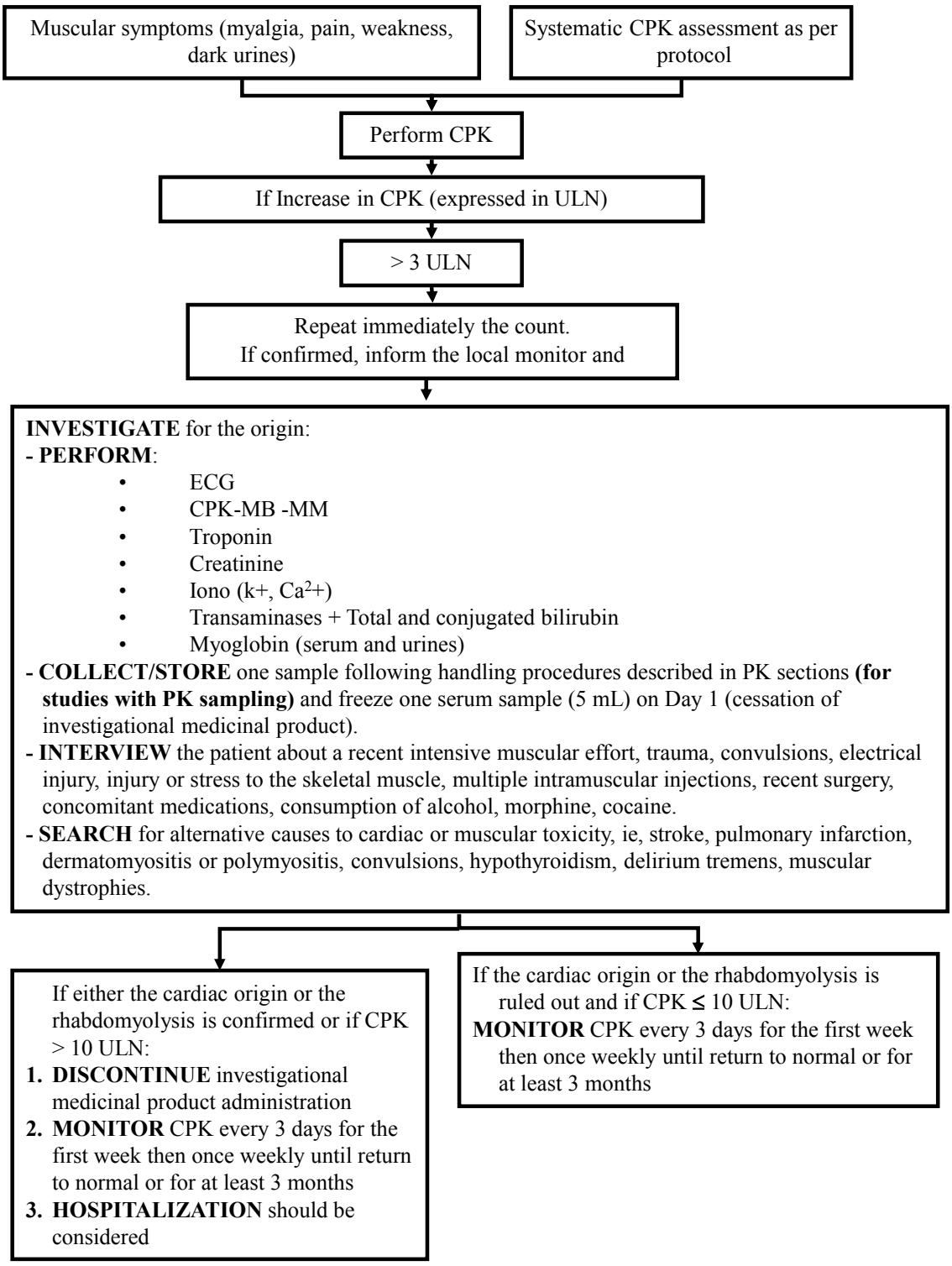
NOTE: ALT ≥3 ULN (IF BASELINE ALT < ULN) OR ALT ≥ 2 TIMES THE BASELINE VALUE (IF BASELINE ALT ≥ ULN) SHOULD BE NOTIFIED WITHIN 24 HOURS TO THE MONITORING TEAM (SEE Section 10.4.1.3, Section 10.4.5, AND Section 10.4.6). IN ADDITION, IF ALT <3 ULN MEETS A SERIOUSNESS CRITERION, THE EVENT SHOULD BE NOTIFIED WITHIN 24 HOURS TO THE MONITORING TEAM.

INCREASE IN SERUM CREATININE



Increase in serum creatinine is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Section 10.4.3 is met.

INCREASE IN CPK SUSPECTED TO BE OF NON-CARDIAC ORIGIN AND NOT RELATED TO INTENSIVE PHYSICAL ACTIVITY



Increase in CPK is to be recorded as an AE only if at least 1 of the criteria in the general guidelines for reporting AEs in Section 10.4.3 is met.

Appendix G. Summary of AE Reporting Instructions

Event category	Reporting timeframe	Specific events in this category	Case report form completion		
			AE form	Safety Complementary Form[a]	Other specific forms
Adverse event (non-SAE, non-AESI)	Routine	Any AE that is not SAE or AESI.	Yes	No	No
Serious adverse event (non-AESI or AESI)	Expedited (within 24 hours)	Any AE meeting seriousness criterion per Section 10.4.1.2.	Yes	Yes	No, unless applicable
Adverse event of special interest (AESI) (non-SAE)	Expedited (within 24 hours)	Pregnancy of female patient/subject (including male subject's partner) in Section 10.4.1.3.	Yes	Yes	Yes
		Symptomatic overdose with IMP.	Yes	Yes	No
		Increase in ALT as follows: ALT >3 x ULN (if baseline ALT < ULN), or ALT ≥2 times the baseline value (if baseline ALT ≥ ULN) Please refer to related flowchart per Appendix F.	Yes	Yes	Yes
		General allergic event regardless of the cause and requiring consultation with another physician as specified in Section 10.4.1.3.	Yes	No	Yes[b]
		Local Injections site reactions related to IMP and requiring consultation with another physician as specified in Section 10.4.1.3.	Yes	Yes	Yes[b]
		Neurocognitive events in Section 10.4.1.3.	Yes	Yes	Yes
		Neurologic events (requiring additional examinations/procedures and/or consultation with a specialist, as described in Section 10.4.1.3).	Yes	Yes	Yes
AE	Routine	Neurologic events without requiring consultation with another physician as per Section 10.4.1.3.	Yes	No	Yes[b]
		Allergic events without requiring consultation with another physician as per Section 10.4.1.3.	Yes	No	Yes[b]
		Local injection site reaction related to IMP without requiring consultation with another physician as per Section 10.4.1.4.	Yes	No	Yes[b]

Event	Reporting	Specific events in this category	Case report form completion		
Laboratory, vital sign, (non-SAE, non-AESI) that is: - Symptomatic - Requiring corrective treatment or consultation - Leading to IMP discontinuation or dose regimen modification	Routine	Neutropenia (per Appendix F).	Yes	No	No
		Thrombocytopenia (per Appendix F).	Yes	No	No
		Acute renal insufficiency (per Appendix F).	Yes	No	No
		Increase in CPK and suspicion of rhabdomyolysis (per Appendix F).	Yes	No	No
Death from any cause	Expedited		Yes	Yes	Yes

AE = adverse event; AESI = adverse event of special interest; ALT = alanine aminotransferase; CPK = creatine phosphokinase; IMP = investigational medicinal product; SAE = serious adverse event; ULN = upper limit of normal

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

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

Appendix H. Assessment of Local Injection Site Reactions

Local, Non-Allergic Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Very Severe (Grade 4)
Pain	Does not interfere with activity	Interferes with activity or repeated use of non-narcotic pain reliever	Prevents daily activity or repeated use of narcotic pain reliever	Emergency Room (ER) visit or hospitalization
Tenderness	Mild pain to touch	Pain with movement	Significant pain at rest	ER visit or hospitalization
Erythema/Redness[a]	2.5 – 5 cm	5.1 – 10 cm	>10 cm	Necrosis or exfoliative dermatitis
Swelling[b]	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)	ER visit or hospitalization
Other (Please specify)[c]	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.	ER visit or hospitalization

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

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

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

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

Appendix I. Country Specific Requirements

AMENDMENT FOR NORWAY AND ARGENTINA

For Norway and Argentina, in accordance with the guidelines of the clinical trials facilitation group (CTFG) and their specific requirements to do monthly pregnancy tests, urine pregnancy tests will be performed as follows:

- From visits 4 to 10, during clinical visits; and
- At home for all other time points' in-between visits. On a monthly basis, urine pregnancy tests should be performed if the patient is at home. A member of site staff will contact the patient via telephone to check on home pregnancy tests performed by the patient at the following time points:

  Weeks 8, 16, 20, 28, 32, 40, 44, and 52.

Sexual counseling should be provided to patients when indicated. In the event of a pregnancy test performed at home reported to be positive, please invite the patient to the clinic for an immediate repeat testing to confirm. For more guidance, see Appendix D .

Of note, in the protocol generic wording was already used to allow pregnancy tests to be performed more frequently in some countries due to local legislations related to women of childbearing potential randomized in clinical trials.

Appendix J. Protocol amendment history

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amended protocol 01 (20-Feb-2018)

The main reason for this amendment is the addition of the IRT contact to Visit 3 (the intermediate visit for injection training) of the screening period with clarifications made regarding this visit.

- Addition of the IRT contact to be performed during Visit 3 (intermediate visit).

In section(s): Tabulated clinical trial summary, Section 1.2, Section 7.1, and Section 10 of the protocol.

Overall Rationale for the Amendment

Injection training kits will be allocated via the IXRS system during the intermediate visit of the screening period for the purposes of injection training. Patients aged ≥12 years (or another designated person such as parent, etc) will be trained to self-inject/inject with placebo for alirocumab. Patients 8 to 11 years old will be assigned a parent or another designated person who will be trained during the injection training visit or an alternative arrangement. However, it was observed that this IRT/allocation of training kits was neither checked in the flowchart in Section 1.2 with an "X" in the "IRT contact" row (that corresponds with the Visit 3 column) nor described in Section 10 (study procedures). This amendment corrects this omission and clarifies the procedures that occur during this visit during the screening period. In addition, several inconsistencies, typographical errors, and other grammatical errors are corrected as well, with some made in the amended protocol only.

EFC14660 16.1.1 Amended Protocol 02

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	Clinical Approval	[redacted]
[redacted]	Clinical Approval	[redacted]