NCT03510884

AMENDED CLINICAL TRIAL PROTOCOL 03

COMPOUND: alirocumab/SAR236553/REGN727

A randomized, double-blind, placebo-controlled study followed by an open label treatment period to evaluate the efficacy and safety of alirocumab in children and adolescents with heterozygous familial hypercholesterolemia

STUDY NUMBER: EFC14643

VERSION DATE/STATUS: 06-Jan-2021/Approved

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NAMES AND ADDRESSES OF

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/Countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 03	All	06-Jan-2021, version 1 (electronic 3.0)
Amended Clinical Trial Protocol 02	All	02-Jan-2019, version 1 (electronic 2.0)
Amended Clinical Trial Protocol 01	All	13-Sep-2018, version 1 (electronic 1.0)
Original Protocol		21-Dec-2017, version 1 (electronic 3.0)

AMENDED PROTOCOL 03 (06-JAN-2021)

This amended protocol 03 is considered to be substantial 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.

OVERALL RATIONALE FOR THE AMENDMENT

The main reasons for this protocol amendment are the following:

- To enable changes in statistical analyses to reflect the sequential enrolment in the 2 cohorts of patients defined by the dosing regimen (see further details below), since enrolment in the every 4 weeks (Q4W) cohort started when enrolment in the every 2 weeks (Q2W) cohort was completed,
- To include the possibility to perform remote monitoring in the context of regional or national emergency such as the current COVID-19 pandemic, and
- To clarify the flexibility that the Interactive Response Technology (IRT) system allows during the open-label extension period with regard to the dose adjustment of alirocumab.

This protocol amendment replaces the 2 primary efficacy hypotheses comparing each alirocumab treatment regimen (Q2W, Q4W) versus a pooled placebo group combining Q2W and Q4W regimens by a comparison of each alirocumab group versus its contemporaneously randomized placebo group (ie, of the same dosing regimen cohort).

This change is driven by a potential temporal bias introduced from sequentially randomizing patients into the first dosing regimen cohort (Q2W), followed by the second dosing regimen cohort (Q4W). Two randomization schemes were produced for this study, with a distinct randomization scheme for each dosing regimen cohort. Therefore, patient background characteristics are expected to be equally distributed between treatment groups within a dosing regimen cohort by randomization process, but not necessarily between the 2 cohorts. Pooling placebo patients' data from both dosing regimen cohorts could introduce a potential temporal bias that would not be balanced by a similar bias in each of the alirocumab cohort groups.

Specifically, this protocol amendment plans that each alirocumab regimen group will be compared to the contemporaneously randomized placebo regimen group within each distinct cohort. This will align the primary efficacy hypothesis treatment comparisons with the randomization scheme for each distinct cohort.

As already defined in the amended protocol 2, the Bonferroni adjustment for multiplicity control will be applied to the primary efficacy endpoint to control the Type-I error, specifically, using a two-sided alpha level of 0.025 within each cohort treatment group comparison. Multiplicity testing of the key secondary endpoints will follow the amended protocol 2, specifically, the overall Type-I error will be controlled by the use of a sequential inferential approach applied independently within each dosing regimen cohort (Q2W and Q4W). Statistical significance of the primary parameter at the 0.025 alpha level is required before drawing inferential conclusions for that dosing regimen cohort about first key secondary parameter, and so on for the remaining key secondary parameters within the cohort (defined in Section 9.2.1).

The Bonferroni adjustment and this fixed hierarchical approach will ensure a strong control of the overall Type-I error rate for the study at the 0.05 level. The current study sample size is sufficient to provide power >90% for testing treatment effect of the primary efficacy endpoint within each cohort at a 2-sided 0.025 alpha level, taking into consideration the reduced sample size of the placebo group.

With respect to safety, in an effort to reduce the temporal bias impact, the present protocol amendment will align the safety result summaries with the already executed randomization scheme within each regimen cohort, showing each alirocumab regimen group with the corresponding placebo regimen group. Additionally, a standard data pooling strategy follows, combining study treatment groups (alirocumab, placebo) regardless of regimen cohort. Pooling safety assessments across the cohorts aims at increasing the chance to identify a safety signal.

Protocol amendment summary of changes table

Section # and name	Description of change	Brief rationale
Clinical Trial Summary - Study Design, And Section 8.1 Investigational Medicinal Product(s)	Update to clarify that the IRT system offers flexibility for dose adjustment of alirocumab in the open-label treatment period based on body weight (BW) change (from Week 24 onwards), low density lipoprotein cholesterol (LDL-C) levels (from Week 32).	The Investigator is able to adjust the dose of alirocumab, for increasing the efficacy or the purpose of patient safety.
Clinical Trial Summary - Statistical Considerations, And Section 11.1 Determination of Sample Size	Revision of the 2 main comparisons: in each dosing regimen cohort, the alirocumab dosing regimen group will be compared to its contemporaneously randomized placebo group (ie, of the same dosing regimen cohort). Study power has been updated accordingly.	Revisions in order to specify analyzing each of the two randomized dosing regimen cohorts separately (use of the contemporaneously randomized placebo group for each dosing regimen cohort (Q2W, Q4W) instead of a combined placebo group) (refer to the rationale above).

Section # and name	Description of change	Brief rationale
Clinical Trial Summary - Statistical Consideration, And Section 11.4.2 Analyses of efficacy endpoints	Revision of the comparisons and of the statistical models (a separate model will be run for each dosing regimen cohort)	Revisions in order to specify analyzing each of the two randomized dosing regimen cohorts separately (use of the contemporaneously randomized placebo group for each dosing regimen cohort (Q2W, Q4W) instead of a combined placebo group) (refer to the rationale above).
	To be consistent with the significance level that will be used for tests (2.5% two-sided), 97.5% CI will be computed instead of 95% CI.	Since two-sided test with a significance level of 2.5% will be performed, 97.5% CI will be computed instead of 95% CI for primary and secondary efficacy endpoints.
Clinical Trial Summary - Statistical Consideration, And Section 11.4.3 Analyses of safety data	Revision of the treatment groups to be displayed in safety result summaries: by treatment groups within each dosing regimen cohort; and by treatment group regardless of the dosing regimen cohorts (pooled across cohorts).	Comparing alirocumab and placebo within dosing regimen cohort might reduce the impact of temporal bias. Pooling safety assessments across the cohorts aims at increasing the chance to identify a safety signal.
Section 6.3 Two-Step analysis	Details added to clarify the two-step analysis process at the completion of the double-blind treatment period and the whole study, respectively.	To define and clarity the two-step analysis
Section 10.2 Definition of Source Data	Updated IRT listings	Clarity
Section 10.4.4 Instructions for reporting serious adverse events	Change the description of process for the management of complementary source documents	As per new process, PI or any designees should no longer proactively send source documentations
Section 11.4.2.3 Multiplicity consider	Update added for clarity	Clarity
Section 11.4.3 Analyses of safety data	Addition of the definition of the treatment period for the Q4W dosing regimen cohort	Information omitted by error in the previous version
Section 11.4.4 Other endpoints	Revision of the treatment groups to be displayed in accordance with safety summaries	Comparing alirocumab and placebo within dosing regimen cohort might reduce the impact of temporal bias. Pooling safety assessments across the cohorts aims at increasing the chance to identify a safety signal.
Section 11.5 Two-Step analysis	Update and reference to Section 6.3 added for clarity	Clarity

Section # and name	Description of change	Brief rationale
Section 13.2 Responsibilities of the Sponsor	Addition of the following text: "Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents".	To include the possibility to perform remote monitoring in the context of regional or national emergency such as the current COVID-19 pandemic
Appendix E Flow mediated dilatation exploratory sub-study of EFC14643 protocol	Addition of the dosing regimen cohort and the treatment-by-dosing regimen cohort effects in the statistical model	Information omitted by error in the previous version
	The use of the multiple imputations process is removed.	Due to the very exploratory nature of the flow mediated dilatation (FMD) sub-study, the multiple imputations process will not be applied
Appendix K Contingency Measures for regional or national emergency that is declared by a governmental agency	Addition of contingency measures for a regional or national emergency that can be declared by a governmental agency such as the current COVID-19 pandemic.	To ensure the safety of the participants, to consider continuity of the clinical study conduct, protect trial integrity, and assist in maintaining compliance with Good Clinical Practice in Conduct of Clinical Trials Guidance during an emergency that prevents access to the study site.
Other Changes	Minor grammatical and editorial revisions throughout protocol. Addition of word “cohort” at relevant places throughout protocol. Appendix numbers updated	Editorial and for clarity

CLINICAL TRIAL SUMMARY

COMPOUND: alirocumab/SAR236553/REGN727 STUDY No.: EFC14643

TITLE	A randomized, double-blind, placebo-controlled study followed by an open label treatment period to evaluate the efficacy and safety of alirocumab in children and adolescents with heterozygous familial hypercholesterolemia
INVESTIGATOR/TRIAL LOCATION	Worldwide
PHASE OF DEVELOPMENT	Phase 3
STUDY OBJECTIVE(S)	**Primary objective:** • To evaluate the efficacy of alirocumab administered every 2 weeks (Q2W) and every 4 weeks (Q4W) versus placebo after 24 weeks of double-blind (DB) treatment on low-density lipoprotein cholesterol (LDL-C) levels in patients with heterozygous familial hypercholesterolemia (heFH) 8 to 17 years of age on optimal stable daily dose of statin therapy ± other lipid modifying therapies (LMTs) or a stable dose of non-statin LMTs in case of intolerance to statins. **Secondary objectives:** • To evaluate the efficacy of alirocumab versus placebo on LDL-C levels after 12 weeks of DB treatment. • To evaluate the effects of alirocumab versus placebo 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 [TGs], Apolipoprotein A-1[Apo A-1] levels) after 12 and 24 weeks of treatment. • To evaluate the safety and tolerability of alirocumab after 24 weeks of treatment in comparison with placebo. • To evaluate the efficacy, safety and tolerability of alirocumab after 80 weeks of open label treatment. • To evaluate the development of anti-alirocumab antibodies after 24 weeks of treatment during the double-blind (DB) treatment period. **Other objectives:** • To evaluate the development of anti-alirocumab antibodies after 80 weeks of open label treatment. • To evaluate the pharmacokinetics (PK) of alirocumab.

STUDY DESIGN	This study is a randomized, 24-week DB, placebo-controlled, parallel-group, multi-national, multi-center study followed by an open label treatment period of 80 weeks. Approximately 150 children and adolescents aged of 8 to 17 years with heFH and LDL-C ≥130 mg/dL (3.37 mmol/L) at screening visit despite stable LMTs will be randomized 2:1 (alirocumab:placebo). Two dosing regimen, Q2W and Q4W, will be evaluated with approximately 75 patients in each dosing regimen cohort. The start of the recruitment in the Q4W dosing regimen cohort will depend on the status of the recruitment in the Q2W dosing regimen cohort and the status of the amendment approval. 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. The optimal dose of statin is defined as the dose prescribed based on regional practice or local guidelines 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 randomization 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. Statin intolerant patient is defined as one with the 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 regimen of a statin (eg, 1 to 3 times weekly) are also considered as not able to tolerate a daily dose. Randomization will be stratified according to previous participation (yes or no) in the Phase 2 DFI14223 study and baseline body weight (<50 or ≥50 kg). The study consists of a run-in period (as needed), screening period, double-blind treatment period, and an open label treatment period. **Run-in period (as needed):** The run-in period is 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. Another possible situation requiring the run-in period include patients with suspected heFH but without confirmation by previous genetic testing and not meeting Simon Broome criteria. Such patients will be asked to undergo centralized genetic testing during the run-in period. **Screening period:** The screening period is up to 2 weeks (+5 days) in duration. Patients who have previously participated in the DFI14223 study and have received alirocumab administration during the open label extension of the DFI14223 study will require a wash-out period of at least 10 weeks between the last injection of alirocumab and the screening lipid

	assessment at the entry of the screening period. However, as these patients have already met this LDL-C requirement when they screened for the DFI14223 study they will not be excluded based on the LDL-C value obtained during the screening for the EFC14643 study. An intermediate visit for injection training may occur during which the patient if aged 12 years and above (or another designated person such as parent, etc) will be trained to self-inject/inject with placebo for alirocumab after the eligibility criteria have been checked and it is confirmed that the patient will likely be randomized. Prior to the injection(s), a local topical anesthetic may be utilized as per the Investigator recommendation. Investigators will have the option of providing a second placebo kit for alirocumab for patients/parents who require additional injection training prior to randomization. Patients can be randomized after injection training and as soon as all inclusion and no exclusion criteria are met.
	Double-blind treatment period: The double-blind treatment period is 24 weeks in duration. Two dosing regimens will be evaluated - either Q2W or Q4W; the start of the recruitment in the Q4W dosing regimen cohort will depend on the status of the recruitment in the Q2W dosing regimen cohort and the status of the amendment approval. Patients will be blinded to study treatment and randomized to either alirocumab or placebo using a 2:1 ratio for each dosing regimen cohort. <u>Q2W dosing regimen cohort:</u> Approximately 75 patients will participate in the Q2W dosing regimen cohort. Patients with BW <50 kg will receive 1 subcutaneous (SC) injection of 0.5 mL Q2W of alirocumab or placebo. Patients with BW ≥50 kg will receive 1 SC injection of 1 mL Q2W of alirocumab or placebo. For patients randomized to receive alirocumab the following dose based on body weight (BW) will be initially administered: • 40 mg for BW <50 kg or, • 75 mg for BW ≥50 kg. At Week 12 patients randomized to alirocumab will either: • Continue alirocumab 40 mg or 75 mg Q2W, if the Week 8 LDL-C* is <110 mg/dL (2.85 mmol/L) OR • Dose up-titrate to alirocumab 75 mg (for patients on 40 mg) or 150 mg (for patients on 75 mg) if the Week 8 LDL-C* is ≥110 mg/dL (2.85 mmol/L). <u>Q4W dosing regimen cohort:</u> Approximately 75 patients will participate in the Q4W dosing regimen cohort. During the first 12 weeks of the double-blind period and before any possible dose-adjustment to Q2W dosing regimen, all patients will receive SC injection(s) Q4W to get a proper evaluation of this dosing regimen. After Week 12, with regard to the possible dose-adjustment and the maintenance of the blind until the end of the double-blind period, all patients will receive SC injection(s) Q2W. Patients receiving alirocumab will be under a “sham Q2W*” regimen from Week 12 to Week 24, with alirocumab Q4W alternating with placebo Q4W. For patients randomized to alirocumab the following dose based on body weight (BW) will be initially administered:

	• 150 mg Q4W for BW <50 kg or, • 300 mg Q4W for BW ≥50 kg. At Week 12 patients randomized to alirocumab will either: • Continue alirocumab 150 mg or 300 mg Q4W, if the Week 8 LDL-C is <110 mg/dL (2.85 mmol/L) OR • Have a dose-adjustment to 75 mg Q2W (for patients on 150 mg Q4W) or 150 mg Q2W (for patients on 300mg Q4W) if the Week 8 LDL-C is ≥110 mg/dL (2.85 mmol/L). *Lipid values obtained at Week 8 for the purpose of up-titration will not be communicated to Investigators to maintain the blind. The continuation or dose up-titration/dose-adjustment of alirocumab will occur in an automated process without site or patient awareness. The first IMP injection (from the double-blind study treatment kit allocated by interactive response technology [IRT]) will be done at the site on the day of randomization or as close as possible after randomization into the study. Patients will be monitored at the investigational site for at least 30 minutes after this first double-blind injection. The subsequent injections will be done at a patient-preferred location (eg, at home). All the IMP injections can be performed by trained patient (self-injection if aged ≥12) or parent, or another designated person or alternative arrangements for injection administration will be allowed as needed (eg, return to the clinic). 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. Injection training: • Further injection training can be provided at the randomization visit Week 0/Day 1 when the patient/parent or a trained designated person injects the first IMP from the double-blind study treatment kit allocated by IRT. • Additional training can be offered at scheduled or unscheduled visits with the scheduled double-blind treatment, as per patient/parent or Investigator's judgment. The laboratory measurement of lipid parameters will be performed by a central lab. The specific results of the central lab testing for lipid parameters from samples obtained after randomization and during the double-blind treatment period will not be communicated to the sites or to the Sponsor's EFC14643 study team. Instead, the central lab will inform sites if patients exceed the triglyceride threshold of 500 mg/dL (5.65 mmol/L). Additionally, the site may receive alert related to LDL-C <50 mg/dL (1.30 mmol/L) and associated safety concerns identified by the independent physician who will carefully monitor, under the auspices of the Data Monitoring Committee (DMC), the patient's LDL-C values during the double-blind treatment period. No local lab testing for lipid parameters should be performed after randomization and throughout the

	study. Of note, the independent physician is external to the EFC14643 study team and not part of any alirocumab activities. Statin and other LMT (if applicable) should be stable during double-blind treatment period barring exceptional circumstances whereby overriding concerns (including but not limited to triglyceride alert posted by the central lab) warrant such changes, as per the Investigator's judgment. Patients will be instructed to follow a diet to treat their hypercholesterolemia in accordance with local guidelines or local practice and they should be on this diet throughout the entire study duration from screening. Patients, who successfully complete the 24-week double-blind treatment period can enter the open label treatment period. A flow mediated dilatation (FMD) exploratory sub-study that will assess endothelial function in the brachial artery will be conducted in a sub-set of the study population during the double-blind treatment period. The details are provided in Appendix E. **Open label treatment period:** The open label treatment period consists of 80 weeks of open label alirocumab SC Q2W or Q4W depending on the dosing regimen initiated at randomization. The first open label alirocumab injection(s) will be done at the site followed by monitoring of the patient for at least 30 minutes. At the first open label treatment period visit (ie, Week 24), after completion of the double-blind treatment period, depending on the dosing regimen cohort participation, both alirocumab and placebo treated patients will receive alirocumab either 40 mg Q2W or 150 mg Q4W if BW is <50 kg, and 75 mg Q2W or 300 mg Q4W if body weight is ≥50 kg, from the weight obtained at the Week 24 visit. After Week 24, the Investigator will manage, based on his/her own judgment, adjustment of alirocumab dose based on changes in BW. However, related to this up-titration/adjustment of the dose, if the Investigator considers that the up-titration/adjustment would potentially negatively impact patient safety, he/she can exercise his/her judgement in a manner that safeguards the safety and wellbeing of the patient. The following will be applied based on changes in BW: • If currently on 40 mg Q2W then adjust dose to 75 mg Q2W if BW changes from <50 kg to ≥50 kg. • If currently on 150 mg Q4W then adjust dose to 300 mg Q4W if BW changes from <50 kg to ≥50 kg. For patients whose weight oscillates around 50 kg the dose will be adjusted only once during the open-label treatment period. The lipid levels will be communicated to the Investigator during the open label treatment period from the second visit (ie, Week 32) onwards. The IRT system is set up to allow the Investigator based on his/her own judgment related to the patient's LDL-C levels and the safety profile, to up-titrate, down-titrate, maintain the dose of alirocumab or discontinue alirocumab throughout the study. From Week 32 onwards: Q2W dosing regimen cohort: The following up-titration or down-titration of alirocumab doses will be possible:

	Up-titration: • 40 mg to 75 mg Q2W if BW <50 kg. • 75 mg to 150 mg Q2W if BW ≥50 kg. Down-titration: • 75 mg to 40 mg Q2W if BW <50 kg. • 150 mg to 75 mg Q2W if BW ≥50 kg. Q4W dosing regimen cohort: Dose-adjustment will be possible, as follows: • 150 mg Q4W to 75 mg Q2W if BW <50 kg. • 300 mg Q4W to 150 mg Q2W if BW ≥50 kg. The statin dose should not be decreased to adjust to the degree of LDL-C lowering and should not be increased unless otherwise indicated. Other LMT (if applicable) can be modified based on the Investigator's judgment throughout the study. Further recommendations for the management and monitoring of patients who achieve LDL-C levels <50 mg/dL (1.30 mmol/L) on one or more occasion are provided in Section 10.6.2.3.
STUDY POPULATION **Main selection criteria:**	**Inclusion criteria:** 1. Male and female children and adolescents aged 8 to 17 years diagnosed with heterozygous familial hypercholesterolemia * inadequately controlled (see threshold mentioned in the exclusion criterion 2) ** 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 *****. 2. A signed informed consent indicating parental permission with or without patient assent, depending on capacity for understanding based on developmental maturity and local requirements. 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. * *Diagnosis of heFH must be made either by previous genotyping, current centralized genotyping, or by clinical criteria according to Simon Broome criteria. Previous genotyping refers to documented results that are available from prior genotyping testing supporting a diagnosis of heFH. Current centralized genotyping refers to patients electing to undergo genotyping during the run-in period with results supporting a diagnosis of heFH. The clinical diagnosis should be based on the Simon Broome criteria for possible or definite heFH (see Appendix A). Once eligibility is confirmed based on prior genetic testing or Simon Broome criteria, results of elective genetic testing will not impact patient's eligibility.* ** *Patients who have previously participated in the DFI14223 study have already met this LDL-C requirement when they screened for the DFI14223 study and thus will not be excluded based on LDL-C <130 mg/dL (3.37 mmol/L).* *** *The optimal dose of statin is defined as the stable daily dose prescribed based on regional practice or local guidelines or is the*

	stable daily dose that is maximally tolerated due to adverse effects on higher doses. For patients not receiving the maximally tolerated dose of statin, statin intensification should be carefully considered prior to randomization 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. **** *Statin intolerant patient is defined as the 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 regimen of a statin (eg, 1 to 3 times weekly) are also considered as not able to tolerate a daily dose.* ***** *Before enrolling more than 2 siblings, the Investigator should discuss with the Sponsor study team.* **Key Exclusion criteria (additional details are in Section 7.2):** 1. 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 of 8 to less than 10 years who have not had previous attempts to lower LDL-C by other means will be excluded.* 2. Patients with LDL-C <130 mg/dL (3.37 mmol/L) (ie, adequately controlled) obtained during the screening period after the patient has been on stable 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. *Note: Patients who have previously participated in the DFI14223 study have already met this LDL-C requirement when they screened for the DFI14223 study and thus will not be excluded based on LDL-C <130 mg/dL (3.37 mmol/L).* 3. Patients with BW less than 25 kg. 4. Patients aged of 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. 5. Patients with secondary hyperlipidemia (such as decompensated hypothyroidism, nephrotic syndrome, obstructive liver disease, anorexia nervosa, obesity, and drug treatment [eg, isotretinoids]). 6. Patients diagnosed with homozygous familial hypercholesterolemia. 7. Patients who have received lipid apheresis treatment within 2 months prior to the screening period, or have plans to receive it during the study. 8. Patients with uncontrolled (ie, HbA_{1c} levels above local guidelines or equivalent) Type 1 or 2 diabetes mellitus.

	9. Patients with known uncontrolled thyroid disease (ie, thyroid stimulating hormone levels above or below the laboratory's reference range within the past 6 months that were obtained due to clinical indication). 10. Patients with uncontrolled (ie, systolic blood pressure [SBP] or diastolic blood pressure [DBP] above local guidelines or equivalent) hypertension. 11. Fasting triglycerides >350 mg/dL (3.95 mmol/L) at the screening visit. 12. Severe renal impairment (ie, estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2) at the screening visit. 13. Alanine aminotransferase [ALT] or aspartate aminotransferase [AST] >2 x upper limit of normal [ULN] (1 repeat lab is allowed). 14. Creatine phosphokinase (CPK) >3 x ULN (1 repeat lab is allowed).
Total expected number of patients:	Approximately 150 patients (approximately 75 patients in each dosing regimen cohort)
Expected number of sites:	Approximately 70 sites
STUDY TREATMENT(s)	
Investigational medicinal product(s)	alirocumab and placebo for alirocumab
Formulation:	Prefilled syringes (PFS) with finger grip, to be replaced by PFS with safety system (PFS-S) as soon as available: alirocumab 75 mg/mL or 150 mg/mL solution will be used as described below. **Q2W dosing regimen cohort:** • BW <50 kg: - 0.5 mL of alirocumab 75 mg/mL solution for 40 mg dose. - 0.5 mL of alirocumab 150 mg/mL solution for 75 mg dose. • BW ≥50 kg: - 1 mL of alirocumab 75 mg/mL solution for 75 mg dose. - 1 mL of alirocumab 150 mg/mL solution for 150 mg dose. Matching placebo - Placebo of 0.5 mL volume for BW <50 kg. - Placebo of 1 mL volume for BW ≥50 kg. **Q4W dosing regimen cohort:** - 1 mL of alirocumab 150 mg/mL solution for 150 mg dose. Matching placebo - Placebo of 1 mL volume regardless of BW category.
Route(s) of administration:	Subcutaneous (SC) injections in the abdomen, thigh or outer area of upper arm.

Dose regimen:	**Q2W dosing regimen cohort:** • Alirocumab 40 mg for BW <50 kg: - During the entire double-blind period if no up-titration needed: 1 SC injection of 0.5 mL Q2W for 40 mg. - In case of up-titration to 75 mg at Week 12 (LDL-C ≥110 mg/dL [2.85 mmol/L] at Week 8): 1 SC injection of 0.5 mL Q2W for 75 mg. • Alirocumab 75 mg for BW ≥50 kg: - During the entire double-blind period if no up-titration needed: 1 SC injection of 1 mL Q2W for 75 mg. • In case of up-titration to 150 mg at Week 12 (LDL-C ≥110 mg/dL [2.85 mmol/L] at Week 8): 1 SC injection of 1 mL Q2W for 150 mg. **Q4W dosing regimen cohort:** • Alirocumab 150 mg for BW <50 kg: - During the first 12 weeks of double-blind period: 1 SC injection of 1 mL Q4W for 150 mg. - After Week 12: 1 SC injection of 1 mL Q2W, consisting of 1 injection of 150 mg Q4W alternating with 1 injection of placebo Q4W. • Alirocumab 300 mg for BW ≥50 kg: - During the first 12 weeks of double-blind period: 2 SC injections of 1 mL each Q4W, consisting of 2 injections of 150 mg. - After Week 12: 2 SC injections of 1 mL each Q2W, consisting of 2 injections of 150 mg Q4W alternating with 2 injections of placebo Q4W. *In case of dose-adjustment at Week 12 (LDL-C ≥110 mg/dL [2.85 mmol/L] at Week 8):* - Alirocumab 75 mg Q2W: 1 SC injection of 1 mL Q2W, consisting of 1 injection of 75 mg for BW <50 kg. - Alirocumab 150 mg Q2W: 2 SC injections of 1 mL each Q2W, consisting of 1 injection of 150 mg and 1 injection of placebo for BW ≥50 kg.
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 because the medication is a potential background therapy: • 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 from baseline to Week 24 in the intent-to-treat (ITT) population, using all LDL-C values regardless of adherence to treatment (ITT estimand). **Key secondary efficacy endpoints:** • Percent change in LDL-C from baseline to Week 12 (ITT estimand). • Percent change in Apo B from baseline to Week 24 (ITT estimand). • Percent change in non-HDL-C from baseline to Week 24 (ITT estimand). • Percent change in Total-C from baseline to Week 24 (ITT estimand). • Percent change in Apo B from baseline to Week 12 (ITT estimand). • Percent change in non-HDL-C from baseline to Week 12 (ITT estimand). • Percent change in Total-C from baseline to Week 12 (ITT estimand). • Proportion of patients achieving a LDL-C level lower than 130 mg/dL (3.37 mmol/L) at Week 24 (ITT estimand). • Proportion of patients achieving a LDL-C level lower than 130 mg/dL (3.37 mmol/L) at Week 12 (ITT estimand). • Proportion of patients achieving a LDL-C level lower than 110 mg/dL (2.84 mmol/L) at Week 24 (ITT estimand). • Proportion of patients achieving a LDL-C level lower than 110 mg/dL (2.84 mmol/L) at Week 12 (ITT estimand). • Percent change in Lp (a) from baseline to Week 24 (ITT estimand). • Percent change in Lp (a) from baseline to Week 12 (ITT estimand). • Percent change in HDL-C from baseline to Week 24 (ITT estimand). • Percent change in fasting TG from baseline to Week 24 (ITT estimand). • Percent change in Apo A-1 from baseline to Week 24 (ITT estimand). • Percent change in HDL-C from baseline to Week 12 (ITT estimand). • Percent change in fasting TG from baseline to Week 12 (ITT estimand). • Percent change in Apo A-1 from baseline to Week 12 (ITT estimand). **Safety endpoints:** • Safety parameters: adverse events (AE), serious AE (SAE), AE of special interest ([AESI], see list in Section 10.4.1.3),

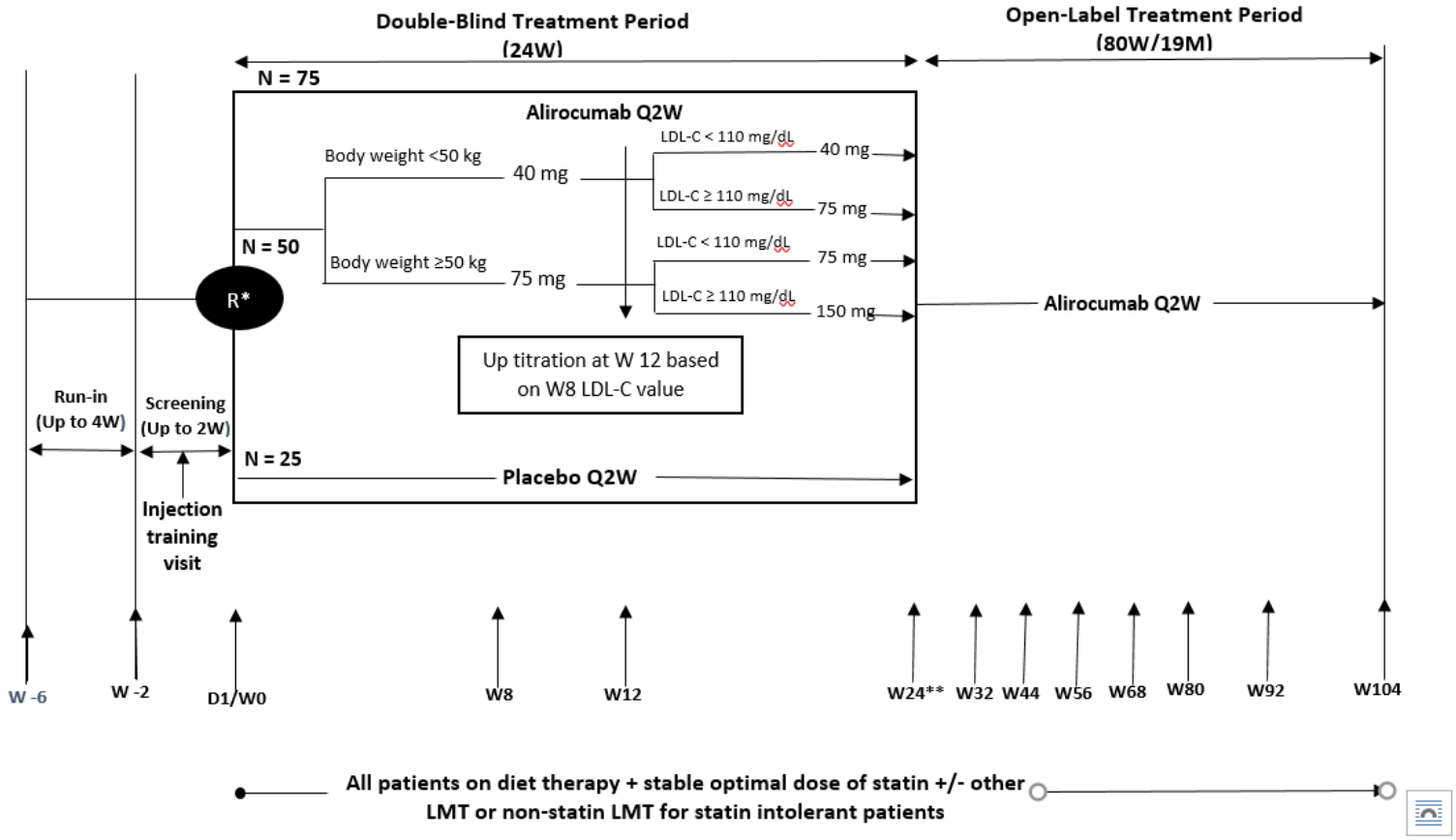
	laboratory data, vital signs, body weight, height, Cogstate battery test, and Tanner stage assessed throughout the study. **Other secondary efficacy endpoints:** • All primary and key secondary endpoints in the modified ITT (mITT) population, using all LDL-C values during the treatment period (on-treatment estimand). • Absolute change in Apo B/Apo A-1 ratio to Week 12 and Week 24 (ITT and on-treatment estimands). • Proportion of patients achieving at least 30% reduction, 50% reduction in LDL-C at Week 24 (ITT and on-treatment estimands). • Proportion of patients achieving at least 30% reduction, 50% reduction in LDL-C at Week 12 (ITT and on-treatment estimands). • Percent change in LDL-C from baseline to Week 104 (ITT and on-treatment estimands). **Other endpoints** • Serum alirocumab concentrations assessed throughout the study. • Anti-alirocumab antibodies assessed throughout the study.
ASSESSMENT SCHEDULE	Run-in period (as needed): The run-in period is up to 4 weeks (+2 days), with 1 visit. Patients can enter the screening period as soon as the criteria for stable LMT are met and/or centralized genotyping data (if no clinical criteria or previous genotyping) is available. Screening period: The screening period is up to 2 weeks (+5 days) in duration. An intermediate/Day 1 visit for injection training may occur during which the patient, if aged ≥12 (or another designated person such as parent, etc) will be trained to self-inject/inject with placebo. Patients can be randomized after injection training and as soon as eligibility is confirmed. Double-blind treatment period: The double-blind treatment period is 24 weeks in duration. Visits will be scheduled as follows: randomization visit (Day 1, Week 0), Week 8, Week 12 and Week 24 (end of the double-blind treatment period visit). Open label treatment period: The first open label treatment period visit will overlap with the end of double-blind treatment period visit. The second visit will take place at Week 32. Subsequent visits will be every 12 weeks until the end of the open label treatment period (ie, Week 44, Week 56, Week 68, Week 80, Week 92 and Week 104 [end of open label treatment period visit]).
STATISTICAL CONSIDERATIONS	**Sample size determination:** With a randomization ratio of 2:1 (alirocumab: placebo) for each dosing regimen cohort, a total sample size of 90 patients (30 in each alirocumab dosing regimen group and 15 in each placebo dosing regimen group) will have 92% power to detect a difference in mean percent change in LDL-C of 30% between each alirocumab dosing regimen group and its contemporaneously randomized placebo dosing regimen group, with a

	0.025 two-sided significance level per comparison and assuming a common standard deviation (SD) of 25%. Nevertheless, in order to have a sufficient number of pediatric patients for properly assessing the safety and tolerability of alirocumab, sample size was increased to 150 patients in total (50 in each alirocumab dosing regimen group and 25 in each placebo dosing regimen group). The enrollment of 150 patients will allow having a safety assessment over 2 years in approximately 128 patients, assuming a discontinuation rate of 15%. **Analysis population:** The primary efficacy analysis population will be the ITT population, defined as all randomized patients. Patients in the ITT population will be analyzed according to the treatment group allocated by randomization. Analyses will compare each alirocumab dosing regimen group to its contemporaneously randomized placebo group. The safety analysis will be performed on the safety population. The safety population consists of the randomized population who did actually receive at least one dose or partial dose of investigational product analyzed according to the treatment actually received. Safety analyses will present each alirocumab dosing regimen group with its contemporaneously randomized placebo dosing regimen group and again each treatment group (placebo, alirocumab) regardless of the dosing regimen cohorts (pooled across the cohorts). **Primary analysis:** The percent change in LDL-C from baseline to Week 24 will be analyzed in the ITT population using a mixed-effect model with repeated measures (MMRM) approach. All post-baseline data available within Week 8 to Week 24 analysis windows will be used and missing data will be accounted for by the MMRM model. A separate model will be run for each dosing regimen cohort, including the fixed categorical effects of treatment group (alirocumab, placebo), randomization strata, time point (Week 8, Week 12, Week 24), treatment-by-time point interaction and strata-by-time point interaction, as well as the continuous fixed covariates of baseline LDL-C value and baseline value-by-time point interaction. Throughout the MMRM models, each alirocumab dosing regimen group will be compared to its contemporaneously randomized placebo dosing regimen group using appropriate contrasts, and the 97.5% confidence interval (CI) of the difference will be provided. **Analysis of secondary endpoints:** Continuous secondary endpoints with normal distribution will be analyzed within each dosing regimen cohort using the same MMRM models as for the primary endpoint with the corresponding baseline and post-baseline values. Analyses of the efficacy parameters during the extension period will be only descriptive (description of change [% or absolute] over time). **Safety analysis:** Safety analyses will be descriptive based on the safety population.

DURATION OF STUDY PERIOD (per patient)	A study duration of up to 110 weeks (run-in period [if needed]: up to 4 weeks [+2 days], screening period: up to 2 weeks [+5 days], double-blind treatment period: 24 weeks, open label treatment period: 80 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 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

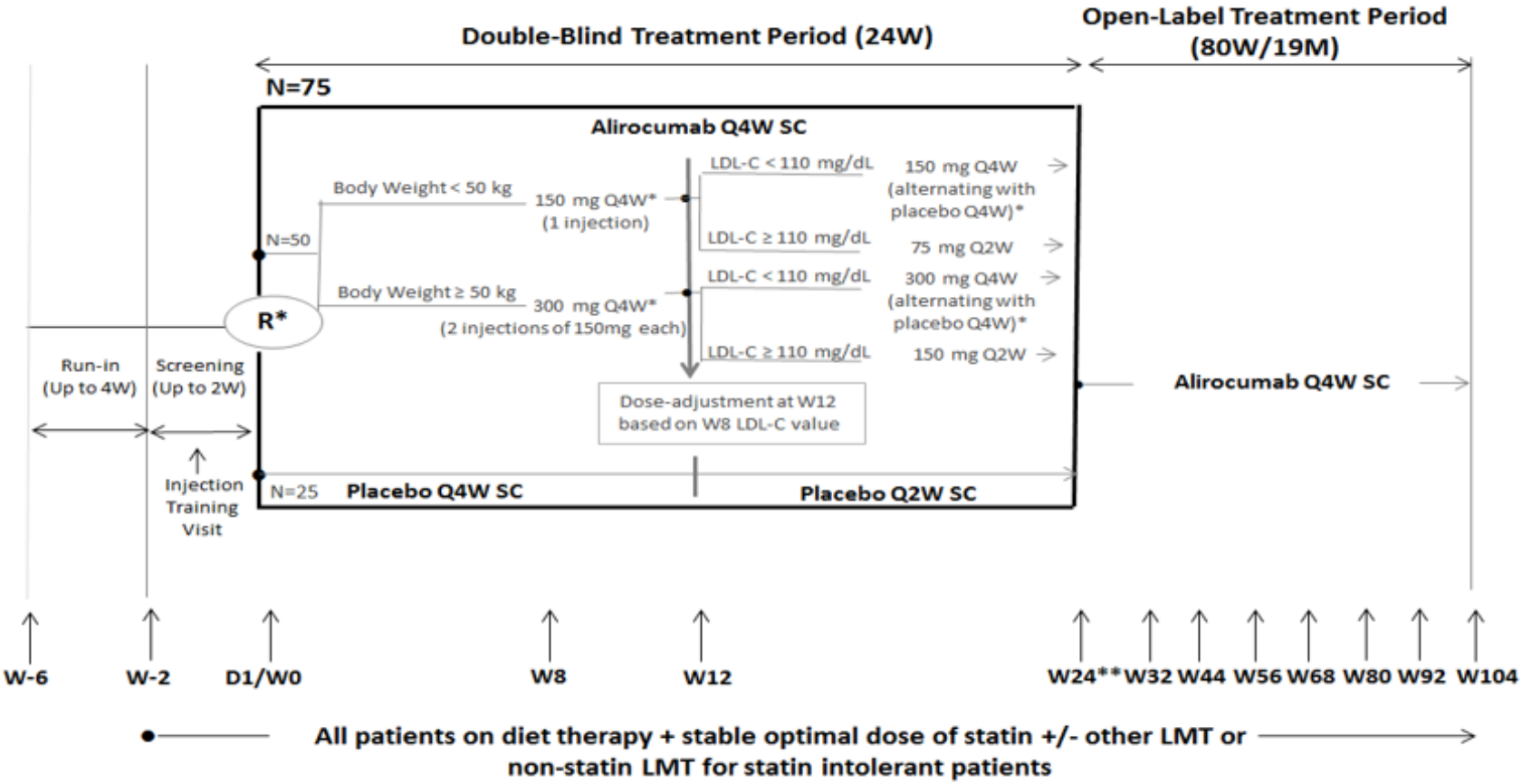
1.1 GRAPHICAL STUDY DESIGN - Q2W DOSING REGIMEN COHORT



*Randomization will be stratified according to previous participation (yes or no) to the phase 2 DFI14223 study and baseline body weight (<50 or ≥50 kg)

**Primary efficacy endpoint at Week 24

1.2 GRAPHICAL STUDY DESIGN - Q4W DOSING REGIMEN COHORT



- First 12 weeks: administration Q4W. From W12 to W24, patients continuing alirocumab Q4W (w/o dose-adjustment) will be under a "fake Q2W*" regimen, with alirocumab Q4W alternating with placebo Q4W.

** Primary endpoint at W24.

1.3 STUDY FLOW CHART

	Run-in (if needed)[a]	Screening		Double- Blind Treatment Period				Open label Treatment Period							
VISIT	1	2	3	4	5	6	7	7	8	9	10[gg]	11	12[gg]	13	14
Week	Up to W-6	Up to W-2	Up to W-1[b]	W0/D1	W8	W12	W24[c]	W24	W32	W44	W56	W68	W80	W92	W104[d]
Visit Window (+/- days)	+2	+5	+/-7		+/-7	+/-7	+/-3	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7
Informed consent	X[e]														
heFH genotyping informed consent (if needed)[e, f]	X														
Inclusion criteria	X	X		X											
Exclusion criteria	X	X		X											
Patient demography	X[g]														
Medical/surgical/family medical history	X[g]														
Alcohol/smoking habits	X[g]														
Prior medication history	X[g ,h]														
General physical examination	X[g]						X			X		X			X
Measured body weight	X[g]			X		X	X		X	X		X		X	X
Measured height	X[g]						X			X		X			X
Tanner stage[i]	X[g]						X			X		X			X
IRT contact	X	X	X	X		X	X[ff]	X	X	X	X	X	X	X	X
Randomization				X											
Treatment:															
Injection training			X[j, l]	X[k, l]											
IMP administration Q2W or Q4W regimen (depending on treatment allocation) [l ,m]				X	←----------										→

	Run-in (if needed)[a]	Screening		Double- Blind Treatment Period				Open label Treatment Period							
VISIT	1	2	3	4	5	6	7	7	8	9	10[gg]	11	12[gg]	13	14
Week	Up to W-6	Up to W-2	Up to W-1[b]	W0/D1	W8	W12	W24[c]	W24	W32	W44	W56	W68	W80	W92	W104[d]
Visit Window (+/- days)	+2	+5	+/-7		+/-7	+/-7	+/-3	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7
Double-blind IMP kit dispensation[n]				X		X									
Compliance check of IMP and data collection on IMP administration					X	X	X		X	X		X		X	X
Open label IMP kit dispensation[n]								X	X	X	X	X	X	X	
Concomitant medication				X	X	X	X	X	X	X	X	X	X	X	X
Check of stability of background LMT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review of diet[o]	X[g]			X		X	X		X	X	X	X	X	X	X
Efficacy:															
Total-C, calculated LDL-C, HDL-C, TG, non-HDL-C[p, q]		X		X	X	X	X		X	X		X			X
Apo B, Apo A-1, ratio Apo B/Apo A-1, and Lp(a)[p, q]				X		X	X								X
Safety:															
AE/SAE recording (if any)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[r]		X		X		X	X		X	X		X			X
Cogstate battery practice test[s]				X											
Cogstate battery test[t]				X			X					X			X
Laboratory testing[p]:															
heFH genotyping[f]	X														
Hematology and chemistry[u]		X				X	X		X	X		X			X
HbA_{1c}		X					X					X			X
Creatine phosphokinase (CPK)		X				X	X		X	X		X			X
Liver panel[v]		X				X	X		X	X		X			X

	Run-in (if needed)[a]	Screening		Double- Blind Treatment Period				Open label Treatment Period							
VISIT	1	2	3	4	5	6	7	7	8	9	10[gg]	11	12[gg]	13	14
Week	Up to W-6	Up to W-2	Up to W-1[b]	W0/D1	W8	W12	W24[c]	W24	W32	W44	W56	W68	W80	W92	W104[d]
Visit Window (+/- days)	+2	+5	+/-7		+/-7	+/-7	+/-3	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7
Urinalysis[w]				X			X								
hs-CRP				X			X								
CPK-MB and troponin[x]				X			X								
Adrenal gland hormones[y]				X			X			X		X			X
Gonadal and pituitary hormones[z]				X			X			X		X			X
Fat soluble vitamins[aa]				X			X			X		X			X
Pregnancy test[bb]		X		X			X		X	X		X		X	X
Anti-alirocumab (drug) antibodies (ADA)[cc]				X		X	X					X			X
Serum alirocumab concentration (Pharmacokinetics)[dd]				X	X	X	X								
Flow mediated dilatation assessment[ee]				X			X								

a Patients, who have not been on stable lipid modifying therapy (LMT)s 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 heFH but without confirmation by previous genetic testing and not meeting Simon Broome criteria 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-double-blind treatment period visit. This visit will overlap with the first visit of the open label treatment period.

d End-of-open label treatment period visit.

e Informed consent should be obtained only once. If patient enters the run-in period then informed consent will be obtained prior to entry into the run-in period. If patient does not require a run-in period, then informed consent will be obtained prior to entry into the screening period.

f Genotyping for heFH 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 clinical diagnosis or no previous documented genotyping. In case of non-mandatory genotyping the sample could be taken preferentially during the screening period but could be done at any visit during the double-blind treatment period.

g The corresponding assessment should be obtained only once. If patient enters the run-in period then the corresponding assessment will be obtained during the run-in period. If patient does not require a run-in period, then the corresponding assessment will be obtained during the screening period.

h 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 found in Benecol, flax seed oil, psyllium).

i See Appendix B for Tanner stage evaluation.
j 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 randomization.
k Further injection training can be provided at the randomization visit Week 0/Day 1 when the patient/parent or a trained designated person injects the first IMP from the double-blind study treatment kit allocated by IRT. Additional training can be offered at scheduled or unscheduled visits with the scheduled double-blind treatment, as per patient/parent or Investigator's judgment.
l Prior to the injection, a local topical anesthetic may be utilized as per the Investigator.
m The first IMP injection during the double-blind treatment period will be done at the site on the day of randomization and as close as possible after randomization into the study. The subsequent injections will be done at a patient-preferred location (home…). These 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. 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. For the Q4W dosing regimen cohort study treatment will be administered every 4 weeks (Q4W) for the first 12 weeks of the double-blind period.
n 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. Open label IMP kit delivery direct to patient (DTP) on Visit 10 and 12.
o Patients will be instructed to follow a diet to treat their hypercholesterolemia in accordance with local guidelines or local practice.
p Prior to any laboratory testing, the site may utilize a local topical anesthetic as per the Investigator. 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 194.8 mL for the entire study); see Section 10.
q The lipid levels will be blinded throughout the double-blind treatment period. The lipid levels will be communicated to the Investigator during the open label treatment period from Week 32 onwards.
r Vital signs include: heart rate, systolic and diastolic BP in sitting position.
s Cogstate battery practice test will be administered at randomization visit with recommended 15 minutes break before recorded Cogstate battery test. Morning administration is also recommended for all Cogstate tests.
t Cogstate battery test consists of identification test, detection test, one card learning test, and the Groton maze learning test. Morning administration is also recommended for all Cogstate tests. For further details see Section 9.2.4.5.
u 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 γGT. (eGFR and creatinine clearance will be calculated at screening; creatinine clearance will be calculated for all subsequent visits where chemistry lab testing is performed)
v 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).
w Urinalysis: macroscopy will be performed at the central lab. If abnormal, then a standard microscope assessment will be conducted.
x CPK-MB and troponin levels will be assayed at baseline and at Week 24 and in case of any clinically relevant cardiovascular effect observed in patients.
y Adrenal gland hormones: cortisol (with reflexive adrenocorticotrophic hormone (ACTH) levels if cortisol < lower limit of normal [LLN]) and dehydroepiandrosterone sulfate (DHEAS).
z Gonadal hormones: testosterone (males) and estradiol (females). Pituitary hormones: luteinizing hormone (LH) and follicle-stimulating hormone (FSH).
aa Fat soluble vitamins: A (retinol), D (25 hydroxy vitamin D), E (alpha-tocopherol), and K (phylloquinone).
bb Pregnancy test with a local urine pregnancy test should be done on females of childbearing potential or females who have experienced menarche (they must have a confirmed negative pregnancy test at screening). Pregnancy tests may be performed more frequently in some countries due to local legislations related to women of childbearing potential randomized in clinical trials see Appendix J. The Screening (Week -2) pregnancy test should be a blood test. All other pregnancy tests will be with a local urine pregnancy test.
cc Patient who prematurely discontinue the 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, at 6 to 12 months after the last alirocumab administration and thereafter, about every 3 to 6 months until titer returns below 240.
dd Blood samples should be collected before IMP injection. PK samples will also be used for free and total proprotein convertase subtilisin/kexin type 9 (PCSK9) analysis.
ee Flow mediated dilatation assessment will be part of a substudy performed at selected sites (see Appendix E).
ff IRT contact for patient who do not continue in the open label treatment period.
gg Telephone contact.

2 TABLE OF CONTENTS

2.1 LIST OF TABLES

3 LIST OF ABBREVIATIONS

ACTH:	adenocorticotrophic hormone
ADA:	anti-alirocumab (drug) antibodies
AE:	adverse event
AESI:	adverse event of special interest
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
Apo:	apolipoprotein
Apo A-1:	apolipoprotein A-1
Apo B:	apolipoprotein B
AST:	aspartate aminotransferase
BP:	blood pressure
BW:	body weight
CHD:	coronary heart disease
CPK:	creatine phosphokinase
CVD:	cardiovascular disease
DB:	double-blind
DBP:	diastolic blood pressure
DHEAS:	dehydroepiandrosterone sulfate
DMC:	Data Monitoring Committee
DTP:	direct-to-patient
e-CRF:	electronic case report form
eGFR:	estimated glomerular filtration rate
ELISA:	enzyme-linked immunosorbent assay
FMD:	flow mediated dilatation
GCP:	good clinical practice
HDL-C:	high density lipoprotein cholesterol
heFH:	heterozygous familial hypercholesterolemia
HLGT:	high-level group term
ICH:	international conference for harmonization
IEC:	independent ethics committee
IMP:	investigational medicinal product
IRB:	institutional review board
IRT:	interactive response technolgy
ITT:	intent-to-treat
LDL-C:	low density lipoprotein cholesterol
LDL-R:	low density lipoprotein receptor
LLN:	lower limit of normal
LLQ:	lower limit of qualification
LMT:	lipid modifying therapy
Lp:	lipoprotein
MedDRA:	Medical Dictionary for Regulatory Activities

NIMP:	non-investigational medicinal product
PCSK9:	proprotein convertase subtilisin/kexin type 9
PFS:	pre-filled syringes
PK:	pharmacokinetics
PT:	preferred term
SAE:	serious adverse event
SBP:	systolic blood pressure
SM:	Site Monitor
SOC:	system organ class
TG:	triglyceride
ULN:	upper limit of normal

4 INTRODUCTION AND RATIONALE

Alirocumab is a fully human monoclonal antibody that targets proprotein convertase subtilisin kexin type 9 (PCSK9). PCSK9 belongs to the subtilisin family of serine proteases and is highly expressed in the liver. PCSK9 is involved in regulating the levels of the low-density lipoprotein receptor (LDL-R) protein (1, 2). Once PCSK9 is secreted into plasma it directly binds to the LDL-R and promotes its degradation. The increased degradation of LDLRs leads to a reduced low-density lipoprotein cholesterol (LDL-C) removal and, therefore higher LDL-C circulating levels. In humans, PCSK9 mutations have been identified; the gain-of-function mutations are rare and cause an autosomal dominant form of severe hypercholesterolemia and premature Coronary Heart Disease (CHD), whereas loss of-function mutations are more common and are associated with reduced plasma levels of LDL-C and protection from CHD (3, 4). Therefore, blocking PCSK9 binding to the LDL-R can potentially benefit patients with hypercholesterolemia by decreasing their plasma LDL-C levels. In addition, PCSK9 messenger ribonucleic acid (mRNA) and protein levels are increased in response to statins, potentially attenuating their cholesterol-lowering effect (1).

Familial hypercholesterolemia (FH) is an inherited disorder of lipid metabolism, characterized by severely elevated levels of LDL-C that lead to premature atherosclerosis and cardiovascular disease (CVD) (5). This disorder has a high prevalence in Caucasian populations, where an estimated 1 in 500 individuals are affected. Defects in at least 3 different genes that code for proteins involved in hepatic clearance of LDL-C can cause FH. These include mutations in the gene coding for the LDL-R that removes LDL-C from the circulation, and less commonly, in the gene for apolipoprotein (Apo) B, which is the major protein of the LDL-C particle. In rare cases, the gene coding for PCSK9, an enzyme involved in degrading the LDL-R (gain of function mutation), is mutated. Additionally, rare mutations in LDL receptor adaptor protein 1 (LDLRAP1), a protein which interacts with the LDL receptor or signal transducing adaptor family member 1 (STAP1) gene have been noted. In all cases, this results in an accumulation of LDL-C in the plasma from birth, and subsequent development of tendon xanthomas, xanthelasmas, atheromata, and CVD. Although genetic testing is useful in the diagnosis of heFH, it has limitations such as it may fail to diagnose some patients with heFH. There are patients who have clinical heFH but no known genetic basis for their heFH. Five to 30% of cases of phenotypic FH may arise from mutations in unidentified genes or have a polygenic cause (6). Accordingly, the protocol allows for patients to be included with either a clinical diagnosis or a genetic diagnosis of heFH.

FH is the most clearly documented to have important cardiovascular consequences beginning in childhood (7). Even though cardiovascular events are rare in childhood, children with heFH already have functional and morphological changes of the vessel wall as illustrated by an impaired flow mediated dilatation (FMD) of the brachial artery (8) and an increased intima media thickness of the carotid artery (cIMT), with a progression rate for cIMT of approximately double to that observed in unaffected siblings (9). Both are surrogate markers for atherosclerotic vascular disease (10) and, thus, indicate that the atherosclerotic process has already been initiated early in childhood. Indeed, there is now strong evidence that lesions of atherosclerosis found in adults begin in childhood and are progressive throughout the life span (11, 12). These findings strongly

suggest that to be effective at preventing CHD, prevention must begin decades prior to the onset of symptoms (13) and support the target population being evaluated in this study.

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 heFH. An LDL-C level of <130 mg/dL (3.37 mmol/L) is considered acceptable and <110 mg/dL (2.85 mmol/L) ideal for children with heFH (14, 15, 16, 17), or the achievement of ≥50% reduction in LDL-C (14). Thus, the protocol will include patients with a screening LDL-C ≥130 mg/dL (3.37 mmol/L) despite being treated with stable LMTs.

The American Heart Association (AHA) has modified the guidelines, suggesting statins supplant bile acid sequestrants not only as first-line treatment but also at a younger age (8 versus 10 years of age) (14). These revised recommendations were supported by the American Academy of Pediatrics (AAP) (17), as well as and in the recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia, in which it is mentioned that statins are the preferred initial pharmacologic treatment in children with FH (18). The highest doses of statins tested in pediatric studies resulted in LDL-C reductions of 24% for pravastatin (19), 27% for lovastatin (20), 40% for atorvastatin (21), and 41% for simvastatin (22). However, use of these statins generally does not result in the attainment of the stringent LDL-C target as illustrated by the study conducted with atorvastatin in children (21) where the highest dose tested (20 mg) resulted in only 60% of the patients who still did not achieve the optimal LDL-C goal of 110 mg/dL (2.85 mmol/L), reflecting the difficulty in meeting this target in many FH patients. Another 1-year study with rosuvastatin conducted in children with FH aged 10 to 17 years showed that less than half (40%) of subjects reached the more stringent LDL-C goal of 110 mg/dL (2.85 mmol/L) (23). Therefore, novel compounds that further reduce LDL-C levels when added to statin therapy are of interest. Limited data are available for the combination of ezetimibe and simvastatin (24) 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. With the highest dose of simvastatin (40 mg), significantly more subjects, achieved an LDL-C target of 130 mg/dL (3.37 mmol/L) and the optimal LDL-C goal of 110 mg/dL (2.85 mmol/L) in the coadministration of ezetimibe with 40 mg simvastatin group than in the simvastatin 40 mg monotherapy group, 77% versus 53% and 63% versus 27%, respectively ($p < 0.01$ for both comparisons). However the therapeutic management of this population requires a careful balance between increased dosing (administration of this high simvastatin dose) and potential side effects versus achieving treatment goals. Taken together, this information supports the age of patients included in this study as well as the definition of stable LMTs as provided for in the inclusion criteria of the protocol and its mandatory use as background therapy. Stable LMTs include stable optimal doses of statin which are based on pediatric guidelines which will be followed by the site (25).

Very little information is available on statin intolerance in the pediatric population. This is likely related to the small size or the limited duration of the studies conducted with statins, adverse events (AE) such as muscle symptoms, creatine phosphokinase (CPK) increase, or elevations in aspartate aminotransferase (AST)/alanine aminotransferase (ALT) were reported in some patients (26). Therefore statin intolerance in pediatric population cannot be ruled out. This is acknowledged by the NICE guidance that recommends to healthcare professionals to consider offering non-statin Lipid modifying therapy (LMT) for lowering LDL-C levels in children and

young people with FH who are intolerant of statins (15). Presently available non-statin LMTs commonly prescribed in the pediatric population, more particularly ezetimibe and colesevalam, appear less effective than statins on LDL-C lowering, 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 for 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 in the pediatric population. It is a randomized, 24-week double-blind (DB), placebo-controlled, parallel group study with an open label treatment period. The assessment of the primary endpoint of LDL-C at Week 24 represents the time point at which stable efficacy is already achieved and maintained based on the data from the large adult alirocumab program. The double-blind treatment duration of 24 weeks as compared with placebo as well as the 80-week open label treatment period should provide a reasonable duration of safety experience in this patient population who are expected to ultimately derive potential benefit from the drug. The choice of control of an injectable placebo containing the same formulation as alirocumab is appropriate for the objectives of this study since it will provide the most robust assessment of efficacy and safety of alirocumab. 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. Additionally, the patients who are randomized to the placebo group will also have the opportunity to enter into an 80-week open label treatment period.

Preliminary clinical data from the DFI14223 study, were based on 31 pediatric patients in 3 different cohorts. This Phase 2 study evaluated a fixed dosage according to body weight (BW) categories, with staggered doses of 30 mg every two weeks (Q2W) (Cohort 1) and 40 mg Q2W (Cohort 2) or 75 mg every four weeks (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 the 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 the 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 (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), as compared with the Cohort 1 using as well the 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. Regarding the Cohort 3, overall the 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 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 doses (40 mg Q2W/75 mg Q2W) as per BW category (<50 kg/≥50 kg) of Cohort 2. Overall for 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 event, treatment-emergent adverse events (TEAE) leading to death, or TEAEs leading to permanent treatment discontinuation. There were no adverse events of special interest (AESI) including, neurological events, neurocognitive events, increase in 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.

Given the unexpected results observed for the Q4W dosing regimen as described above for Cohort 3 with 75 mg Q4W for BW <50 kg and 150 mg Q4W for BW ≥50 kg), no formal conclusion could be drawn. The doses evaluated were likely not high enough to achieve larger and sustained reductions in the LDL-C over the entire dosing interval in children receiving statin as background therapy. Therefore, before investigating this Q4W dosing regimen in the Phase 3 EFC14643 study, further evaluation with higher doses 150 mg/300 mg Q4W depending on the BW category was conducted through an additional Cohort 4 in the Phase 2 DFI14223study. The primary efficacy endpoint, as measured by the percent change from baseline in LDL-C at Week 8, for Cohort 4 (mean LS change from baseline -44.5%) showed a clinically meaningful reduction comparable to results observed for Cohort 2 using the 40 mg and 75 mg Q2W dosing regimen (mean LS change from baseline -46.1%). Substantial reductions were seen across both Cohort 4 doses ranging from -31.9% to -59.8 % for 150 mg and 300 mg Q4W, respectively. Overall for combined doses, the proportion of patients who achieved a LDL-C value <110 mg/dL (2.85 mmol/L) was 86.4%. Alirocumab was well tolerated with a similar favorable safety profile in Cohort 4 as compared with the other cohorts. No new clinically significant safety findings were noted in pediatric patients treated with alirocumab in this additional cohort.

Based on these results, the doses selected to be evaluated for the EFC14643 study are 40 mg Q2W for BW<50 kg and 75 mg Q2W for BW ≥50 kg in the Q2W dose regimen, and 150 mg Q4W for BW<50 kg and 300 mg Q4W for BW ≥50 kg in the Q4W dose regimen. However as described above although a majority of patients achieved a LDL-C value <110 mg/dL (2.85 mmol/L) (76.4% of patients in Cohort 2, and 86.4% in Cohort 4), about 20% of patients still had elevated LDL-C in the context of the lifelong exposure to high levels of plasma LDL-C and the increased risk of developing atherosclerosis. It is therefore the expectation that using an up-titration/dose-adjustment scheme as already done for adults will result in additional decrease of LDL-C and will optimize the proportion of patients achieving the LDL-C ideal goal. Regarding the up-titration scheme and based on the data from Phase 3 adults studies, doubling the dose of alirocumab should result in an additional decrease in LDL-C of about 10%.

Given the baseline levels expected in this heFH pediatric population, the chance to have patients experiencing LDL-C levels <50 mg/dL is expected to be very low. Nevertheless, as done in the adult development program, a specific monitoring plan for patients reaching LDL-C values below 50 mg/dL will be implemented with the collaboration of the DMC and an independent physician. Therefore, the following scheme will be applied according to the BW category:

- Q2W dosing regimen: A starting dose of 40 mg Q2W with possible up-titration to 75 mg Q2W for BW <50 kg, and a starting dose of 75 mg Q2W with possible up-titration to 150 mg Q2W for BW ≥50 kg.

- Q4W dosing regimen: A starting dose of 150 mg Q4W with possible dose-adjustment to 75 mg Q2W for BW <50 kg and a starting dose of 300 mg Q4W with possible dose-adjustment to 150 mg Q2W for BW ≥50 kg.

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-C, Apo B, non- high-density lipoprotein-C (non-HDL-C), a decrease in lipoprotein Lp(a), and a favorable trend for high-density lipoprotein-C (HDL-C) and triglycerides (TG). Maximum efficacy was observed as early as 4 weeks after the initial dose, and efficacy was well maintained up to 2 years.

In the DFI14223 pediatric study, treatment with alirocumab over 8 weeks demonstrated significant LDL-C lowering effect with both the Q2W and Q4W dosing regimen. The percent change from baseline in LDL-C at Week 8 demonstrated a greater and consistent reduction, overall, in Cohort 2 using the Q2W dosing regimen and in Cohort 4 using the Q4W dosing regimen as compared with Cohorts 1 and 3.

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

Immunogenicity and systemic hypersensitivity are considered as identified risks for alirocumab.

The following safety information is based on the adult clinical trials. Injection site reactions (including erythema/redness, itching, swelling, pain, tenderness), upper respiratory tract signs and symptoms (including mainly oropharyngeal pain, rhinorrhea, sneezing), pruritus, hypersensitivity, eczema nummular, urticaria, and hypersensitivity vasculitis are identified as adverse drug reactions (ADRs) for alirocumab. 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, alanine aminotransferase (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 to 0.8% of alirocumab-treated patients who did not achieve such low levels. Although limitation has to be considered with regard to this post-randomization comparison and there were no statistically significant differences in the incidence of cataracts in this subgroup of patients when compared to control groups, cataract in patients with very low LDL-C levels is 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 adverse event of special interest (AESI).

In the DFI14223 pediatric study, treatment with alirocumab over 8 weeks and during 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.

With regard to the neurocognitive function, a specific assessment will be performed through formal neurocognitive testing with Cogstate battery test in this study.

This specific study is undertaken to demonstrate the efficacy and safety of alirocumab in the heFH pediatric population. Because of the rapid clinical progression of atherosclerotic disease in children and adults with familial hypercholesterolemia pediatric guidelines (14, 15, 16, 17, 18) recommend LDL-C lowering intervention starting with statins. However, not all patients can achieve target LDL-C reductions with currently available LMTs, and these pediatric patients represent a group with an identified unmet medical need that can be addressed by adding alirocumab to their LDL-C lowering therapies.

5 STUDY OBJECTIVES

5.1 PRIMARY

To evaluate the efficacy of alirocumab administered every 2 weeks (Q2W) and every 4 weeks (Q4W) versus placebo after 24 weeks of double-blind treatment on low-density lipoprotein cholesterol (LDL-C) levels in patients with heterozygous familial hypercholesterolemia (heFH) 8 to 17 years of age on optimal stable daily dose of statin therapy ± other lipid modifying therapies (LMTs) or a stable dose of non-statin LMTs in case of intolerance to statins.

5.2 SECONDARY

- To evaluate the efficacy of alirocumab versus placebo on LDL-C levels after 12 weeks of double-blind treatment.
- To evaluate the effects of alirocumab versus placebo 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 (TGs), apolipoprotein A-1 (Apo A-1) levels after 12 and 24 weeks of treatment.
- To evaluate the safety and tolerability of alirocumab after 24 weeks of treatment in comparison with placebo.
- To evaluate the efficacy, safety and tolerability of alirocumab after 80 weeks of open label treatment.
- To evaluate the development of anti-alirocumab antibodies after 24 weeks of treatment during the double-blind treatment period.

5.3 OTHER

- To evaluate the development of anti-alirocumab antibodies after 80 weeks of open label treatment.
- To evaluate the pharmacokinetics (PK) of alirocumab.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

This study is a Phase 3, randomized, 24-week double-blind treatment, placebo-controlled, parallel- group, multi-national, multi-center study followed by an open label treatment period of 80 weeks.

Approximately 150 children and adolescents aged of 8 to 17 years with heFH and LDL-C ≥130 mg/dL (3.37 mmol/L) at screening visit despite stable LMTs will be randomized with a 2:1 ratio (alirocumab: placebo). Two dosing regimens, Q2W and Q4W, will be evaluated with approximately 75 patients in each dosing regimen cohort. The start of the recruitment in the Q4W dosing regimen cohort will depend on the status of the recruitment in the Q2W dosing regimen cohort and the status of the amendment approval. This process will be managed by the Interactive Response Technology (IRT) system, depending on the overall recruitment status and amendment approval status. 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. The optimal dose of statin is defined as the dose prescribed based on regional practice or local guidelines 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 randomization 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. Statin intolerant patient is defined as one with the 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 regimen of a statin (eg, 1 to 3 times weekly) are also considered as not able to tolerate a daily dose.

Genotyping for heFH 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 clinical diagnosis or no previous documented genotyping. In case of non-mandatory genotyping the sample could be taken preferentially during the screening period but could be done at any visit during the double-blind treatment period.

Randomization will be stratified according to previous participation (yes or no) in the Phase 2 DFI14223 study and baseline BW (<50 or ≥50 kg).

The study consists of a run-in period (as needed), screening period, double-blind treatment period, and an open label treatment period.

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 1.3, 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 double-blind treatment Period 24 weeks in duration.
- A 80-week open label treatment period.

The total duration of the study will be up to 110 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 TWO-STEP ANALYSIS

The analyses will be conducted in 2 steps. The first analysis will be conducted when all patients have been randomized and all data up to Week 24 (double-blind period) have been collected and validated; this will consist of the final analysis of the double-blind primary and secondary endpoints and safety up to Week 24. The safety analysis of the open-label treatment period will be performed on all safety data collected and validated at the time of the first analysis. The first analysis may be used for regulatory consultation purpose.

The second analysis will be conducted at the end of the study with the data from the open-label treatment period and will consist of the final analysis of the open-label treatment period for the safety and other efficacy measures.

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 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 also 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 10.6.2.3) in conjunction with the independent physician that is external to the EFC14643 study team and not part of any alirocumab activities. Only the independent physician will have access to the patient information during the double-blind treatment period. Details will be given 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 diagnosed with heterozygous familial hypercholesterolemia[1] inadequately controlled (see threshold mentioned in the exclusion criterion 2)[2] 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[5].

I 02. A signed informed consent indicating parental permission with or without patient assent, depending on capacity for understanding based on developmental maturity and local requirements. 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.

7.2 EXCLUSION CRITERIA

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

[1] Diagnosis of heFH must be made either by previous genotyping, current centralized genotyping, or by clinical criteria according to Simon Broome criteria. Previous genotyping refers to documented results that are available from prior genotyping testing supporting a diagnosis of heFH. Current centralized genotyping refers to patients electing to undergo genotyping during the run-in period with results supporting a diagnosis of heFH. The clinical diagnosis should be based on the Simon Broome criteria for possible or definite heFH (see Appendix A). Once eligibility is confirmed based on prior genetic testing or Simon Broome criteria, results of elective genetic testing will not impact patient's eligibility.

[2] Patients who have previously participated in the DFI14223 study have already met this LDL-C requirement when they screened for the DFI14223 study and thus will not be excluded based on LDL-C <130 mg/dL (3.37 mmol/L).

[3] The optimal dose of statin is defined as the stable daily dose prescribed based on regional practice or local guidelines or is the stable daily dose that is maximally tolerated due to adverse effects on higher doses. For patients not receiving the maximally tolerated dose of statin, statin intensification should be carefully considered prior to randomization 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] Statin intolerant patient is defined as the 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 regimen of a statin (eg, 1 to 3 times weekly) are also considered as not able to tolerate a daily dose.

[5] Before enrolling more than 2 siblings, the Investigator should discuss with the Sponsor study team.

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 of 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 less than 130 mg/dL (3.37 mmol/L) (ie, adequately controlled) obtained during the screening period after the patient has been on stable 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.

Note: Patients who have previously participated in the DFI14223 study have already met this LDL-C requirement when they screened for the DFI14223 study and thus will not be excluded based on LDL-C <130 mg/dL (3.37 mmol/L).

E 03. Patients with body weight less than 25 kg.

E 04. Patients aged of 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 B).

E 05. Daily dose of statin that is above the maximum recommended dose for pediatric patients as per the local prescribing label.

E 06. Patients who will receive statin de novo during the run-in period.

E 07. 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 08. Patients not previously instructed on a cholesterol-lowering diet prior to the screening visit.

E 09. Patients with secondary hyperlipidemia (such as decompensated hypothyroidism, nephrotic syndrome, obstructive liver disease, anorexia nervosa, obesity, and drug treatment [eg, isotretinoids]).

E 10. Patients diagnosed with homozygous familial hypercholesterolemia.

E 11. Patients who have received lipid apheresis treatment within 2 months prior to the screening period, or have plans to receive it during the study.

E 12. Patients with uncontrolled (ie, HbA1c levels above local guidelines or equivalent) Type 1 or 2 diabetes mellitus.

E 13. Patients with known uncontrolled thyroid disease (ie, thyroid stimulating hormone levels above or below the laboratory's reference range within the past 6 months that were obtained due to clinical indication).

E 14. Use of systemic corticosteroids.

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

E 15. Patients with uncontrolled (ie, systolic blood pressure [SBP] or diastolic blood pressure [DBP] above local guidelines or equivalent) hypertension.

E 16. Fasting triglycerides >350 mg/dL (3.95 mmol/L) at the screening visit.

E 17. Severe renal impairment (ie, estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2 at the screening visit).

E 18. ALT or AST >2 x upper limit of normal (ULN) (1 repeat lab is allowed).

E 19. CPK >3 x ULN (1 repeat lab is allowed).

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

E 21. 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 sub-Investigator would preclude safe completion of the study or constrain endpoints assessment such as major systemic diseases.
- Patients considered by the Investigator or any sub-Investigator as inappropriate for this study for any reason, eg:
  - Those deemed unable to meet specific protocol requirements, such as scheduled visits,
  - Those deemed unable to administer or tolerate long-term injections as per the patient or the Investigator,
  - 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 22. Known or suspected alcohol and/or drug abuse.

E 23. Patients who have previously received evolocumab.

E 24. Treatment with any investigational medicinal product (IMP) within 8 weeks or 5 half-lives prior to the screening period, whichever is longer (except for patients who participated in the DFI14223 study, where within 10 weeks will be applied for alirocumab administration).

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 25. 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 alirocumab

E 26. Hypersensitivity to alirocumab or to any of the ingredients of alirocumab injections.

E 27. 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 legislations related to women of childbearing potential randomized in clinical trials.

E 28. Positive pregnancy test in females who have experienced menarche.

E 29. Females who are breast-feeding.

E 30. 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 the study treatment and for at least 10 weeks after the last injection.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

IMP: alirocumab and placebo for alirocumab

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

Q2W dosing regimen cohort:

- BW <50 kg:
  - 0.5 mL of alirocumab 75 mg/mL solution for 40 mg dose,
  - 0.5 mL of alirocumab 150 mg/mL solution for 75 mg dose.
- BW ≥50 kg:
  - 1 mL of alirocumab 75 mg/mL solution for 75 mg dose,
  - 1 mL of alirocumab 150 mg/mL solution for 150 mg dose.

Placebo formulation: Sterile solution consisting of 10 mM histidine, pH 6.0, polysorbate 20, and sucrose as described below:

- Placebo of 0.5 mL volume for BW <50 kg.
- Placebo of 1 mL volume for BW ≥50 kg.

Q4W dosing regimen cohort:

- 1 mL of alirocumab 150 mg/mL solution for 150 mg dose.

Placebo formulation: Sterile solution consisting of 10 mM histidine, pH 6.0, polysorbate 20, and sucrose as described below:

- Placebo of 1 mL volume regardless of BW category.

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

Dose regimen double-blind period:

Q2W dosing regimen cohort:

During the double-blind (DB) treatment period, for up to half of the total patient population (approximately 75 patients) alirocumab or placebo will be administered Q2W SC, starting at the randomization Visit (Week 0) continuing up to the end of the DB period.

- During the first 12 weeks
  - Alirocumab 40 mg: 1 SC injection of 0.5 mL Q2W for BW <50 kg.

- Alirocumab 75 mg: 1 SC injection of 1 mL Q2W for BW ≥50 kg.

- At Week 12, based on their LDL-C at Week 8, patients randomized to alirocumab will, in a blinded manner, either:
  - Continue alirocumab 40 mg or 75 mg Q2W, if the Week 8 LDL-C is <110 mg/dL (2.85 mmol/L) OR
  - Receive a dose that is up-titrated to alirocumab 75 mg (for patients on 40 mg) or 150 mg (for patients on 75 mg) Q2W, if the Week 8 LDL-C* is ≥110 mg/dL (2.85 mmol/L).

Q4W dosing regimen cohort:

The remaining half of the patient population (ie, approximately 75 patients) will be enrolled to a Q4W dosing regimen cohort. The start of this Q4W dosing regimen cohort will depend on the status of the recruitment in the Q2W dosing regimen cohort and the status of the amendment approval. During the first 12 weeks of the double-blind period and before any possible dose-adjustment to Q2W dosing regimen, all patients will receive SC injection(s) Q4W to get a proper evaluation of this dosing regimen. After Week 12 with regard to the possible dose-adjustment and the maintenance of the blind until the end of the double-blind period, all patients will receive SC injection(s) Q2W. Patients receiving alirocumab will be under a "sham Q2W*" regimen from Week 12 to Week 24 with alirocumab Q4W alternating with placebo Q4W.

- During the first 12 weeks:
  - Alirocumab 150 mg for BW <50 kg: 1 SC injection of 1 mL Q4W, consisting of 1 injection of 150 mg.
  - Alirocumab 300 mg for BW ≥50 kg: 2 SC injections of 1 mL each Q4W, consisting of 2 injections of 150 mg.
- At Week 12, based on their LDL-C at Week 8, patients randomized to alirocumab will, in a blinded manner:
  - For BW <50 kg, either continue alirocumab 150 mg with 1 SC injection of 1 Ml Q4W alternating with 1 injection of placebo Q4W OR if LDL-C ≥110 mg/dL (2.85 mmol/L) receive a dose that is dose -adjusted to 75 mg Q2W with 1 SC injection of 1 mL of 75 mg.
  - For BW ≥50 kg, either continue alirocumab 300 mg with 2 SC injections of 1 mL each Q4W (consisting of 2 injections of 150 mg Q4W alternating with 2 injections of placebo Q4W) OR if LDL-C ≥110 mg/dL [2.85 mmol/L] receive a dose that is dose -adjusted to 150 mg Q2W with 2 SC injections of 1 mL each (consisting of 1 injection of 150 mg and 1 injection of placebo).

**Lipid values obtained at Week 8 for the purpose of up-titration/dose-adjustment will not be communicated to Investigators to maintain the blind. The continuation or dose up-titration/dose-adjustment of alirocumab will occur in an automated process without site or patient awareness.*

Open label period

The open label treatment period consists of 80 weeks of open label alirocumab SC Q2W or Q4W depending on the dosing regimen initiated at randomization.

At the first open label treatment period visit (ie, Week 24), after completion of the double-blind treatment period, depending on the dosing regimen cohort participation, both alirocumab and placebo treated patients will receive alirocumab either 40 mg Q2W or 150 mg Q4W if BW is <50 kg, and 75 mg Q2W or 300 mg Q4W if BW is ≥50 kg, from the weight obtained at the Week 24 visit.

After Week 24, the Investigator will manage, based on his/her own judgment, adjustment of alirocumab dose based on changes in BW. However, related to this up-titration/ adjustment of the dose, if the Investigator considers that the up-titration/adjustment would potentially negatively impact patient safety, he/she can exercise his/her judgement in a manner that safeguards the safety and wellbeing of the patient. The following will be applied based on changes in BW:

- If currently on 40 mg Q2W then adjust dose to 75 mg Q2W if BW changes from <50 kg to ≥50 kg.
- If currently on 150 mg Q4W then adjust dose to 300 mg Q4W if BW changes from <50 kg to ≥50 kg.

For patients whose weight oscillates around 50 kg the dose will be adjusted only once during the open-label treatment period.

The lipid levels will be communicated to the Investigator during the open label treatment period from the second visit (ie, Week 32) onwards. The IRT system is set up to allow the Investigator based on his/her own judgment related to the patient's LDL-C levels and the safety profile, to up-titrate, down-titrate, maintain the dose of alirocumab or discontinue alirocumab throughout the study.

From Week 32 onwards, based on the patient LDL-C value, the following change of alirocumab doses will be possible:

<u>Q2W dosing regimen cohort:</u>

Up-titration:

- 40 mg to 75 mg Q2W if BW <50 kg.
- 75 mg to 150 mg Q2W if BW ≥50 kg.

Down-titration:

- 75 mg to 40 mg Q2W if BW <50 kg.
- 150 mg to 75 mg Q2W if BW ≥50 kg.

Q4W dosing regimen cohort:

- 150 mg Q4W to 75 mg Q2W if BW <50 kg.
- 300 mg Q4W to 150 mg Q2W if BW ≥50 kg.

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 can 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 set in a safe location at room temperature for about 30 to 40 minutes. Thereafter, the IMP should be administered as soon as possible.

Double-blind IMP will start as soon as possible after the call for randomization using the treatment kit numbers provided by the Interactive Response Technology (IRT). If possible, the first injection after randomization 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 double-blind injection. IMP should ideally be administered 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.

Provision of investigational medicinal product:

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 study Sponsor. For this reason, the IMP delivery will be managed by the service provider. The clinical site will instruct the patient, as appropriate, as to how the DTP process operates before the DTP process 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 products (NIMP) because the medication is a potential background therapy:

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

An additional open label treatment period with alirocumab will be offered for this patient population. Treatment will continue until one of the following occurs:

- Risk/benefit of alirocumab in this patient population is deemed not favorable.
- The study will end in July 2023 or until the drug is approved for the patient in the respective country, whatever comes first.

8.3 BLINDING PROCEDURES

8.3.1 Methods of blinding

During the double-blind treatment period, alirocumab and placebo for alirocumab will be provided in identically matched PFS (with or without safety system, depending on the time in the study) and packaged identically which includes labeling to protect the blind. Each double-blind treatment kit will be labeled with a number, which will be generated by a computer program from Sanofi. The treatment kit numbers will be obtained by the Investigator at the time of patient randomization and subsequent patient visits scheduled via a centralized treatment allocation system that will be available 24 hours-a-day, 7 days-a-week. In accordance with the double-blind design, study patients, Investigators and study site personnel will remain blinded to study treatment and will not have access to the randomization (treatment codes) except under circumstances described in Section 8.3.2.

8.3.1.1 PK and anti-alirocumab antibodies

At the assay institutions charged for PK/anti-alirocumab (drug) antibodies (ADA) measurements, some of the samples will be analyzed prior to database lock leading to unblinding of responsible bioanalysts. Bioanalysts are excluded from the operation's team and a process will be set up to prevent any potential unblinding. Patients' anti-alirocumab antibody results will not be communicated to the sites, during the double-blind phase, so that the patient's ADA levels do not influence the Investigator's safety evaluation.

Patients who do not enter the open label treatment period or who prematurely discontinue the double-blind phase and have a titer at or above 240 for anti-alirocumab antibody at the end of treatment visit will have additional antibody sample(s), at 6 to 12 months after the last dose and thereafter about every 3 to 6 months until titer returns below 240. Patients who enter the open label treatment period will be monitored for anti-alirocumab antibodies as per the study flowchart (Section 1.3).

8.3.1.2 Lipid parameters

Lipid parameter values from blood samples obtained after the randomization visit and during the double-blind phase, run by the central lab, will not be communicated to the sites so that the patient's LDL-C values do not influence the Investigator's safety evaluation or potentially break the blind. The Sponsor's EFC14643 study team will not have access to these values either.

During the open label treatment period, from Week 32 the lipid levels will be communicated to the Investigator. The Investigator will be responsible, based on his/her own judgment related to the patients' LDL-C levels and the safety profile, to up-titrate, down-titrate, maintain the dose of alirocumab or discontinue alirocumab throughout the study. The reasons of any adjustment should be documented and recorded in the electronic case report form (e-CRF).

8.3.2 Randomization code breaking during the double-blind treatment period of the study

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

Code breaking can be performed at any time by using the proper module of the centralized treatment allocation system and/or by calling any other phone number provided by the Sponsor for that purpose. However, it is preferable to contact the Medical Monitor to discuss the case before unblinding the case.

If the blind is broken, the Investigator must document the date, time of day, and reason for code breaking, and report this information (or "relevant information as required by") on the appropriate page of the e-CRF. Note that when documenting the reason for unblinding, the Investigator must not provide any detail regarding the nature of the IMP. The Investigator should not divulge IMP detail to the Sponsor's representative from the EFC14643 study or to any staff members until database closure. Furthermore, when completing forms (eg, AE, serious AE [SAE]), the study treatment should not be disclosed on the forms.

The code-breaking can also be performed by contacting the "24 hour alert system"; but this system should be used in very exceptional cases only (ie, unavailability of a centralized treatment allocation system or inability to contact Investigator and/or site staff). However, the preferred option is to unblind using a centralized treatment allocation system. The Investigators will be

informed by the clinical monitoring team about the availability of the local code-breaking details (through an emergency centralized 24 hour telephone system for use with e-SMS). A patient card, including the relevant "24 hour alert system" telephone number will be provided to every patient who will participate in the study.

Unblinding may also be performed by the Sponsor for some Serious Adverse Events that are both related and unexpected in order to conform to regulatory reporting requirements. Refer to Section 10.5 for suspected unexpected serious adverse drug reaction unblinding by the Sponsor.

If the code is broken by the Investigator, the patient must withdraw from IMP administration.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

The lists of treatment kit numbers will be generated centrally by Sanofi; separate lists will be prepared for Q2W and Q4W dosing regimen cohort. 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 according to which it will allocate the treatment kits to the patients.

Two dosing regimens will be evaluated - either Q2W or Q4W. For each dosing regimen cohort patients will be allocated to receive repeated doses of SC alirocumab injections or matching placebo.

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

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

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

8.5 INVESTIGATIONAL MEDICINAL PRODUCT PACKAGING AND LABELING

For the double-blind treatment period, each kit will contain pre-filled syringes with finger grip (PFS) to be replaced by pre-filled syringes with safety system (PFS-S) when they become available of alirocumab 75 mg/mL or alirocumab 150 mg/mL or placebo for alirocumab as described in Section 8.1.

For the open label treatment period, each kit will contain pre-filled syringes (PFS-S) 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°-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 alirocumab 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 Site and Sponsor (eg, patient unable to attend a clinic visit due to special circumstances) some IMP kits could be supplied, when feasible, directly from site to patient via a Sponsor-approved courier company. This process (which requires maintenance of the cold chain) would be implemented only at selected sites/countries (where certain conditions would be fulfilled, and where permitted locally) and for selected patients (who could handle and would consent to such a process). This direct-to-patient (DTP) process will be described in detail in a separate document and would be implemented after appropriate training of Monitoring Teams and Investigational Sites.

8.7 RESPONSIBILITIES

The Investigator, the 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) should 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, 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

IMP administration data will be recorded by the Investigator on e-CRF 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 patient's diary.
- The Investigator/study coordinator will enter data in the appropriate e-CRF pages, according to data recorded in the treatment log form.
- The monitor will check the data consistency between e-CRF pages, treatment log forms using patient's diary, and returned unused syringes of a corresponding kit.

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 and reconciliation 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 to 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 e-CRF 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, during the screening period and maintained during double-blind treatment period. During the open label 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 found in Benecol, flax seed oil, and psyllium.

Any adjustment will be documented in the e-CRF.

8.8.1 Management of background lipid modifying therapy

Patients must have been on stable optimal dose of statin with or without other LMT(s) for at least 4 weeks prior to the screening LDL-C sample being obtained, and from the screening visit to Day 1.

For background LMT (statin ± other LMT), sites must follow the national product label for the safety monitoring and management of patients.

Double-blind treatment phase:

From the randomization visit (Day 1) until Week 24 of the double-blind treatment period, the background LMT should not be changed. No dose-adjustment, discontinuation or initiation of other statins or other LMT should take place during this time, barring exceptional circumstances whereby overriding concerns warrant such changes, as per Investigator's judgment.

During the double-blind treatment phase, lipid profile values from samples obtained after randomization will be blinded.

Open label treatment period:

During the open label treatment period, starting after the Visit 7 (Week 24), the lipid levels will be communicated to the Investigators from Visit 8 (Week 32).

The Investigator will be responsible, based on his/her own judgment related to the patients' LDL-C levels and the safety profile, to up-titrate, down titrate, maintain the dose of alirocumab or

discontinue alirocumab throughout the study. The daily dose of statin should be maintained; in particular any decreases in statin dose are strongly discouraged, except in case of medical reason. The statin dose should not be decreased to adjust to the degree of LDL-C lowering; the Investigator has the option to discontinue alirocumab. Other LMT (if applicable) can be modified (including addition of another LMT) based on the Investigator's judgment throughout the study.

Any adjustment will be documented in the e-CRF.

8.8.2 Contraception

Females of childbearing potential must use an effective contraceptive method throughout the entire duration of the study treatment (including the double-blind treatment period and the open label treatment period) 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 follow-up visit include the following:

- Oral and injectable corticosteroids.
- Fibrates (except fenofibrates).
- Immunosuppressants.

Prohibited concomitant medications from the start of the open label treatment period until the end of study will include the same prohibited concomitant medication as in the main treatment period.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 PRIMARY ENDPOINT

9.1.1 Primary efficacy endpoint

Percent change in LDL-C from baseline to Week 24 in the intent-to-treat (ITT) population, using all LDL-C values regardless of adherence to treatment (ITT estimand).

The LDL-C at Week 24 will be the LDL-C level obtained within the Week 24 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 above definition. In case both calculated and measured LDL-C are provided for the same sampling, the measured LDL-C will be considered. The analysis window used to allocate a time point to a measurement will be defined in the SAP.

9.2 SECONDARY ENDPOINTS

9.2.1 Key secondary efficacy endpoints

- Percent change in LDL-C from baseline to Week 12 (ITT estimand).
- Percent change in Apo B from baseline to Week 24 (ITT estimand).
- Percent change in non-HDL-C from baseline to Week 24 (ITT estimand).
- Percent change in Total-C from baseline to Week 24 (ITT estimand).
- Percent change in Apo B from baseline to Week 12 (ITT estimand).
- Percent change in non-HDL-C from baseline to Week 12 (ITT estimand).
- Percent change in Total-C from baseline to Week 12 (ITT estimand).
- Proportion of patients achieving a LDL-C level lower than 130 mg/dL (3.37 mmol/L) at Week 24 (ITT estimand).
- Proportion of patients achieving a LDL-C level lower than 130 mg/dL (3.37 mmol/L) at Week 12 (ITT estimand).
- Proportion of patients achieving a LDL-C level lower than 110 mg/dL (2.84 mmol/L) at Week 24 (ITT estimand).
- Proportion of patients achieving a LDL-C level lower than 110 mg/dL (2.84 mmol/L) at Week 12 (ITT estimand).
- Percent change in Lp (a) from baseline to Week 24 (ITT estimand).
- Percent change in Lp (a) from baseline to Week 12 (ITT estimand).
- Percent change in HDL-C from baseline to Week 24 (ITT estimand).

- Percent change in fasting TG from baseline to Week 24 (ITT estimand).
- Percent change in Apo A-1 from baseline to Week 24 (ITT estimand).
- Percent change in HDL-C from baseline to Week 12 (ITT estimand).
- Percent change in fasting TG from baseline to Week 12 (ITT estimand).
- Percent change in Apo A-1 from baseline to Week 12 (ITT estimand).

9.2.2 Other secondary efficacy endpoints

- All primary and key secondary endpoints in the modified ITT (mITT) population, using all LDL-C values during the treatment period (on-treatment estimand).
- Absolute change in Apo B/Apo A-1 ratio to Week 12 and Week 24 (ITT and on-treatment estimands)
- Proportion of patients achieving at least 30% reduction, 50% reduction in LDL-C at Week 24 (ITT and on-treatment estimands)
- Proportion of patients achieving at least 30% reduction, 50% reduction in LDL-C at Week 12 (ITT and on-treatment estimands)
- Percent change in LDL-C from baseline to Week 104 (ITT and on-treatment estimands).

9.2.3 Efficacy assessment method

9.2.3.1 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 1.3. LDL-C will be calculated using the Friedewald formula by the Central Laboratory as per the schedule in Section 1.3. If TG values exceed 400 mg/dL (4.52 mmol/L) then the central lab will reflexively measure (via the beta quantification method) the LDL-C rather than calculating it. 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.

9.2.4 Safety endpoints

Safety parameters: adverse events (AE), serious AE (SAE), AE of special interest ([AESI] laboratory data, vital signs, body weight, height, Cogstate battery test, and Tanner stage will be assessed throughout the study.

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

The AESIs are defined in Section 10.4.1.3.

9.2.4.1 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 double-blind IMP.
- Double-blind treatment-emergent adverse event (TEAE) period: The double-blind TEAE observation period is defined as the time from the first dose of double-blind IMP to the last dose of double-blind IMP injection +70 days (10 weeks) for those patients not proceeding into the open label treatment period as residual effect of alirocumab is possible until 10 weeks after the stop of treatment IMP injection, or up to the day before first dose of open label IMP for those patients proceeding into the open label treatment period.
- Open label TEAE period: The open label TEAE observation period is defined as the time from the first dose of open label IMP to the last dose of open label IMP injection +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 double-blind and open label TEAE periods up to the end of the study for each patient.

9.2.4.2 Adverse events

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 MedDRA (Medical Dictionary for Regulatory Activities) 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 adverse events (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 e-CRF 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, "post-study" death includes all deaths reported after the end of the study (see definition of end of study period per patient in Section 6.2.2).

9.2.4.3 Laboratory safety variables

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

High-sensitivity C reactive protein (hs-CRP) will be monitored at baseline and at Week 24.

9.2.4.4 Vital signs

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

9.2.4.5 Cogstate battery test

Cogstate battery test consists of identification test, detection test, one card learning test, and Groton maze learning test. The results will be automatically calculated. Details are provided in Section 10.

9.2.4.6 Tanner stages measurement

The Tanner stages will be measured (see Appendix B) throughout the study according to the schedule in Section 1.3. 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) at Week 0 (randomization visit) and then at several visits as per the study flowchart (see Section 1.3).

Exact date and time of last IMP administration and PK sampling are to be recorded.

9.3.1.2 Pharmacokinetics handling procedure

Table 1 - Pharmacokinetics handling for alirocumab

Sample type	alirocumab
Matrix	serum
Blood sample volume	5 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. 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). The lower limit of quantification (LLQ) for this assay is 0.078 µg/mL [redacted].

PK samples will be also analyzed for the determination of the total and free PCSK9 levels using validated ELISA. The LLQ is 0.156 µg/mL for the total PCSK9 assay [redacted] and 0.0312 µg/mL for the free PCSK9 assay [redacted].

9.3.2 Anti-alirocumab antibody assessments

Anti-alirocumab antibodies (ADA) include the antibody status (positive/negative), antibody titers and neutralizing activity for positive ADA.

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 1.3. All scheduled samples will be obtained before IMP injection (predose).

9.3.2.2 Sampling procedure

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

9.3.2.3 Bioanalytical method

All anti-alirocumab antibody (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 anti-alirocumab antibodies in the sample. [redacted]

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

9.3.3 Pharmacogenetic assessment

No pharmacogenetic testing will be done in this study.

9.3.4 Pharmacodynamic variables

The PD 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 Low-density lipoprotein-C (LDL-C) <50 mg/dL (<1.30 mmol/L)

Other endpoints related to LDL-C <50 mg/dL (1.30 mmol/L) will be the proportion of patients with 2 consecutives results, spaced out by at least 21 days, of LDL-C <50 mg/dL (1.30 mmol/L), LDL-C <25 mg/dL (0.65 mmol/L), LDL-C <15 mg/dL (0.39 mmol/L) during the treatment period and the time to the first LDL-C <50 mg/dL (1.30 mmol/L) for these patients.

9.3.6 Urinalysis

Urine test will be monitored at baseline and at Week 24. Macroscopy will be performed at the central lab. If abnormal, then a standard microscope assessment will be conducted.

9.3.7 CPK-MB and cardiac troponin

CPK-MB and cardiac troponin levels will be assessed at baseline and at Week 24 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 (randomization visit), a timeframe of a certain number of days will be allowed. The window period for all visits including during the open label treatment period is ±7 days except for Week 24 (±3 days).

For all visits after Day 1/randomization visit, if one visit date is changed, then the next visit should take place according to the original schedule as outlined in Section 1.3.

Blood samplings:

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, 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. Blood sampling for adrenal gland, pituitary and gonadal hormones should be obtained in the morning and at the same time if possible. 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 max blood volume of 38.0 mL/day or 50.9 mL/month [27, 28, 29]).

Laboratory tests:

The laboratory data are collected in accordance with the study schedule in Section 1.3 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 GT.

  Note: eGFR and creatinine clearance will be calculated at screening; creatinine clearance will be calculated for all subsequent visits where chemistry lab testing is performed. The formula for calculating eGFR and creatinine clearance is provided in Appendix I.
- Lipid panel 1: TC, calculated LDL-C, HDL-C, TG, 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).
- Creatine Phosphokinase (CPK).
- $HbA_{1c.}$
- Hs-CRP.
- CPK-MB, troponin.
- Adrenal gland hormones: cortisol (with reflexive adrenocorticotrophic hormone [ACTH] levels if cortisol <LLN) and dehydroepiandrosterone sulfate (DHEAS).
- Pituitary hormones: luteinizing hormone (LH) and follicle-stimulating hormone (FSH).
- Gonadal hormones: testosterone (male) and estradiol (females).
- Fat soluble vitamins: A (retinol), D (25 hydroxy vitamin D), E (alpha-tocopherol), and K (phylloquinone).
- 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.
- Urinalysis: macroscopy will be performed at the central lab. If abnormal, then a standard microscope assessment will be conducted.

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 H.

Serum samples for assessment of alirocumab concentration will be obtained periodically throughout the study as per schedule note in study flowchart of Section 1.3. Blood samples should be collected before IMP injection. 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 1.3. If a new clinically significant abnormality or worsening from baseline is detected after randomization, then an AE should be reported and the patient should be considered for further clinical investigations and/or specialist consultation as per the Investigator's medical judgment.

Blood pressure (BP)/heart rate:

BP should be measured in sitting position under standardized conditions, 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 e-CRF; both systolic BP and diastolic BP should be recorded. At the first screening visit, BP should be measured in both arms. The arm with the highest diastolic pressure will be determined at this visit, and BP should be measured on this arm throughout the study. This highest value will be recorded in the e-CRF.

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

Cogstate battery test:

The Cogstate battery test (30) will include a detection test, identification test, one card learning test, and Groton maze learning test. These individual tests assess maturing cognition across a broad number of key developmental functions such as processing speed, attention, visual learning and executive functioning, respectively. Details of the Cogstate battery test are provided in Appendix C. Briefly, the battery of tests is administered by trained clinical site personnel and will take the patient approximately 16 to 19 minutes to complete. It will be administered electronically and is standardized. The results will be automatically calculated. The results will not be used for detection of adverse events and will not trigger further consultation or investigation.

Tanner stages:

The Tanner stages (31, 32) should be measured by the Investigator at the time points indicated in the study schedule flowchart Section 1.3. Tanner stages are provided in Appendix B. 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.

Flow mediated dilatation assessment:

Will be conducted in a subset of population as part of a sub-study (see Appendix E).

10.1 VISIT SCHEDULE

The visit schedule and procedures/assessments are listed in the study flow chart in Section 1.3.

The aim of this section is to provide details on how some of the procedures/assessments have to be performed. The study consists of 12 on-site visits and 2 telephonic visits.

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

The run-in and screening periods will take place up to 6 weeks (+2 days) or 42 (+2) days (and as short as possible, upon receipt of laboratory eligibility criteria) prior to randomization/ Day 1 visit, and may include more than one site visit for patients for whom not all screening procedures can be done at the first visit.

For patients who consent to participate in the study, but who do not have a stable background LMT [optimal statin dose ± other LMTs or non-statin LMTs if statin intolerant] for at least 4 weeks and/or patients suspected of being heFH but without a confirmed diagnosis and consenting to undergo the centralized genotyping, a run-in period up to 4 weeks (+2 days) in duration will be allowed.

The screening visit can take place up to 14 (+5) days before the randomization visit for patients with a stable LMT background therapy [optimal statin dosing ± other LMT] for at least 4 weeks prior to the screening visit and confirmed diagnosis of heFH. Not all screening assessments and procedures need to be done at the same 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) for at least 4 weeks.

10.1.1 Run-in period (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. It is not authorized to select patients who will be treated with statin de novo to avoid the potential for multiple titration steps during the run-in period. The run-in period is up to 4 weeks (+2 days) in duration.

Another possible situation requiring the run-in period include patients with suspected heFH but without confirmation by previous genetic testing and not meeting Simon Broome criteria. Such patients will be asked to undergo centralized genetic testing during the run-in period.

Patients who have previously participated in the DFI14223 study and have received alirocumab administration during the open label extension of the DFI14223 study will require a wash-out period of at least 10 weeks between the last injection of alirocumab and the screening lipid assessment at the entry of the screening period.

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 heFH Genotyping Informed Consent from the dedicated section in the main ICF (if needed)
- 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
- Prior medication history (within the previous 12 weeks)
- Physical examination including vital signs (SBP and DBP in sitting position, heart rate in sitting position) in both arms
- Body weight measurement
- Height without shoes
- Tanner stage
- Check of stability of background LMT
- Review of diet
- Collect AEs from this point onward:
  - All AEs and SAEs will be collected from the time of informed consent signature and throughout the study
- heFH genotyping (if needed)
- IRT will be contacted for notification of screening and for patient number allocation

10.1.2 Screening period (Up to Week -2)

The duration of the screening period is up to 2 weeks from Visit 2 (Week -2) to Visit 4 (Week 0) which has a window of 14 + 5 days.

Patients will be screened at Visit 2. All laboratory tests measured at central laboratory needed for checking the exclusion criteria of the patients will be performed during the screening period. Patients who meet the inclusion criteria and who have no exclusion criteria, as noted in Section 7.1 and Section 7.2, will be randomized at Visit 4 (Week 0) after the injection training visit (unless deemed not needed). The IRT will be contacted at Visit 1 for notification of screening and for patient number allocation.

10.1.2.1 Visit 2 (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 1.3 and for detailed description of assessments Section 9 and Section 10.6.

The following procedures/assessments will be performed at Visit 2 (Week -2):

- 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
- If not collected before:
  - 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
  - Prior medication history (within the previous 12 weeks)
  - Physical examination including vital signs (systolic blood pressure [SBP] and diastolic blood pressure [DBP] in sitting position, heart rate in sitting position).
  - Body weight measurement
  - Height without shoes
  - Tanner stage
  - Review of diet
- Check of stability of background LMT
- Collect AEs
- Vital signs
- Fasting blood sampling for:
  - Total-C, LDL-C, HDL-C, TG, non-HDL-C
  - Hematology and chemistry
  - HbA1c
  - Creatine phosphokinase
  - Liver panel
  - Pregnancy test

10.1.2.2 Visit 3 (Week -1, injection training)

An intermediate visit for injection training may occur during which the patient (if aged 12 years and above or another designated person such as parent, etc) will be trained to self-inject/inject with placebo for alirocumab after the eligibility criteria have been checked and it is confirmed that the patient will likely be randomized. Prior to the injection, a local topical anesthetic may be utilized as per the Investigator recommendation. Investigators will have the option of providing a second placebo kit for alirocumab for patients/parents who require additional injection training prior to randomization. Please note that this visit (injection training visit) 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 (Week -1):

- IRT contact
- Check of stability of background LMT
- Collect AEs

10.1.3 Twenty-four-week double-blind treatment period

The double-blind treatment period is 24 weeks in duration. Patients will be blinded to study treatment (alirocumab or placebo).

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

The laboratory measurement of lipid parameters will be performed by a central lab. Local lab testing for lipid parameters is generally prohibited after randomization of the patient. The specific results of the central lab testing for lipid parameters from samples obtained after randomization and during the double-blind treatment period will not be communicated to the sites or the Sponsor's EFC14643 study team. Instead, the central lab will inform sites of triglyceride alert (if patients exceed the triglyceride threshold of 500 mg/dL [5.65 mmol/L]). Additionally, the site may receive alert related to LDL-C <50 mg/dL (1.30 mmol/L) based on safety concerns by the independent physician who will carefully monitor the patient's LDL-C values during the double-blind treatment period under the auspices of the DMC. The independent physician is external to the EFC14643 study team and not part of any alirocumab activities.

Statin and other LMT (if applicable) should be stable during double-blind treatment period barring exceptional circumstances whereby overriding concerns (including but not limited to triglyceride alert posted by the central lab) warrant such changes, as per the Investigator's judgment. Patients will be instructed to follow a diet to treat their hypercholesterolemia in accordance with local guidelines or local practice and they should be on this diet throughout the entire study duration from screening.

A flow mediated dilatation exploratory sub-study will be conducted in a sub-set of the study population. The details are provided in Appendix E.

10.1.3.1 Visit 4 (Week 0, randomization)

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

- Assessment of inclusion/exclusion criteria
- Body weight
- IRT contact
- Randomization
- Concomitant medication recording
- Check of stability of background LMT
- Review of diet
- Collect AEs
- Vital signs
- Cogstate battery practice test
- Cogstate battery test
- Fasting blood sampling for:
  - Total-C, LDL-C, HDL-C, TG, non-HDL-C
  - Apo B, Apo A-1, ratio Apo B/Apo A-1, and Lp(a)
  - Hs-CRP
  - CPK-MB, troponin
  - Adrenal gland hormones
  - Gonadal and pituitary hormones
  - Fat soluble vitamins
  - Anti-alirocumab antibodies (ADA)
  - Serum alirocumab concentration (Pharmacokinetics)
- Injection training (optional)
- Urinalysis
- Pregnancy test
- Double-blind IMP kit dispensation
- IMP administration patients will remain under observation at the site for 30 minutes post-injection
- Flow mediated dilatation assessment only for patient included in the sub-study.

Injection training: Further injection training can be provided at the randomization visit Week 0/Day 1 when the patient/parent or a trained designated person injects the first IMP from

the double-blind study treatment kit allocated by IRT. Additional training can be offered at scheduled or unscheduled visits with the scheduled double-blind treatment, as per patient/parent or Investigator's judgment.

10.1.3.2 Visit 5 (Week 8, Day 56 ±7)

The following procedures/assessments will be performed at Visit 5.

- Compliance check of IMP and data collection on IMP administration
- Concomitant medication recording
- Check of stability of background LMT
- Collect AEs
- Fasting blood sampling for:
  - Total-C, LDL-C, HDL-C, TG, non-HDL-C
  - Serum alirocumab concentration (Pharmacokinetics)
- IMP administration.

10.1.3.3 Visit 6 (Week 12, Day 84 ±7)

The following procedures/assessments will be performed at Visit 6.

- Body weight
- IRT contact
- 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
- Fasting blood sampling for:
  - Total-C, LDL-C, HDL-C, TG, non-HDL-C
  - Apo B, Apo A-1, ratio Apo B/Apo A-1, and Lp(a)
  - Hematology and chemistry
  - Creatine phosphokinase
  - Liver panel
  - Anti-alirocumab antibodies (ADA)
  - Serum alirocumab concentration (Pharmacokinetics)

- Double-blind IMP kit dispensation
- IMP administration.

10.1.3.4 Visit 7 (Week 24, Day 168 ±3, end of double-blind treatment period)

The following procedures/assessments will be performed at Visit 7.

- Physical examination including vital signs (systolic blood pressure [SBP] and diastolic blood pressure [DBP] in sitting position, heart rate in sitting position)
- Body weight
- Height without shoes
- Tanner stage
- Compliance check of IMP and data collection on IMP administration
- Concomitant medication recording
- Check of stability of background LMT
- Review of diet
- Collect AEs
- Cogstate battery test
- Fasting blood sampling for:
  - Total-C, LDL-C, HDL-C, TG, non-HDL-C
  - Apo B, Apo A-1, ratio Apo B/Apo A-1, and Lp(a)
  - Hematology and chemistry
  - HbA_{1c}
  - Creatine phosphokinase
  - Liver panel
  - Hs-CRP
  - CPK-MB, troponin
  - Adrenal gland hormones
  - Gonadal and pituitary hormones
  - Fat soluble vitamins
  - Anti-alirocumab antibodies (ADA)
  - Serum alirocumab concentration (Pharmacokinetics)
- Urinalysis
- Pregnancy test

- IRT contact to document end of double-blind treatment for patient not continuing in the open label part
- Flow mediated dilatation assessment only for patient included in the sub-study.

In addition, for patients continuing into the open label part, the following procedures/assessments will be performed:

- IRT contact
- Open label IMP kit dispensation
- IMP administration

10.1.4 Eighty-week open label treatment period

After patients successfully complete the 24-week double-blind treatment period, they can enter the open label treatment period which consists of 80 weeks of open label alirocumab.

The first open label alirocumab injection will be done at the site followed by monitoring of the patient for at least 30 minutes. The patient's regimen will be a continuation of their regimen from the double-blind treatment period. The dose of alirocumab may be adjusted based on patients body weight (ie, patients who previously were with BW <50 kg can be dose adjusted if their weight is ≥50 kg) at each study visit starting from the first visit (ie, Week 24) of the open label treatment period. For patients whose weight varies close to 50 kg the dose will be adjusted only once at the onset of the open label treatment period.

The lipid levels will be communicated to the Investigator during the open label treatment period from the second visit (ie, Week 32) onwards. The Investigator will be responsible, based on his/her own judgment related to the patients' LDL-C levels and the safety profile, to up-titrate, down-titrate, maintain the dose of alirocumab or discontinue throughout the study. The statin dose should not be decreased to adjust to the degree of LDL-C lowering and should not be increased; unless otherwise indicated. Other LMT (if applicable) can be modified based on the Investigator's judgment throughout the study. Further recommendations for the management and monitoring of patients who achieve LDL-C levels <50 mg/dL (1.30 mmol/L) on one or more occasion are provided in the protocol.

10.1.4.1 Visit 8 (Week 32, Day 224 ±7)

The following procedures/assessments will be performed at Visit 8:

- Body weight
- IRT contact
- 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
- Fasting blood sampling for:
  - Total-C, LDL-C, HDL-C, TG, non-HDL-C
  - Hematology and chemistry
  - Creatine phosphokinase
  - Liver panel
- Pregnancy test
- Open label IMP kit dispensation
- IMP administration

10.1.4.2 Visit 9 (Week 44, Day 308 ±7)

The following procedures/assessments will be performed at Visit 9:

- Physical examination including vital signs (systolic blood pressure [SBP] and diastolic blood pressure [DBP] in sitting position, heart rate in sitting position).
- Body weight
- Height without shoes
- Tanner stage
- IRT contact
- 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
- Fasting blood sampling for:
  - Total-C, LDL-C, HDL-C, TG, non-HDL-C
  - Hematology and chemistry
  - Creatine phosphokinase (CPK)
  - Liver panel
  - Adrenal gland hormones

- Gonadal and pituitary hormones
- Fat soluble vitamins

- Pregnancy test
- Open label IMP kit dispensation
- IMP administration

10.1.4.3 Visit 10 (Week 56, Day 392 ±7, telephone contact)

The following procedures/assessments will be performed remotely at Visit 10:

- IRT contact
- Open label IMP kit delivery DTP (if applicable)
- Concomitant medication recording
- Check of stability of background LMT
- Review of diet
- Collect AEs
- IMP administration

10.1.4.4 Visit 11 (Week 68, Day 476 ±7)

The following procedures/assessments will be performed at Visit 11:

- Physical examination including vital signs (systolic blood pressure [SBP] and diastolic blood pressure [DBP] in sitting position, heart rate in sitting position).
- Body weight
- Height without shoes
- Tanner stage
- IRT contact
- 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
- Cogstate battery test
- Fasting blood sampling for:

- Total-C, LDL-C, HDL-C, TG, non-HDL-C
- Hematology and chemistry
- HbA_{1c}
- Creatine phosphokinase
- Liver panel
- Adrenal gland hormones
- Gonadal and pituitary hormones
- Fat soluble vitamins
- Anti-alirocumab antibodies (ADA)

- Pregnancy test
- Open label IMP kit dispensation
- IMP administration

10.1.4.5 Visit 12 (Week 80, Day 560 ±7, telephone contact)

The following procedures/assessments will be performed remotely at Visit 12:

- IRT contact
- Open label IMP kit delivery (DTP) (if applicable)
- Concomitant medication recording
- Check of stability of background LMT
- Review of diet
- Collect AEs
- IMP administration

10.1.4.6 Visit 13 (Week 92, Day 644 ±7)

The following procedures/assessments will be performed at Visit 13:

- Body weight measurement
- IRT contact
- Compliance check of IMP and data collection on IMP administration
- Open label IMP kit dispensation
- Concomitant medication recording
- Check of stability of background LMT
- Review of diet

- Collect AEs
- Pregnancy test
- IMP administration

10.1.4.7 Visit 14, End of Treatment (Week 104, Day 728 ±7)

The following procedures/assessments will be performed at Visit 14:

- Physical examination including vital signs (systolic blood pressure [SBP] and diastolic blood pressure [DBP] in sitting position, heart rate in sitting position)
- Body weight
- Height without shoes
- Tanner stage
- 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
- Cogstate battery test
- Fasting blood sampling for:
  - Apo B, Apo A-1, ratio Apo B/Apo A-1, and Lp(a)
  - Total-C, LDL-C, HDL-C, TG, non-HDL-C
  - Hematology and chemistry
  - HbA_{1c}
  - Creatine phosphokinase (CPK)
  - Liver panel
  - Adrenal gland hormones
  - Gonadal and pituitary hormones
  - Fat soluble vitamins
  - Anti-alirocumab antibodies (ADA)
- Pregnancy test
- IRT contact to document end of open label treatment

10.2 DEFINITION OF SOURCE DATA

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

- Agreement, date, and signature of informed consent mentioning the study identification.
- Patient identification, last participation in a clinical trial, medical history, associated diseases, and data related to the studied pathology.
- Contraception methods for females of childbearing potential who are sexually active.
- Previous and concomitant medication (including the lipid modifying therapy).
- Study identification.
- Treatment number, dates of administration.
- Dates of visits and assessments including the examination report.
- Vital signs, height, body weight, Tanner stage.
- Faxed central lab reports (dated and signed by the Principal Investigator or Sub-Investigator).
- IRT confirmation fax (run-in, screening, screen failure, randomization, treatment (re)allocation, discontinuation, end of double-blind treatment period, end of open label treatment period, dose change alert).
- 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 e-CRF. In any case, the patient should remain in the study as long as possible.

Pregnancy will lead to definitive treatment discontinuation in all cases.

10.3.1 Temporary treatment discontinuation with investigational medicinal product(s)

Temporary treatment discontinuation (also referred to as treatment interruption) may be considered by the Investigator because of suspected AEs. Reinitiating 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 in the occurrence of the concerned event was unlikely and if the selection criteria for the study are still met (refer to Section 7.1 and Section 7.2). All treatment interruption duration must be recorded by the Investigator in the appropriate e-CRF screens when considered as confirmed.

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

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 reasons for treatment discontinuation and this should be documented in the e-CRF.

Patients should discontinue the IMP for the following reasons:

- Pregnancy, intention for pregnancy, or no longer with effective contraceptive method of birth control (females of childbearing potential who are sexually active only).
- Acute injection reaction of clinical concern.
- Serious adverse event (or non-serious but severe in intensity) of hypersensitivity 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.
- Patient receives treatment prior to randomization.

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

Any code-breaking requested by the Investigator will lead to permanent treatment discontinuation.

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

10.3.4 Handling of patients after permanent treatment discontinuation

In case of permanent treatment discontinuation, the recommendation is to limit the collection to critical data, ie, primary endpoint/main secondary endpoint and safety endpoints.

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

Premature treatment discontinuation during the double-blind treatment period:

- At the time of treatment discontinuation, the patient should have, as soon as possible, an unscheduled visit with assessments normally planned at end of treatment period visit including lipids, PK and ADA.
- Week 24 visit, as described in Section 1.3, should be performed regardless of timing of the last alirocumab injection, including for patients included and not treated.

All efforts should be done to perform these assessments.

Premature treatment discontinuation during the open label treatment period:

- At the time of treatment discontinuation, the patient should have, as soon as possible, an unscheduled visit with assessments normally planned at end of open label treatment period visit including lipids and ADA.
- Week 104 visit, as described in Section 1.3, should be performed regardless of timing of the last alirocumab injection.

Whatever the period of premature treatment discontinuation, the patient, at a minimum, should be followed up for recovery or stabilization of any AE as specified in this protocol.

All definitive discontinuation of study treatment should be recorded by the Investigator in the appropriate screens of the e-CRF and in the patient's medical records when considered as "confirmed". IRT should be notified when a patient prematurely discontinues study treatment.

10.3.5 Procedure and consequence for patient withdrawal from study

The patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason 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 e-CRF 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 re-included (treated) in the study. Their randomization and treatment number must not be reused.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

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

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 adverse event of special interest (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. Adverse events of special interest may be added, modified or removed during a study by protocol amendment.

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

The following AEs are considered as AESIs in the study:

- ALT >3 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 H 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 e-CRF 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 e-CRF screen (see Section 10.6.2)
- Pregnancy:
  - Pregnancy occurring in a female patient or the partner of a male patient included in the clinical trial. Pregnancy will be recorded as a pre-specified AESI with immediate notification in all cases. It will be qualified as an SAE only if it fulfills the SAE criteria,
  - In the event of pregnancy of a female patient included in the trial, IMP should be discontinued,
  - The follow-up of the pregnancy in a female participant or in a female partner of a male participant will be mandatory until the outcome has been determined.
- Symptomatic Overdose with IMP alirocumab:
  - 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 e-CRF 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,

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

10.4.1.4 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 e-CRF 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 e-CRF 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 e-CRF.

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

Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP.

Laboratory, vital signs are to be recorded as AEs only if:

- Symptomatic and/or
- Requiring either corrective treatment or consultation, and/or
- Leading to IMP discontinuation or modification of dosing, and/or
- Fulfilling a seriousness criterion, and/or
- Defined as an AE of special interest with immediate notification.

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.

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

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 e-CRF; the system will automatically send the notification to the Monitoring Team and Pharmacovigilance after approval of the Investigator within the e-CRF or after a standard delay.
- It is not acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor's representative in lieu of completion of the AE/SAE CRF page. There may be instances when copies of medical records for certain cases are requested by the Sponsor's representative. In such case, 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 source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the e-CRF as appropriate. In addition, any effort should be made to further document each Serious AE that is fatal or life threatening within the week (7 days) following initial notification.
- A backup plan will be used (using paper flow) when the e-CRF system does not work.

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

10.4.5 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 e-CRF. Instructions for AE reporting are summarized in Table 2 and in Appendix F.

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 H.

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

- Neutropenia
- Thrombocytopenia
- Acute renal insufficiency
- Increase in ALT
- 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 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	Yes
		Neurocognitive events	Yes	Yes	Yes

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.

Non investigational medicinal product 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 (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 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 e-CRF screens are to be filled in to assess allergic adverse events or allergic-like AE that may occur during the clinical studies conducted with alirocumab.

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

Adverse events that may constitute an allergic reaction (eg, generalized itch, nasal itch, swelling at injection site, flushing, hives, swelling at lips, eyes, face, tongue, hands, feet, lump in throat, difficulty to swallow, hoarseness, change in pitch of voice, incapacity to speak, wheezing, chest tightness, stridor, etc) should be documented on the General Allergic adverse event 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 adverse event 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 one week of the site first becoming aware of the event.

The Investigator should evaluate the patient for possible etiologies (new medications, etc) and extracutaneous symptoms and signs. An unscheduled 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 adverse event that occurs during or shortly after injection of the IMP (characterized by but not limited to hypotension, bronchoconstriction, urticaria, edema, angioedema, nausea, vomiting). Emergency equipment and medication for the treatment of these potential adverse effects (eg, antihistamines, bronchodilators, IV saline, corticosteroids, acetaminophen, and epinephrine) must be available for immediate use for the injections at the site visits.

Patients will be observed at the investigational site for at least 30 minutes following the injection that takes place at the randomization visit. Patients should be treated symptomatically if any AEs are observed. Patients are to remain 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.

10.6.2.3 Independent physician monitoring for patients reaching LDL-C levels <50 mg/dL (1.30 mmol/L) during the double-blind treatment period and recommendations for the Investigator in case of an alert

An independent physician, that is external to the EFC14643 clinical trial team, will be notified by the central laboratory of LDL-C values reaching <50 mg/dL (1.30 mmol/L). The independent physician will have access to patient information during the double-blind treatment period that the Sponsor's EFC14643 study team will not have any access to. The independent physician will get central laboratory results. The independent physician will review the case in detail including unmasked LDL-C values and patient safety data. Based upon the clinical judgment of the independent physician, and after consulting with the DMC, the central laboratory may be instructed to send a site alert for corresponding patient. If no site alert is deemed needed, then the independent physician will continue to closely monitor the patient's data throughout the double-blind treatment period and may consider instructing the central lab to issue an alert at any time after discussions with the DMC. Further details of this monitoring and responsibilities will be thoroughly described in the independent physician related documents and the DMC charter.

If the site receives an alert, the Investigator should follow the recommend steps as outlined below:

- Call the patient as soon as possible to inquire about interval occurrence of AEs, particularly any AEs related to visual problems.

- 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 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 study treatment temporary or permanent discontinuation, or continuation. Regardless of the action taken regarding study treatment, the patient should continue the study,
  - Assess the need to have blood drawn from the patient for adrenal gland hormones, gonadal hormones, pituitary hormones, and fat soluble vitamins if not planned per protocol at this visit.

10.6.2.4 Recommendations for managing and monitoring patients with very low LDL-C levels (ie, LDL-C<50 mg/dL [1.30 mmol/L]) during the open label treatment period

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

- Call the patient/parent as soon as possible to inquire about interval occurrence of AEs, particularly any AEs related to visual problems.
- 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, or maintenance of the dose or down-titration (if possible) of the dose.
  - Assess the need to have blood drawn from the patient for adrenal gland hormones, gonadal hormones, pituitary hormones, and fat soluble vitamins if not planned per protocol at this visit.

10.7 ADVERSE EVENTS MONITORING

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

11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

Each alirocumab dosing regimen group will be compared to its contemporaneously randomized placebo group (ie, of the same dosing regimen cohort) as follows:

- alirocumab Q2W versus placebo Q2W
- alirocumab Q4W versus placebo Q4W.

Of note, Q2W and Q4W refer to the dosing regimens initiated at randomization.

Multiplicity will be controlled using Bonferroni adjustment, hence using a two-sided alpha level of 0.025 for each comparison.

With a randomization ratio of 2:1 (alirocumab: placebo) for each dosing regimen cohort, a total sample size of 90 patients (30 in each alirocumab dosing regimen group and 15 in each placebo dosing regimen group) will have 92% power to detect a difference in mean percent change in LDL-C of 30% between each alirocumab dosing regimen group and its contemporaneously randomized placebo dosing regimen group, with a 0.025 two-sided significance level per comparison and assuming a common standard deviation (SD) of 25%.

Nevertheless, to have a sufficient number of pediatric patients for properly assessing the safety and tolerability of alirocumab, sample size was increased to 150 patients in total (50 in each alirocumab dosing regimen group and 25 in each placebo dosing regimen group). The enrollment of 150 patients will allow having a safety assessment over 2 years in approximately 128 patients, assuming a discontinuation rate of 15%.

Calculations were made using nQuery Advisor 7.0.

11.2 DISPOSITION OF PATIENTS

Screened patients are defined as any patient who signed the informed consent.

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

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

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy populations

The primary efficacy analysis population will be the ITT population as defined below.

11.3.1.1 Intent-to-treat population

The ITT population is defined as all randomized patients.

Patients in the ITT population will be analyzed according to the treatment group allocated by randomization (ie, as-randomized treatment).

11.3.1.2 Modified intent-to-treat population

The mITT population is defined as all randomized patients who actually received at least one dose or partial dose of double-blind Investigational Medicinal Product (IMP).

Patients in the mITT population will be analyzed according to the treatment group allocated by randomization.

11.3.2 Safety population

The safety analysis will be performed on the safety population. The safety population consists of the randomized population who did actually receive at least one dose or partial dose of investigational product.

Patients in the safety population will be analyzed according to the treatment actually received.

In addition:

- Nonrandomized but treated patients will not be part of the safety population, but their safety data will be presented separately.
- Randomized patients for whom it is unclear whether they took the study medication will be included in the safety population as randomized.
- For patients receiving more than 1 study treatment during the trial, the treatment group allocation for as-treated analysis will be the one to which the patient was treated with the longest duration.

11.3.3 Other analysis population

The anti-alirocumab antibody 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 double-blind IMP injection.

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

The analysis of the open label extension (OLE) data will be performed on the OLE population defined as patients who did actually receive at least one dose or partial dose of investigational product during the open label treatment period.

11.4 STATISTICAL METHODS

This section describes the statistical methods for the analysis of the double-blind treatment period. The statistical methods for the analysis of the open label treatment period will be described in the statistical analysis plan (SAP).

11.4.1 Extent of study treatment exposure and compliance

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

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:
  - For the Q2W dosing regimen cohort: (last dose of double-blind IMP injection date - first dose of double-blind IMP injection date + 14 days)/7, regardless of unplanned intermittent discontinuations.
  - For the Q4W dosing regimen cohort: (last dose of double-blind IMP injection date - first dose of double-blind IMP injection date + 28 days for patients who stopped definitively the IMP before the switch to Q2W regimen at Week 12 (actual or sham), +14 days otherwise)/7, regardless of unplanned intermittent discontinuations.
- The total number of injections by patient.

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

11.4.1.2 Compliance

Compliance will be assessed using the following parameters:

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

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

11.4.2 Analyses of efficacy endpoints

In the double-blind period, statistical analyses for the primary and secondary efficacy endpoints will compare each alirocumab dosing regimen group versus its contemporaneously randomized placebo group (ie, of the same dosing regimen cohort) as follows:

- alirocumab Q2W versus placebo Q2W
- alirocumab Q4W versus placebo Q4W

Of note, Q2W and Q4W refer to the dosing regimens initiated at randomization.

Efficacy endpoints analyzed with the ITT estimand will be analyzed in the ITT population. Efficacy endpoints analyzed with the on-treatment estimand will be analyzed in the mITT population.

Analyses of the efficacy parameters during the extension period will be only descriptive.

11.4.2.1 Analysis of primary efficacy endpoint(s)

The percent change from baseline in LDL-C (see Section 9.1) to Week 24 will be analyzed using a MMRM model within each dosing regimen cohort. All post-baseline data available within Week 8 to Week 24 analysis windows will be used and missing data will be accounted for by the MMRM model.

For the Q2W dosing regimen cohort, the model will include the fixed categorical effects of treatment group (alirocumab, placebo), randomization strata (previous participation [yes or no] to DFI14223 study, baseline body weight [<50 or ≥50 kg]), time point (Week 8, Week 12, Week 24), treatment-by-time point interaction, and strata-by-time point interaction, as well as the continuous fixed covariates of baseline LDL-C value and baseline value-by-time point interaction.

The same model will be run for the Q4W dosing regimen cohort except that strata related to the previous participation in the DFI14223 Phase 2 study will not be included in the model, as too few patients from this Phase 2 study are enrolled in the Q4W dosing regimen cohort due to the late start of enrollment in this cohort.

Model assumptions for normality will be explored prior to the analysis testing.

These two models 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 models, least-square (LS) mean and standard error (SE) at Week 24 will be provided for each treatment group within each dosing regimen cohort and LS means difference will be provided for the comparison of each alirocumab dosing regimen group versus its contemporaneously randomized placebo group (ie, of the same dosing regimen cohort), with the SE, 97.5% confidence interval (CI) and p-value, using appropriate contrasts.

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 (example: percent change in LDL-C), continuous measurements expected to have a non-normal distribution (example: TG), and binary measurements (example: proportion of patients achieving a LDL-C <130 mg/dL).

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 within each dosing regimen cohort, using the same MMRM models 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 models within each dosing regimen cohort, but only including on-treatment values. The treatment period is defined as:

- For the Q2W dosing regimen cohort, the time period from the first double-blind IMP injection up to the day of last double-blind IMP injection +21 days.
- For the Q4W dosing regimen cohort, the time period from the first double-blind IMP injection up to the day of last double-blind IMP injection +35 days for patients who stopped definitively the IMP before the switch to Q2W regimen at Week 12 (actual or sham), +21 days otherwise.

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).

For the Q2W dosing regimen cohort, the model will include treatment group (alirocumab, placebo) and randomization strata (previous participation [yes or no] to Phase 2 DFI14223 study, baseline body weight [<50 or ≥50 kg]) as main effects and corresponding baseline value as covariate.

For the Q4W dosing regimen cohort, the model will include treatment group and randomization strata (baseline body weight [<50 or ≥50 kg]) as main effects and corresponding baseline value as covariate.

Missing values will be addressed using a multiple imputation approach, which will be described in the SAP. The imputation model will at least include the variables included in the robust

regression model. The treatment group combined means will be provided with respective SE estimates. The combined mean difference between the treatment groups will be provided with the SE, 97.5% CI and p-value.

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 within each dosing regimen cohort but only including on-treatment values in these models.

Binary endpoints

Binary secondary efficacy endpoints analyzed with the ITT estimand will be analyzed using stratified logistic regression.

For the Q2W dosing regimen cohort, the model will include treatment group (alirocumab, placebo) as main effect and corresponding baseline value as covariate, stratified by randomization factors (previous participation [yes or no] to DFI14223 study, baseline body weight [<50 or ≥50 kg]).

For the Q4W dosing regimen cohort, the model will include treatment group (alirocumab, placebo) as main effect and corresponding baseline value as covariate, stratified by randomization factor (baseline body weight [<50 or ≥50 kg]).

Missing values will be addressed using a multiple imputation approach which will be described in the SAP. The imputation model will at least include the variables included in the logistic regression model. Treatment effects (within each dosing regimen cohort) will be compared and the combined odds ratio estimate between the treatment groups, with their corresponding 97.5% CIs and p-value will be provided.

In the data dependent case that the logistic regression method is not applicable (eg, the response rate is zero in 1 treatment group and thus the maximum likelihood estimate may not exist), the Last Observation Carried Forward (LOCF) approach would be used for handling of missing values and a stratified exact conditional logistic regression would be performed to compare treatment effects.

Binary secondary efficacy endpoints analyzed with the on-treatment estimand will be analyzed using the same imputation and analysis models within each dosing regimen cohort but only including on-treatment values in these models.

In addition, the difference in terms of percent change from baseline in LDL-C between the 2 alirocumab dosing regimen groups will be explored.

Analyses of the efficacy parameters during the extension period will be only descriptive.

11.4.2.3 Multiplicity considerations

The Bonferroni adjustment will be applied to handle multiplicity for the comparison of each alirocumab dosing regimen group versus its contemporaneously randomized placebo group

(ie, alirocumab Q4W versus placebo Q4W and alirocumab Q2W versus placebo Q2W) for the primary efficacy endpoint (0.025 two-sided alpha level will apply for each comparison).

In order to handle multiple key secondary endpoints, the overall Type-I error will be controlled by the use of a sequential inferential approach applied independently within each dosing regimen cohort (Q2W and Q4W). Statistical significance of the primary parameter at the 2-sided 0.025 alpha level is required before drawing inferential conclusions for that dosing regimen cohort about first key secondary parameter (refer to order of list in Section 9.2.1). Inferential conclusions about successive key secondary parameters for a given dosing regimen cohort require statistical significance of the prior one in that dosing regimen cohort.

The Bonferroni adjustment and this fixed hierarchical approach will ensure a strong control of the overall Type-I error rate for the study at the 0.05 level.

No further adjustments will be made for other secondary endpoints for which p-values will be provided for descriptive purpose only (no claim).

11.4.3 Analyses of safety data

The summary of safety results (see Section 9.2.4) will be presented by treatment group (placebo, alirocumab) within each dosing regimen cohort, and by treatment group regardless of the dosing regimen cohorts (pooled across the cohorts). 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 double-blind 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.
- 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:
  - For the Q2W dosing regimen cohort, as the time from first dose of double-blind IMP injection to the last dose of double-blind IMP injection +21 days.
  - For the Q4W dosing regimen cohort, as the time from first dose of double-blind IMP injection to the last dose of double-blind IMP injection +35 days for patients who stopped definitively the IMP before the switch to Q2W regimen at Week 12 (actual or sham), +21 days otherwise

Adverse event (AE) definition:

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

Drug-induced liver injury

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

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

11.4.3.1 Adverse events

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

Adverse event incidence table will be provided by treatment group for all types of TEAEs: all TEAEs, all treatment-emergent AESI 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, post-study) summarized on the safety population by treatment received.
- Death in non-randomized patients or randomized and not treated patients.
- TEAE leading to death (death as an outcome on the AE CRF page as reported by the Investigator) by primary SOC, HLGT, HLT and PT showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT.

11.4.3.2 Laboratory data and vital signs

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

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

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

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

High-sensitivity-CRP (value and percent change from baseline) at Week 24 will be summarized on the safety population using number of available data, mean, SD, median, Q1, Q3, minimum, and maximum for each treatment group. In addition, the incidence of PCSA at any time during the TEAE period will be summarized by treatment group using descriptive statistics.

Further details on the analyses of laboratory parameters will be provided in SAP.

11.4.3.3 Cogstate battery test

Cognitive scores (including by domains: Detection Test [DET; Psychomotor Function], Identification Test [IDN; Attention]; One Card Learning Test [OCL; Visual Learning]; Groton Maze Learning Task [GML; Executive Function]) will be described by treatment group on the safety population.

11.4.4 Other endpoints

The summary of other endpoints (for definitions see Section 9.3) will be presented by treatment group (placebo, alirocumab) within each dosing regimen cohort. A summary by treatment group regardless of the dosing regimen cohorts (pooled across the cohorts) will be also displayed, except for pharmacokinetics and anti-alirocumab antibody assessments.

11.4.4.1 Pharmacokinetics

Serum total alirocumab concentrations, total and free PCSK9 concentrations will be summarized by treatment group and visit using descriptive statistics. Serum concentration time profiles will be provided by treatment group. 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 treatment group and visit using descriptive statistics. If appropriate, correlations between antibody titers, safety and/or efficacy endpoints will be provided.

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

The number and percentage of patients with two 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 (1.30 mmol/L) respectively, will be provided by treatment group.

Further details will be provided in SAP.

11.4.4.4 Urinalysis

The proportion of patients with at least one finding of proteinuria, hematuria or an abnormality on urine microscopy during the TEAE period will be summarized by treatment group using descriptive statistics.

11.4.4.5 CPK-MB and troponin

CPK-MB and troponin (value and percent change from baseline) at Week 24 will be summarized on the safety population using number of available data, mean, SD, median, Q1, Q3, minimum, and maximum for each treatment group. In addition, the incidence of PCSA at any time during the TEAE period will be summarized by treatment group using descriptive statistics.

11.5 TWO-STEP ANALYSIS

The analyses will be conducted in 2 steps (see details in Section 6.3). The first analysis would not be conducted before completion of the double-blind treatment period.

Since the double-blind primary and key secondary efficacy analyses will have been concluded at the time of the first analysis, the overall significance level remains at 0.05 for the study.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

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

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

12.2 INFORMED CONSENT

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

Prior to a patient’s participation in the clinical trial, the 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 Ethics Committee (IRB/IEC) approved standard practice for pediatric participants at each participating center (age of assent to be determined by the IRB’s/IEC’s or be consistent with the local requirements):

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

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

Prior to collection of blood for genotyping for heFH 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.

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

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

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

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

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the health authorities (competent regulatory authority), as required by local regulation, in addition to the IRB/IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the health authorities (competent regulatory authority) and the IRB/IEC should be informed as soon as possible. They should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the Investigator's Brochure 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 e-CRF, Discrepancy Resolution Form [DRF] or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

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

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

13.2 RESPONSIBILITIES OF THE SPONSOR

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

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

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.

13.3 SOURCE DOCUMENT REQUIREMENTS

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

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

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

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

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

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

13.5 USE OF COMPUTERIZED SYSTEMS

The complete list of computerized systems used for the study is provided in a separate document which is maintained in the Sponsor trial master file.

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

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

14.2 RECORD RETENTION IN STUDY SITES

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

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

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

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

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

14.3 CONFIDENTIALITY

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

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

The Sub-Investigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Sub-Investigators of the confidential nature of the clinical trial.

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

14.4 PROPERTY RIGHTS

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

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

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

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

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

14.5 DATA PROTECTION

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

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

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

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

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

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

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

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

14.8.1 By the Sponsor

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

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

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

14.8.2 By the Investigator

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

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

14.9 CLINICAL TRIAL RESULTS

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

14.10 PUBLICATIONS AND COMMUNICATIONS

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

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

The Investigator shall not use the name(s) of the Sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s). The Sponsor has the right at any time to publish the results of the study.

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

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

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

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

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

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

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17 APPENDICES

Appendix A Simon Broome register diagnostic criteria for heterozygous familial hypercholesterolemia

Definite familial hypercholesterolemia is defined as:

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

PLUS

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

OR

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

Possible familial hypercholesterolemia is defined as:

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

And at least one of the following:

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

Appendix B Tanner stages

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 (1, 2).

- **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.

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Appendix C Cogstate battery test

The Cogstate battery test will include a detection test, identification test, one card learning test, and Groton maze learning test. These individual tests assess maturing cognition across a broad number of key developmental functions such as processing speed, attention, visual learning and executive functioning, respectively. Details of the Cogstate battery test are provided in the description subsection below. Briefly, the battery of tests is administered by trained clinical site personnel and will take the patient approximately 16 to 19 minutes to complete. It will be administered electronically and is standardized. The results will be automatically calculated. The results will not be used for detection of adverse events and will not trigger further consultation or investigation.

Cogstate battery test description:

- Detection (DET; Psychomotor Function)

  The Detection test is a measure of psychomotor function and uses a well-validated simple reaction time paradigm with playing card stimuli. In this test, the playing cards all depict the same joker. The subject is asked to press the **Yes** key as soon as the card in the center of the screen turns face up. The software measures the speed and accuracy of each response.

  Duration of Test: 3 minutes

- Identification (IDN; Attention)

  The Identification test is a measure of visual attention and uses a well-validated choice reaction time paradigm with playing card stimuli. In this test, the playing cards are all either red or black jokers. The subject is asked whether the card displayed in the center of the screen is red. The subject responds by pressing the **Yes** key when the joker card is red and **No** when it is black. The software measures the speed and accuracy of each response.

  Duration of Test: 3 minutes

- One Card Learning (OCL; Visual Learning)

  The One Card Learning test is a measure of visual learning and uses a well-validated pattern separation paradigm with playing card stimuli. In this test, the playing cards are identical to those found in a standard deck of 52 playing cards (without the joker cards). The subject is asked whether the card displayed in the center of the screen was seen previously in this test. The subject responds by pressing the **Yes** or **No** key. The software measures the speed and accuracy of each response.

  Duration of Test: 6 minutes

- The Groton Maze Learning Test (GML; Executive Function)

  The Groton Maze Learning test is a measure of problem solving and reasoning and uses a well-validated maze learning paradigm. In this test, the subject is shown a 10 × 10 grid of boxes on a computer screen. A 28-step pathway is hidden among these 100 possible locations. Each box represents move locations, and the grid refers to the box array (ie, 10 × 10). Subjects are required to find the hidden pathway guided by four search rules. These rules are: do not move diagonally, do not move more than one box (ie, do not jump), do not move back on the pathway, and return to the last correct location after an error. At each step only the most recently selected box is shown. Feedback is given with visual and auditory cues (green check marks and red crosses) to indicate whether the selected box is correct or incorrect. The head of path, or the last correct location, flashes with a green check when two errors are made in succession to indicate to the subject that they must return to this location. There are [20] well-matched alternate pathways available. The software records each move as an error or as a correct move.

  Duration of Test: 7 minutes

Appendix D Guidance on contraceptive methods and collection of pregnancy information

Reproductive potential (WOCBP)

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

CONTRACEPTIVE GUIDANCE

Sexual counseling should be provided to patients when indicated.

Female subjects:

Highly Effective Contraceptive Methods That Are User Dependent

Failure rate of <1% per year when used consistently and correctly[6]

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
  - Oral,
  - Intravaginal,
  - Transdermal.
- Progestogen-only hormone contraception associated with inhibition of ovulation:
  - Oral,
  - Injectable.

Highly Effective Methods That Are User Independent

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).

Sexual abstinence

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

[6] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.

COLLECTION OF PREGNANCY INFORMATION

Female subjects who become pregnant

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

Male subjects with partners of reproductive potential who become pregnant

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

Appendix E Flow mediated dilatation exploratory sub-study of EFC14643 protocol

Protocol Number: Exploratory Sub-study of EFC14643 Protocol: Flow Mediated Dilatation (FMD) Sub-study

SUBSTUDY PROTOCOL ACKNOWLEDGEMENT

I have read this exploratory sub-study of EFC14643 protocol: FMD sub-study, and understand that it and an accompanying additional informed consent must be reviewed by the Institutional Review Board/Ethics Committee overseeing the conduct of the study and approved or given favorable opinion before implementation.

Introduction

The healthy endothelium plays a principal role in keeping arterial homoeostasis. Many of its functions are controlled by the bioavailability of nitric oxide, including inflammation, adhesion, coagulation, smooth muscle cell proliferation, and vasomotion (1). The vascular endothelial layer has anti-atherogenic properties. However, this physiological atheroprotective function of the endothelium can be diminished in the presence of atherosclerotic risk factors and toxic substances and conditions (2). The diminution of endothelial function may play a role in atherogenesis, which may occur before structural and clinical atherosclerosis (3). In addition to being an early event in atherogenesis, endothelial dysfunction is influential in the later stages of atherosclerotic diseases, predisposing individuals to complications, such as thrombotic events. Endothelial dysfunction is characterized by reduced bioavailability of nitric oxide through decreased production and/or increased degradation of nitric oxide. Even with adequate production, nitric oxide may not reach its biological targets (vascular smooth muscle and circulating cells) to exert its effect because of the lack of its bioavailability. In hyperlipidemia, excess LDL synthesis increases the formation of oxidized LDL. The resultant increase of oxidative stress enhances nitric oxide destruction, thereby reducing its biological effects and attenuating endothelium-dependent vasodilation (4).

Flow-mediated dilatation (FMD) measures the vasomotor effects of this modification in the phenotype of the arterial wall and can therefore be used to study the vascular biology of atherosclerosis as it progresses from childhood (5). Over the past several decades, a noninvasive technique has matured to evaluate FMD, an endothelium-dependent function, in the brachial artery. This stimulus incites the endothelium to release nitric oxide (NO) with resultant vasodilation that can be imaged and quantitated as an index of vasomotor function (6). The use of ultrasound to assess FMD is noninvasive, and safe and has been applied in prior clinical trial in a similar setting (7). The test is based on the measurement of the brachial artery diameter at baseline and after an increase in blood flow caused by inflating and then deflating a forearm blood pressure cuff. In this test, the proportional increase in luminal diameter induced by hyperemia is calculated and used as a marker of systemic endothelial function.

In the general population, several risk factors that are associated with CVD such as hypertension, diabetes, hyperlipidemia, hyperhomocysteinemia, inflammation, advanced age, and cigarette smoking have been associated with impairment in FMD prior to vascular disease (8).

Improvement in endothelial function has been noted following statin treatment in adults with coronary artery disease and in asymptomatic patients with cardiovascular risk factors (9). While most factors, which improve endothelial function, have been shown to be of cardiovascular benefit, exceptions include antioxidant supplementation and hormone replacement therapies. These 2 later agents have shown improvement in endothelial function but without corresponding cardiovascular benefit.

The negative effect of cholesterol on endothelial function was initially observed in pediatric patients with heFH from as early as 8 years of age (4). In this study, the degree of endothelial impairment as measured by FMD obtained via high resolution ultrasound correlated with both LDL-C and Lp(a) levels. Other studies have also shown that children with heFH have reduced endothelial function (as measured by FMD) as compared to healthy controls and that the degree of endothelial function was worse in the patients who had a family history of premature CVD (8).

Early simvastatin therapy of 10 to 40 mg daily restores endothelial function in 28 weeks in 9- to 18-year-old children with heFH (10) as measured by FMD of the brachial artery. However, despite this promising result whether an improvement in endothelial function during childhood will translate into decreased risk of future cardiovascular disease is unknown (7).

Primary objective

To explore the effect of alirocumab versus placebo on endothelial function after 24 weeks of treatment in heterozygous familial hypercholesterolemia (heFH) patients aged of 8 to 17 years on optimal stable daily dose of statin therapy ± other lipid modifying therapies (LMTs) or a stable dose of non-statin LMTs in case of intolerance to statins.

Study design

Select sites from the EFC14643 trial, will be asked to participate in the sub-study. Study centers that have access to the assessment of FMD will be approached. These centers that are willing to take part in the sub-study must undergo further qualification. Sites selected to participate in the sub-study will have IRB/EC approval for the main EFC14643 study and for the sub-study and an additional informed consent.

Patients who have provided signed informed consent for the main study of the EFC14643 trial at these select sites will be asked to participate in the sub-study. The participation in the sub-study is voluntary and declining participation in the sub-study does not prevent participation in the main study. Once the additional written informed consent is obtained for the sub-study and if patients fulfil the additional eligibility criteria for the sub-study, then they will undergo a baseline FMD assessment during the screening period. The patients will undergo a second FMD assessment at Week 24.

A standardized setting for testing will be implemented (11). Experienced ultrasonographers who will be involved in image acquisition will be trained prior to undertaking FMD assessments. The same scanning protocol will be employed at all sites. The same trained ultrasonographer should perform the FMD assessment at baseline and Week 24 on the patient, if at all possible. A central reading lab will review and analyze the images. Details will be provided in separate study related

documents. As the FMD assessment will take place during the double-blind treatment period, the personal involved in the FMD assessments will be blinded, including the central reading lab.

To assess brachial FMD, the brachial artery diameter will be measured both at rest and during the reactive hyperemia. Reactive hyperemia will be induced by sphygmomanometer or equivalent placed around the forearm, followed by release. The vessel diameter after reactive hyperemia will be expressed as the percentage relative to the resting scan (ie, [lumen diameter after reactive hyperemia – lumen diameter at rest]/lumen diameter at rest *100). The per cent maximum flow meditated dilatation of the brachial artery measured via ultrasound will be determined by a central reading laboratory with pre-specified methodology as detailed in the study related documents.

Primary endpoint

The absolute change from baseline to Week 24 in flow mediated dilatation of the brachial artery (as determined by the central reading laboratory) regardless of adherence to treatment (ITT estimand).

Study procedures

Each patient will undergo an FMD assessment at baseline and at Week 24. The baseline FMD assessment can be done at Week -2, Week -1 or another day of the screening period, or on Day 1, but prior to randomization into the main EFC14643 study. The Week 24 FMD assessment can be done on the same day as the Week 24 visit or at an alternative day corresponding to the time window (+/- 3 days) of the main EFC14643 study. However, the Week 24 FMD assessment must be done prior to entry into the open label treatment period.

Numerous factors affect flow mediated vascular reactivity. Thus, patients will need to comply with more details provided in the consent form. Briefly, patients will need to be fasting for at least 8 to 12 h before the FMD assessment. All vasoactive medications should be withheld for at least four half-lives, if possible. In addition, subjects will be asked to refrain from exercise and should not ingest substances that might affect FMD such as caffeine, high-fat foods and vitamin C or use tobacco for at least 4 to 6 h before the study.

The site will have access to an ultrasound system with specific equipment requirements as detailed in the study related documents. The same scanning protocol (which will be provided in study related documents) will be implemented across sites. During the procedure, the subject will be supine with the arm in a comfortable and outstretched position. A sphymomanometric cuff or equivalent will be placed on the forearm. After the patient has an adequate period of rest (which will be standardized), a baseline rest image and associated data will be acquired by the trained operator. Thereafter, arterial occlusion is created by cuff inflation or equivalent. Deflation of the cuff or equivalent will induce a brief high flow state through the brachial artery (reactive hyperemia) to accommodate the resistance vessels. The resulting increase in shear stress causes the brachial artery to dilate. An image and associated data will be acquired during this reactive hyperemia period. The total duration of the FMD assessment at either baseline or Week 24 is expected to be approximately 30 minutes.

Selection of patients

Additional inclusion criteria:

- A signed informed consent for FMD sub-study of EFC14643 protocol 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.

Additional exclusion criteria:

- Patients who withdraw consent for FMD sub-study of EFC14643 protocol during the screening period (patient who is not willing to continue or anticipated not to continue).
- Patients who are anticipated to have difficulty with complying with the procedure for the FMD assessment, based on Investigator judgment.
- Patients who are anticipated to require prohibited new (ie, treatment initiated after Week 0 FMD and until Week 24 FMD) concomitant medications.
- Patients who have initiated treatment with prohibited new concomitant medications within the past 4 weeks from the Week 0 FMD.

Patients who are not eligible for the sub-study based on the additional eligibility criteria may still take part in the main study of the EFC14643 protocol.

Prohibited new concomitant medications

Patients should avoid **new** treatment with the following medications as they may confound the results of the FMD (9):

- Vitamin C
- Vitamin E
- Angiotensin Converting Enzyme (ACE) inhibitors
- Angiotensin Receptor Blockers (ARBs)
- Estrogen

Patients, who are already taking the above concomitant medications prior to the Week 0 FMD assessment, may continue to take these medications during the study only if they will continue them at a stable dose until the Week 24 FMD assessment.

Handling of patient after permanent treatment discontinuation and of patient study discontinuation

Patients who wish to withdraw their participation in this sub-study may do so at any time. If they do so, they may continue participation in the main study. Patients, who discontinue the main study, must also discontinue participation in the sub-study.

Patients, who prematurely discontinue study treatment (regardless of the reason) and continue the main study, should be encouraged to complete the scheduled Week 24 FMD assessment.

Statistical considerations

Sample Size Determination and Randomization:

Assuming that 30 to 39 patients (regardless of the dosing regimen cohort: 20 to 26 in the alirocumab group and 10 to 13 in the placebo group) will participate to the sub-study, the statistical power to demonstrate superiority of alirocumab versus placebo at 0.05 two sided significance level is provided in Table 1 according to several assumptions for the mean difference and standard deviation (SD) of the absolute change from baseline to Week 24.

Table 1 - Statistical power according to mean difference and SD of the FMD absolute change from baseline to Week 24

Expected number of patients (2:1 ratio)	Standard deviation (%)	Delta mean (%)		
		2	2.5	3
30	2.5	51%	70%	84%
	4	23%	34%	46%
39	2.5	63%	81%	93%
	4	29%	43%	57%

Analysis:

The absolute change from baseline in FMD at Week 24 will be analyzed using an ANCOVA model. The model will include the fixed categorical effects of treatment group (alirocumab, placebo), the dosing regimen cohorts (Q2W, Q4W), the treatment by dosing regimen cohort interaction and the continuous fixed covariate of baseline FMD value. Model assumptions for normality will be explored prior to the analysis testing. Throughout the ANCOVA model, least-square (LS) mean and standard error (SE) will be provided for each treatment group and LS means difference will be provided for the comparison of the alirocumab group versus the placebo group with the 95% CI, using appropriate contrasts.

All Week 24 FMD values will be included in the analysis regardless of individual patient adherence to treatment.

Administration

Informed Consent:

A separate informed consent will be obtained from patients who voluntarily agree to participate in the sub-study. The Informed Consent Form reflecting this sub-study will be submitted for review and approval to the IRB/EC charged with this responsibility.

Confidentiality:

Data collection and handling by the Sponsor for this sub-study will be will be in accordance with that described in the main EFC14643 protocol, and every effort will be made to protect patient confidentiality. In case the results are published, they will be done so anonymously.

Institutional Review Board/Ethics Committee:

This sub-study, the Informed Consent Form for this sub-study, and any advertisement for patient recruitment will be submitted for review and approval to the IRB/EC charged with this responsibility.

Records Retention:

Investigators must retain records pertaining to this sub-study as described in the main EFC14643 study protocol.

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11. Jongh S, Lilien MR, Bakker HD, et al. Family history of cardiovascular events and endothelial dysfunction in children with familial hypercholesterolemia. Atherosclerosis. 2002;163:193-7.

Appendix F Summary of adverse event 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 H.	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 10.4.3).	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 10.4.1.4.	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]
Laboratory, vital sign,	Routine	Neutropenia (per Appendix H).	Yes	No	No
		Thrombocytopenia (per Appendix H).	Yes	No	No

Event category	Reporting timeframe	Specific events in this category	Case report form completion		
			AE form	Safety Complementary Form[a]	Other specific forms
(non-SAE, non-AESI) that is: - Symptomatic - Requiring corrective treatment or consultation - Leading to IMP discontinuation or dose regimen modification		Acute renal insufficiency (per Appendix H).	Yes	No	No
		Increase in CPK and suspicion of rhabdomyolysis (per Appendix H).	Yes	No	No
Death from any cause	Expedited		Yes	Yes	Yes

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 G Assessment of local injection site reactions

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

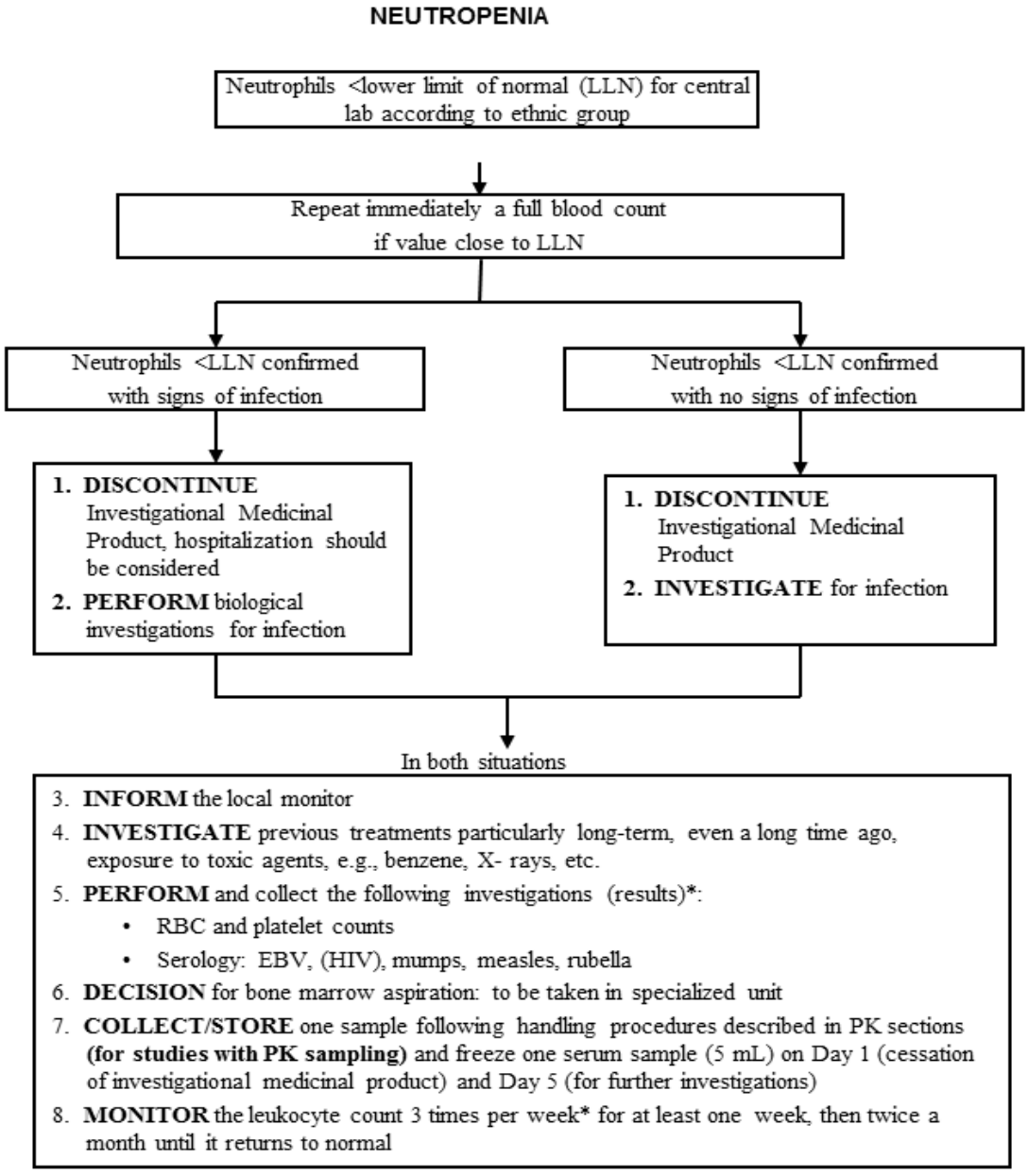
* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable

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

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

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

Appendix H General guidance for the follow-up of laboratory abnormalities by sanofi

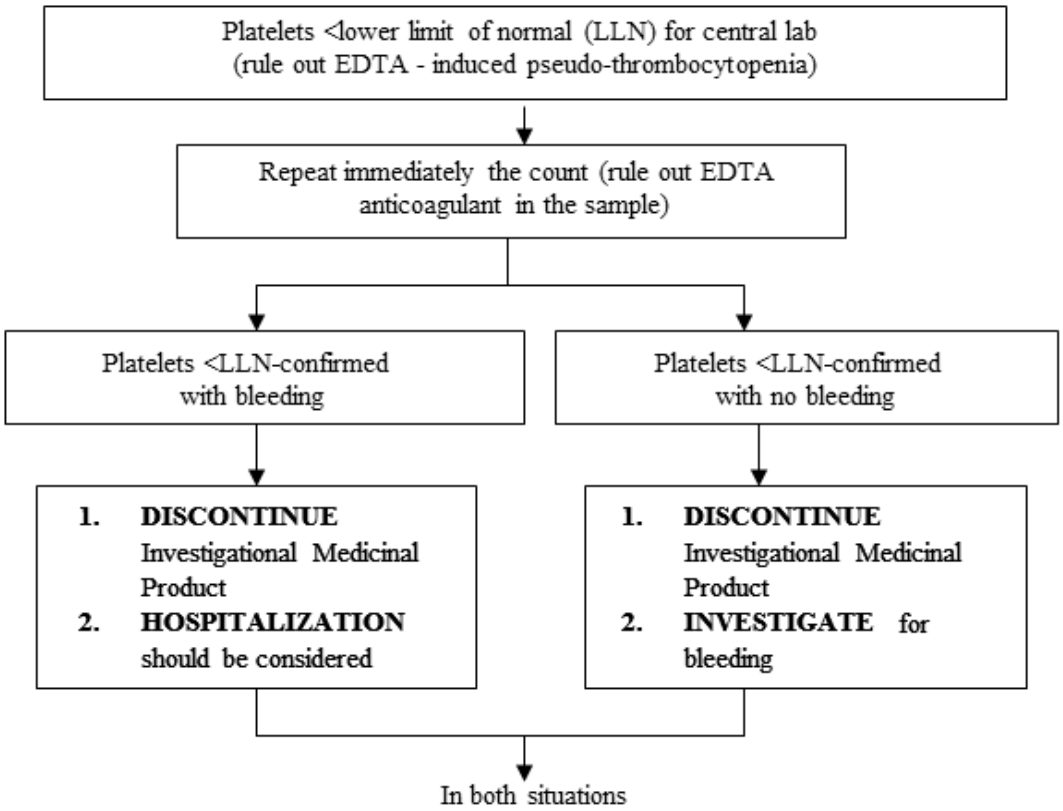


Note

- 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.
  Neutropenia is to be recorded as AE only if it at least one criterion in the General guidelines for reporting adverse events in Section 10.4 is met.
- * Clinical judgment to be used to prioritize additional testing, considering limits on total amount of blood to be drawn and/or patient safety. Use of local lab for additional testing is encouraged.

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

THROMBOCYTOPENIA

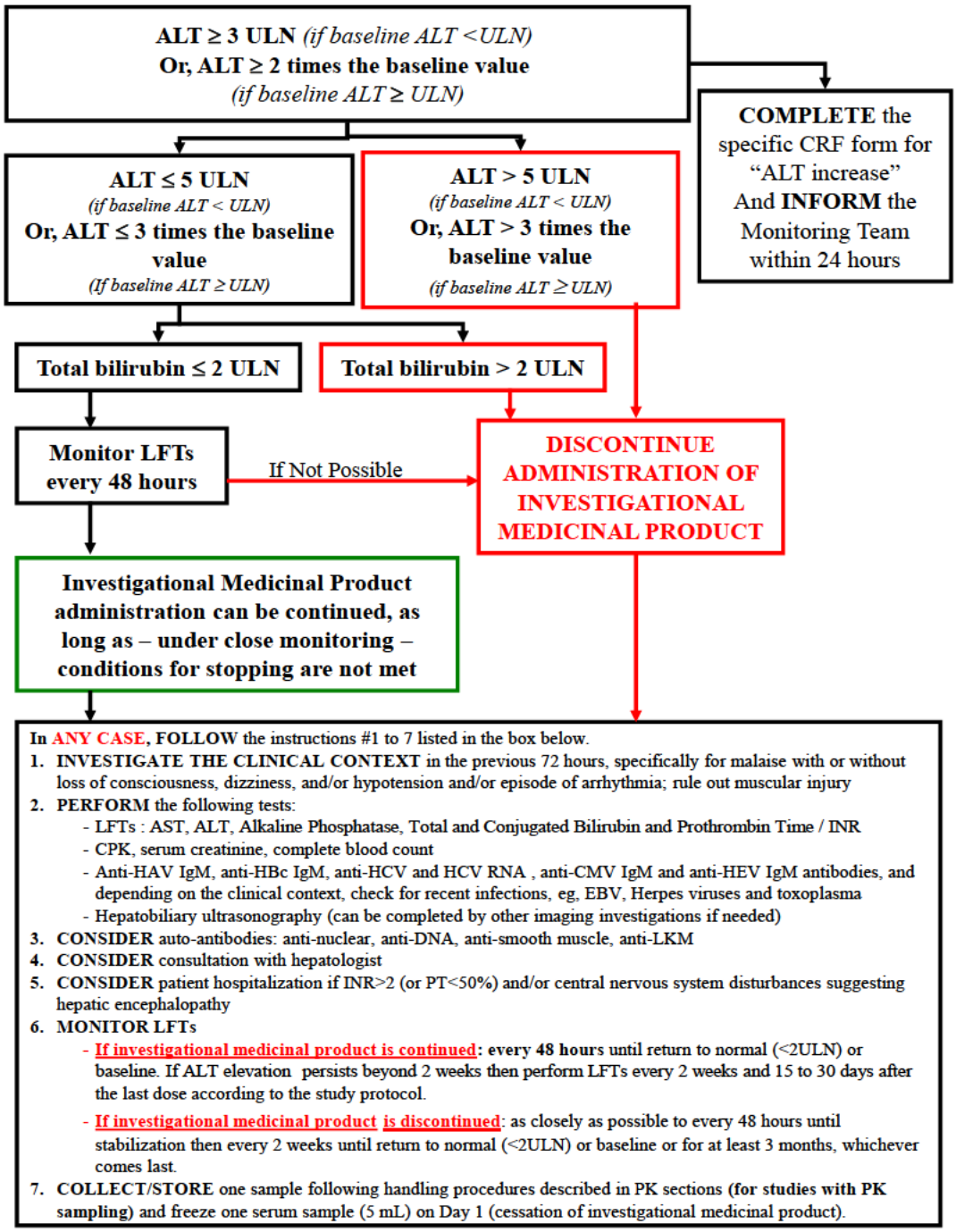


3. **INFORM** the local monitor
4. **QUESTION** about last intake of quinine (drinks), alcoholism, heparin administration
5. **PERFORM** or collect the following investigations*:
   - Complete blood count, schizocytes, creatinine
   - Bleeding time and coagulation test (fibrinogen, INR or PT, aPTT), Fibrin Degradation Product
   - Viral serology: EBV, HIV, mumps, measles, rubella
6. **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)
7. **DECISION** for bone marrow aspiration: to be taken in specialized unit
   - On Day 1 in the case of associated anemia and/or leukopenia
   - On Day 8 if the Platelets remain <50 000/mm^3
8. **MONITOR** the platelet count every day* for at least one week and then regularly until it returns to normal

NOTE:
The procedures above flowchart are to be discussed with the patient only in case described in 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. Use of local lab for additional testing is encouraged.
Thrombocytopenia is to be recorded as AE only if it at least one of the criteria in the General guidelines for reporting adverse events in Section 10.4 is met.

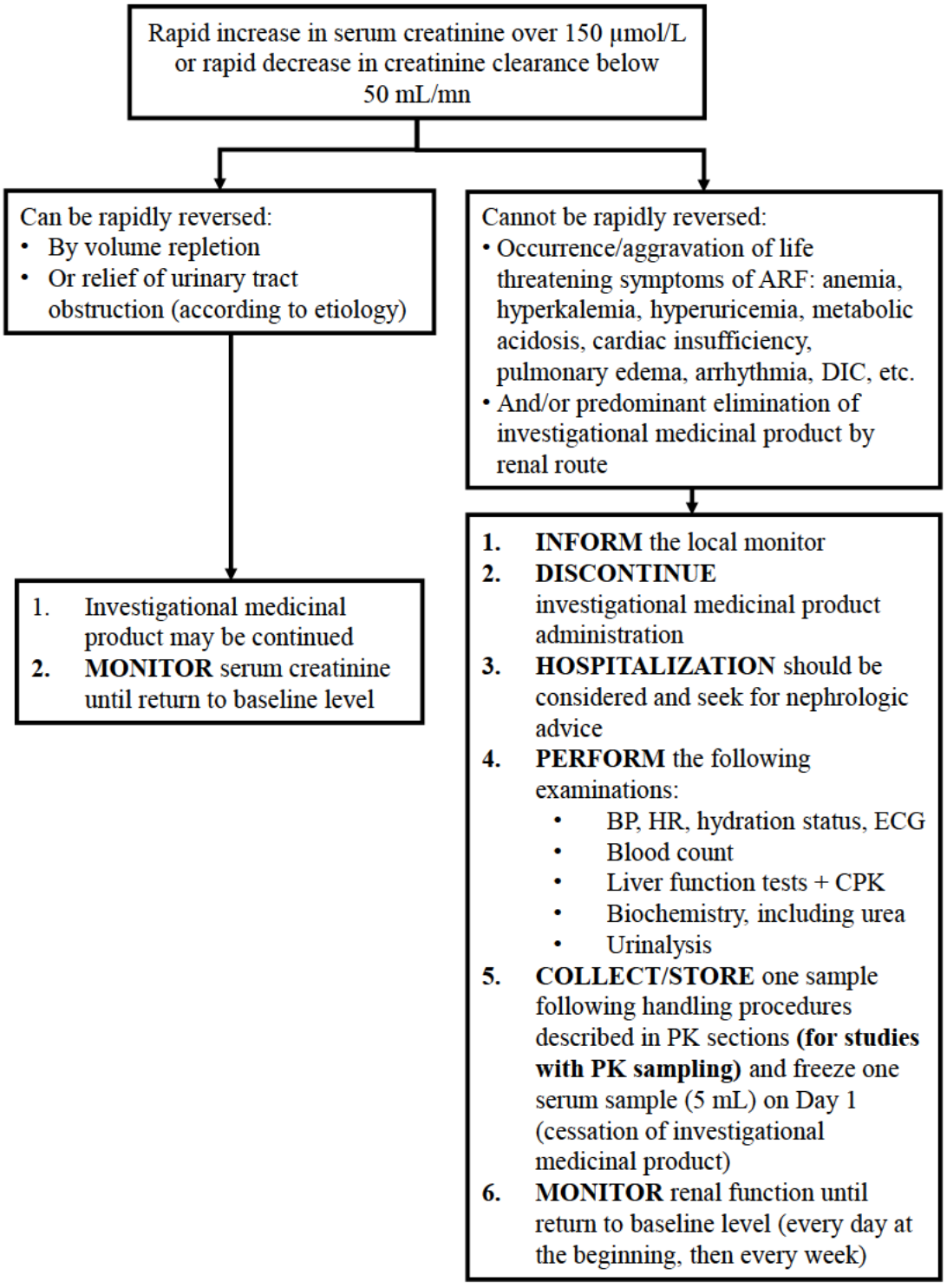
* Clinical judgment to be used to prioritize additional testing done, considering limits on total amount of blood to be drawn and/or patient safety.

INCREASE IN ALT



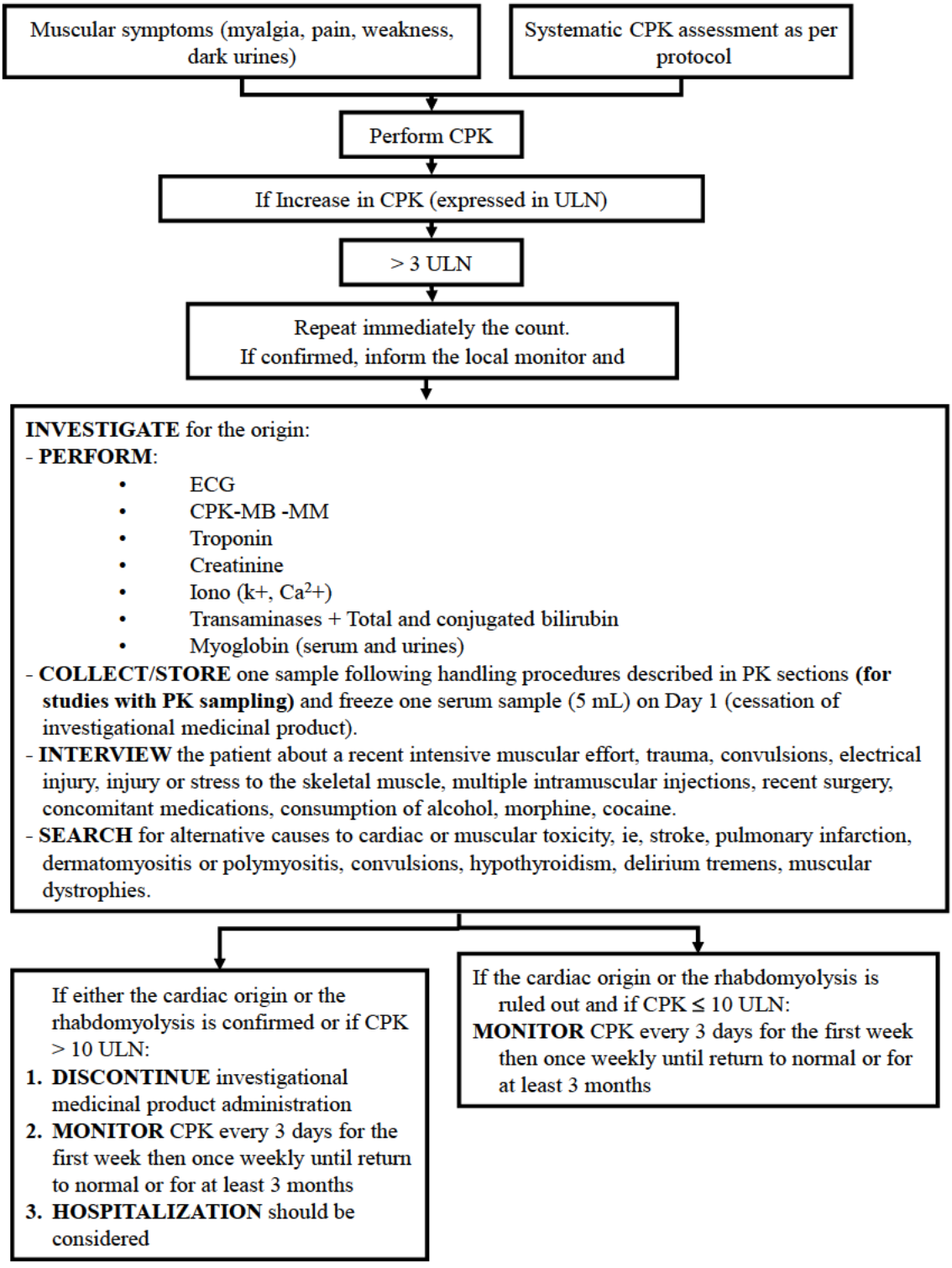
NOTE: ALT >3 ULN (IF BASELINE ALT < ULN) OR ALT ≥2 TIMES THE BASELINE VALUE (IF BASELINE ALT ≥ ULN) SHOULD BE NOTIFIED WITHIN 24 HOURS TO THE MONITORING TEAM (SEE SECTIONS 10.4.1.3, 10.4.5, AND 10.4.6). IN ADDITION, IF ALT <3 ULN MEETS A SERIOUSNESS CRITERION, THE EVENT SHOULD BE NOTIFIED WITHIN 24 HOURS 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 adverse events 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 adverse events in Section 10.4.3 is met.

Appendix I Pediatric formulas 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 J Country specific requirements

AMENDMENT FOR NORWAY, ARGENTINA, CZECH REPUBLIC AND ALL APPLICABLE COUNTRIES

For Norway, Argentina, the Czech Republic and all applicable countries, 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 14, during clinic 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 4, 16, 20, 28, 36, 40, 48, 52, 56, 60, 64, 72, 76, 80, 84, 88, 96, and 100

Sexual counseling should be provided to patients when indicated. In the event that a pregnancy test performed at home is 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 K Contingency Measures for regional or national emergency that is declared by a governmental agency

A regional or national emergency declared by a governmental agency (eg, public health emergency, natural disaster, pandemic, and terrorist attack) may prevent access to the clinical trial site.

Remote monitoring, also referred to as off-site monitoring, enables clinical research associates Site Monitor (SM) to remotely conduct monitoring activities without physically traveling to the site.

Deploying remote monitoring, inclusive of remote source data verification, should always be driven by risk assessment and analysis at the outset.

Due to levels of safety information required for the EFC14643 study, attempts should be made to perform all assessments in accordance with the approved protocol to the extent possible. In case this is not possible due to a temporary disruption caused by an emergency, focus should be given to assessments necessary to ensure the safety of participants and those important to preserving the main scientific value of the study.

The decision for each individual participant to remain on treatment and/or in the study should be made on a case by case basis based on best Investigator medical judgment. The clinical judgment of the treating physician should guide the management plan of each participant based on individual benefit/risk assessment and the evolving situation at the site.

Procedures to be considered in the event of a regional or national emergency declared by a governmental agency:

- If onsite visits are not possible, remote visits (eg, with home nurses, home health vendor, etc) may be planned for the collection of possible safety and efficacy data as listed below:
  - Blood sampling for LDL-C at baseline, Week 8, Week 12, and Week 24
  - Blood sampling for lipid parameters (Apo B, non-HDL-C, Total-C, Lp(a), TG, HDL-C, and Apo A-1) at baseline, Week 8, Week 12 and Week 24
  - AE collection reported, including AE complementary forms
    - injection site reactions
  - Laboratory parameters - adrenal gland hormones; gonadal and pituitary hormones
  - Collection of weight at Day 1, at Week 24 (time of dose evaluation) and after Week 24 up to the last IMP dispensation
  - Collection of Tanner Stage at Screening Visit 1 or Visit 2 and at last patient visit
  - Blood sampling for PK and ADA parameters at any visit
- If onsite visits are not possible, remote visit windows may be extended for assessments of any of the data listed above that cannot be obtained remotely within the visit window planned per protocol
- Use of local clinic or laboratory locations may be allowed for the laboratory procedures from the list above except for lipid parameters during the double-blind treatment period
- Contingencies implemented due to emergency will be documented.

Appendix L Protocol amendment history

The Protocol Amendment Summary of Changes Table for the current amended protocol 03 is located directly before Clinical Trial Summary.

AMENDED PROTOCOL 02 (02-JAN-2019)

This amended protocol (amendment 02) is considered to be substantial 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 either significantly impacts the safety or physical integrity of participants or the scientific value of the study.

OVERALL RATIONALE FOR THE AMENDMENT

The main reason for this protocol amendment is to include the Q4W dosing regimen alongside the Q2W dosing regimen currently ongoing. This Q4W dosing regimen should be applicable to approximately half of the heFH patients to be randomized in the Phase 3 EFC14643 study (ie, approximately 75 patients).

The selection of the Q2W dosing regimen currently evaluated in this Phase 3 EFC14643 study was based on the results of the Phase 2 DFI14223 study, as described in Section 4 - Introduction and Rationale. This Phase 2 study was an 8 week open label, sequential, repeated dose-finding study to evaluate the efficacy and safety of alirocumab in children and adolescents with heFH through 3 cohorts, initially; the repeated dose-finding study was followed by an open label extension phase. Two body weight (BW) categories (BW <50 kg and BW ≥50 kg) were used and patients were treated with a fixed dosage of alirocumab in each BW category according to the evaluated cohort, as described below:

- Cohort 1: 30 mg Q2W for BW <50 kg and 50 mg Q2W for BW ≥50 kg.
- Cohort 2: 40 mg Q2W for BW <50 kg and 75 mg Q2W for BW ≥50 kg.
- Cohort 3: 75 mg Q4W for BW <50 kg and 150 mg Q4W for BW ≥50 kg.

Following the review of the combined efficacy, safety and pharmacokinetics results of the first 3 cohorts, doses of the Cohort 2 were selected for the Q2W regimen since the results observed were those expected to provide an overall reduction in LDL-C of -46.1%. Consistent reductions were seen across the 2 doses ranging from -40.6% to -49.8% for 40 mg Q2W and 75 mg Q2W, respectively.

For the Q4W dosing regimen no formal conclusion could be drawn given the unexpected results observed in Cohort 3. The doses evaluated were likely not high enough to achieve larger and sustained reductions in the LDL-C over the entire dosing interval in children receiving statin as background therapy. Therefore, an additional cohort (Cohort 4) was added in the Phase 2 DFI14223 study to evaluate further the Q4W dose regimen using higher doses of 150 mg/300 mg Q4W depending on the BW category.

Regarding this Cohort 4, the primary efficacy endpoint as measured by the percent change from baseline in LDL-C at Week 8 showed a comparable reduction to that observed in Cohort 2 with a mean LS change from baseline of -46.1% and -44.5% for Cohort 2 and Cohort 4, respectively. Substantial reductions were seen in both BW categories ranging from -31.9% for 150 mg Q4W in the lower BW category to -59.8 % for 300 mg Q4W in the higher BW category. Overall, alirocumab was well tolerated with a favorable safety profile in this additional cohort over the open label dose finding and the open label extension (OLDFI/OLE) combined period, as already observed in the first 3 cohorts. No new clinically significant safety findings were noted in these patients treated with alirocumab.

Based on the positive results from Cohort 4, the doses of 150 mg and 300 mg Q4W have been deemed efficacious and to be adequately safe, and therefore will be also evaluated in the Phase 3 EFC14643 study. Similar to what is done in the study for the Q2W dosing regimen, a dose-adjustment will be allowed to optimize the response as needed. Rules for the dose-adjustment will be similar to those applied for the Q2W dosing regimen as shown below:

Patients enrolled in the Q4W alirocumab dosing regimen will receive:

- 150 mg Q4W for BW <50 kg or,
- 300 mg Q4W for BW ≥50 kg.

At Week 12:

- If the Week 8 LDL-C is <110 mg/dL (2.85 mmol/L), patients will continue alirocumab 150 mg or 300 mg Q4W according to BW category.
- If the Week 8 LDL-C is ≥110 mg/dL (2.85 mmol/L), patients will have a change in the dose from 150 mg Q4W to 75 mg Q2W or from 300mg Q4W to 150 mg Q2W, in a blinded manner.

Protocol amendment summary of changes table

Section # and name	Description of change	Brief rationale
Clinical Trial Summary - Primary objective; Section 5.1 Primary	Every 4 week (Q4W) efficacy evaluation has been added to the primary objectives.	Based on positive results from Cohort 4 of the Phase 2 DFI14223 study, efficacy and safety assessments of the Q4W dosing regimen are also planned in this study. Revisions presented in this section of the table are related to the addition of the Q4W dosing regimen in the study.
Clinical Trial Summary - Study design: Double-blind treatment period	Dosing regimen of Q4W (alirocumab 150 mg and 300 mg; n~75 patients) is added and number of enrolled patients in Q2W dosing regimen who will be administered study treatment (alirocumab 40 mg and 75 mg is changed to approximately half; n~75).	
Clinical Trial Summary - Study design: Double- blind treatment period and Open label treatment period; Study Flow chart 1.3	Description of the Q4W dosing regimen and information on maintaining the blind is added for patients in Q4W dosing regimen to indicate administration of alirocumab every 4 weeks during the first 12 weeks and then after Week 12 administration of alirocumab every 4 weeks alternating with placebo every 4 weeks in order to maintain the blind at the time of a possible dose-adjustment.	
Clinical Trial Summary - Study design: Open label treatment period	Dose-adjustment information at Week 24 and from Week 32 added for patients enrolled Q4W dosing regimen.	
Clinical Trial Summary - Investigational medicinal products: Formulation, Section 8.1: Investigational medicinal products	1 mL of alirocumab 150 mg/mL solution for 150 mg dose added.	
Clinical Trial Summary - Investigational medicinal products: Dose regimen; Section 8.1: Investigational medicinal products	Information of the Q4W dose used added: alirocumab 150 mg Q4W for BW <50 kg and 300 mg Q4W for BW ≥50 kg.	
Clinical Trial Summary - Statistical consideration	Revision of statistical analysis - sample size determination and addition of alirocumab Q4W and placebo Q4W to the treatment groups to be analyzed	
Section 11.1 Determination of sample size	Description of sample size calculations and considerations for the Q2W and Q4W dosing regimens	
Section 11.4.1.1 Extent of Investigational Medicinal Product exposure	Description of the duration of exposure is added for the Q4W dosing regimen	
Section 11.4.2.3 Multiplicity considerations	A revision and description of how the multiplicity will be handled.	
Flow chart 1.2: Graphical study design - Q4W dosing regimen	Graphical study design for Q4W dosing regimen added as Flow chart 1.2	
Section 4: Introduction and rationale	Addition of clinical information of the additional cohort (Cohort 4) conducted with Q4W dosing regimen in the DFI14223 that support the evaluation of the Q4W dosing regimen in the EFC 14643 study.	

Section # and name	Description of change	Brief rationale
Clinical Trial Summary - Study design: Open label treatment period	Correction in the Q2W dose-adjustment according to BW as per Investigator's judgment.	Error in the information of the dose adjustment for the Q2W according to BW as per investigator's judgement; only dose adjustment from 40 mg to 75 mg is possible if BW becomes ≥50 kg.
Flow chart 1.1: Graphical study design - Q2W dosing regimen	Information on the fact that from the total number of 150 patients, half of those will be enrolled in each dosing regimen has been added.	Although the overall number of patients (150) is not modified, approximately half of this number will be enrolled in each of the Q2W and Q4W dose regimens, respectively.
Throughout	Minor editorial revisions to reflect the rationale stated above.	Minor, hence not summarized.
Appendix J	Addition of the Czech Republic and all applicable countries to Appendix J (currently provisioned as a country specific change in the protocol).	To clarify that all countries are allowed to perform the monthly urine pregnancy tests, in keeping with the clinical trials facilitation group (CTFG) guidelines.

Amended protocol 01 (13-Sep-2018)

This amended protocol (amendment 01) 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

The protocol description of the independent physician is being revised to show that he/she is external to the EFC14643 study, and not necessarily external to the Sponsor.

Since the main purpose of using an independent physician involved in the monitoring of patients reaching LDL-C levels <50 mg/dL (1.30 mmol/L) during the 24-week double-blind treatment period is to have an individual that is not part of the EFC14643 study team, the Sponsor's initial intention was to use a physician part of an academic group, however the attempt to implement such a process within the study teams predetermined timelines was not possible. As a result, the Sponsor will use physicians within the company who are not part of the EFC14643 study team and as well not involved in any alirocumab activities. The protocol is revised accordingly to clarify that other physicians can be involved in the process of this monitoring, as long as they are external to the EFC14643 study team and any alirocumab activities. This change will allow the Sponsor to respect the objectives set forth in the original protocol with regard to the monitoring of patients reaching LDL-C levels <50 mg/dL (1.30 mmol/L) during the 24-week double-blind treatment period. The blinding process remains unchanged for the EFC14643 study team.

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 that a separate informed consent form should be used for heterozygous familial hypercholesterolemia (heFH) genotyping. However, the consent for heFH 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. Also in the description of the two-step analysis in the Section 6.3 and Section 11.5, revision of the text is done with removal of the sentence "The results of the first step analysis will not be used to change the conduct of the ongoing study in any aspect". In the context of the design of the study (double-blind period followed by an open label treatment period) this sentence is not appropriate since the double-blind period will be completed at the time of the first step analysis with the final comparison between the 2 treatment groups, therefore there will be no bias in this comparison.

Protocol amendment summary of changes table

Section # and name	Description of change	Brief rationale
Clinical Trial Summary- Study Design	Removed the word "academic" and added a sentence to specify that the independent physician is not part of the EFC14643 study team and any alirocumab activities.	This revision is to clarify that the independent physician is not necessarily an academic physician but nevertheless is external to the EFC14643 study team and any alirocumab activities.
6.3 and 11.5 Two-step analysis	Removed the sentence "The results of the first step analysis will not be used to change the conduct of the ongoing study in any aspect".	This sentence is not appropriate in the context of the design of the study (double-blind period followed by an open label treatment period).
6.4.2 Data monitoring committee	Description of how the independent physician will have access to patient treatment information during the double-blind treatment period.	To better assure that the study team members will be blinded to the data that the independent physician reviews.
8.3.1.2 Lipid parameters	Clarification with regard to the Sponsor, that the EFC14643 study team is blinded for lipid parameters.	To better assure that the study team members will be blinded to the data that the independent physician reviews.
10.1.1.1 Visit 1 (Week 6, run in) and 12.2 Informed consent	Specifying that the optional consent for genotyping is part of the main informed consent form.	Clarification that the heFH consent is not a separate document from the informed consent form.
10.1.3 Twenty-four week double-blind treatment period	Removed the word "academic" and added a sentence to specify that the independent physician is not part of the EFC14643 study team and any alirocumab activities.	This revision is to clarify that the independent physician is not necessarily an academic physician but nevertheless is external to the EFC14643 study team and any alirocumab activities.
10.6.2.3 Independent physician monitoring for patients reaching LDLC levels <50 mg/dL (1.30 mmol/L) during the double-blind treatment period and recommendations for the Investigator in case of an alert	Clarification on how the independent physician will have access to patient treatment information during the double-blind period and Sponsor's EFC14643 study team will not have access to.	To better assure that the study team members will be blinded to the data that the independent physician reviews.
17. Appendices- Appendix J Country Specific Requirements and 1.2 Study flowchart-footnote "bb"	Monthly urine pregnancy tests to be performed at home added as country specific changes.	Added as Appendix J 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.

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