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),

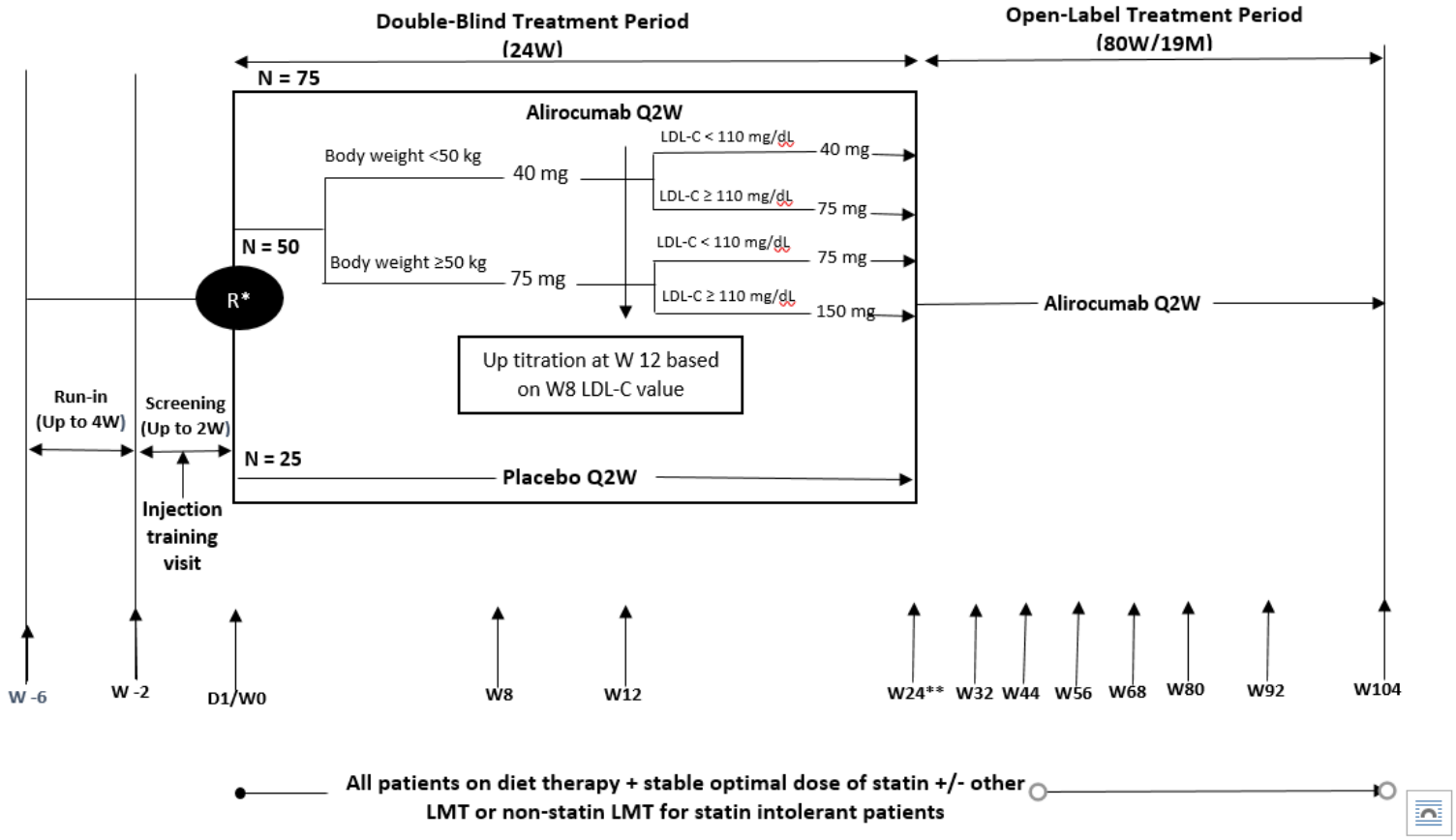
	laboratory data, vital signs, body weight, height, Cogstate battery test, and Tanner stage assessed throughout the study. **Other secondary efficacy endpoints:** • All primary and key secondary endpoints in the modified ITT (mITT) population, using all LDL-C values during the treatment period (on-treatment 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

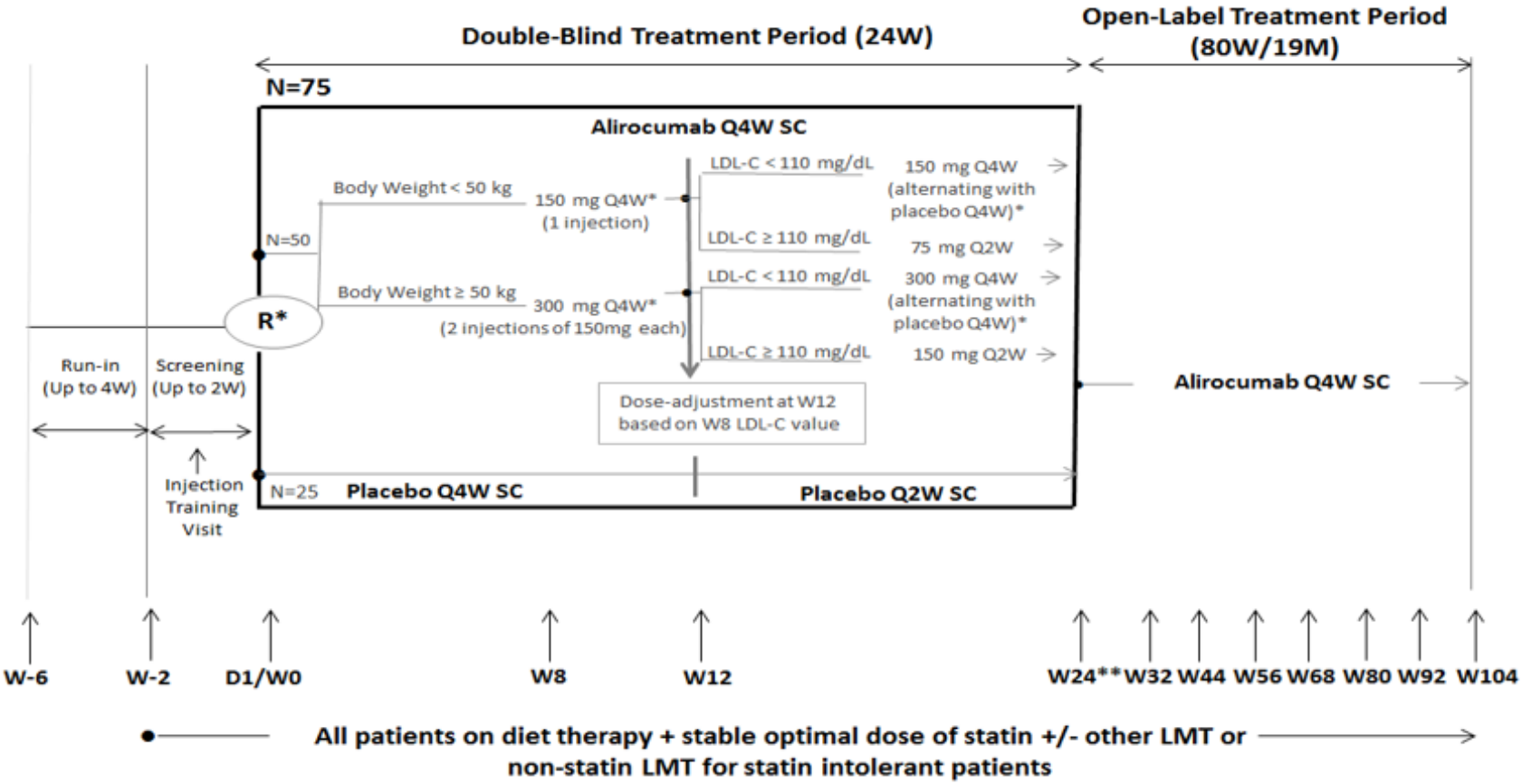
1.1 GRAPHICAL STUDY DESIGN - Q2W DOSING REGIMEN COHORT



*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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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

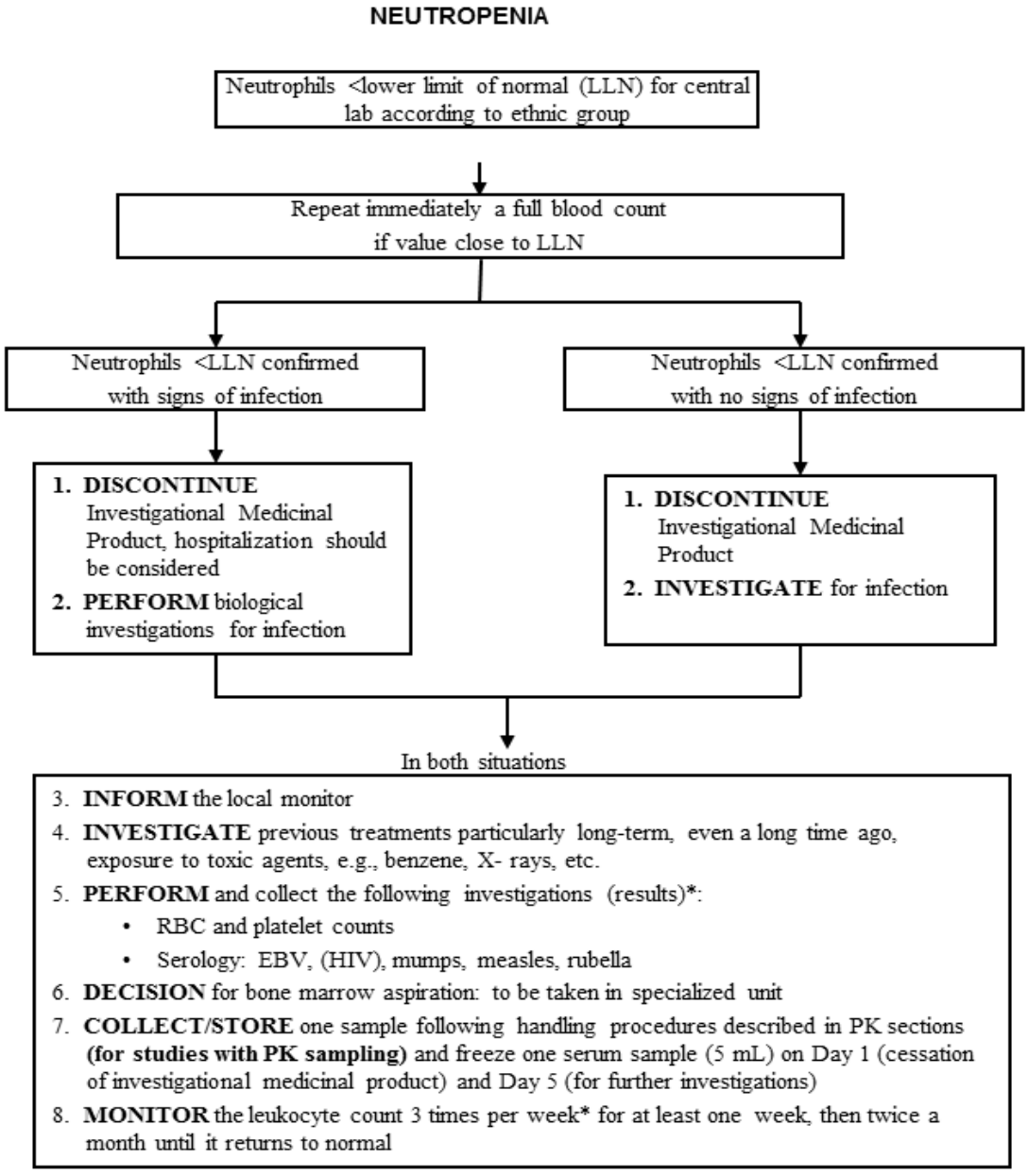
* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable

** 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

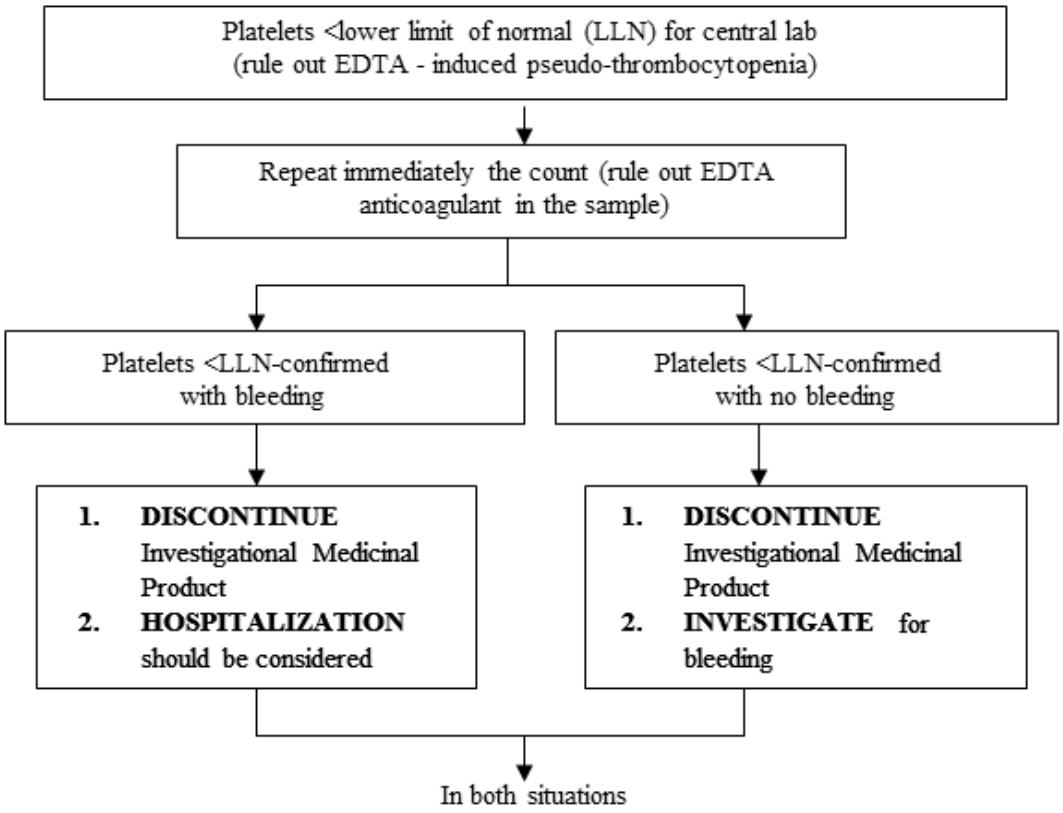


Note

- 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

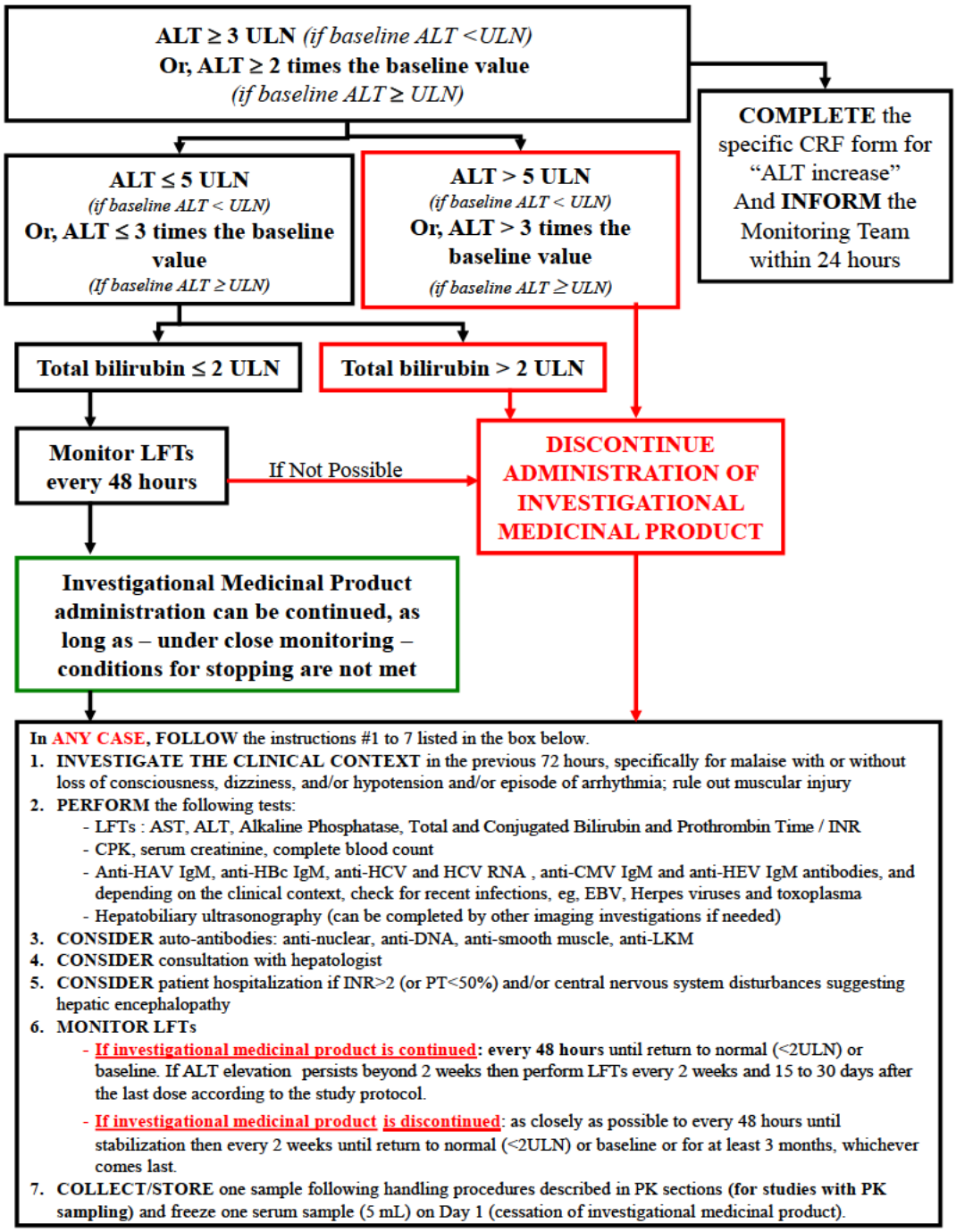


3. **INFORM** the local monitor
4. **QUESTION** about last intake of quinine (drinks), alcoholism, heparin administration
5. **PERFORM** or collect the following investigations*:
   - Complete blood count, schizocytes, creatinine
   - Bleeding time and coagulation test (fibrinogen, INR or PT, aPTT), 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.

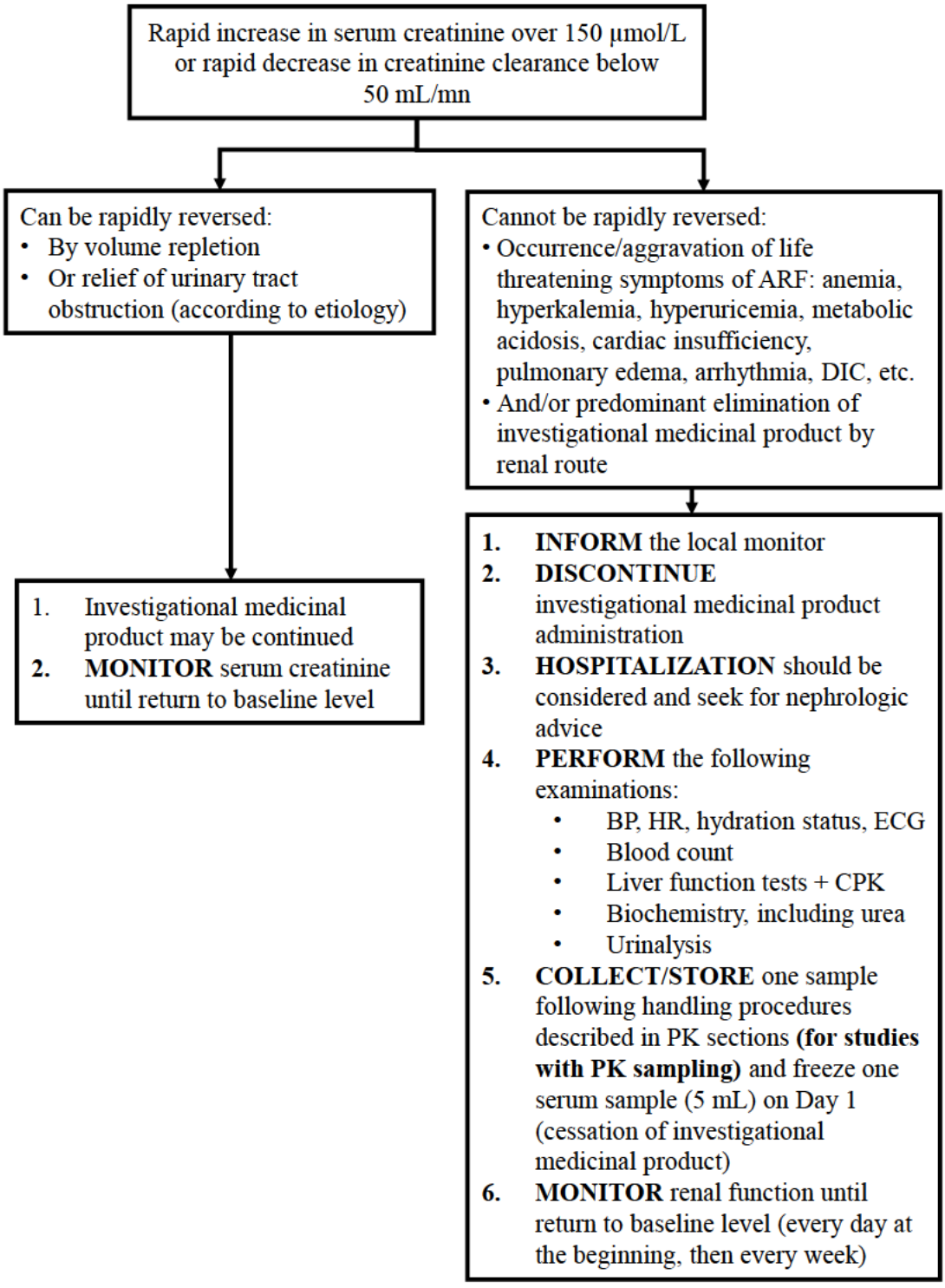
* Clinical judgment to be used to prioritize additional testing done, considering limits on total amount of blood to be drawn and/or patient safety.

INCREASE IN ALT



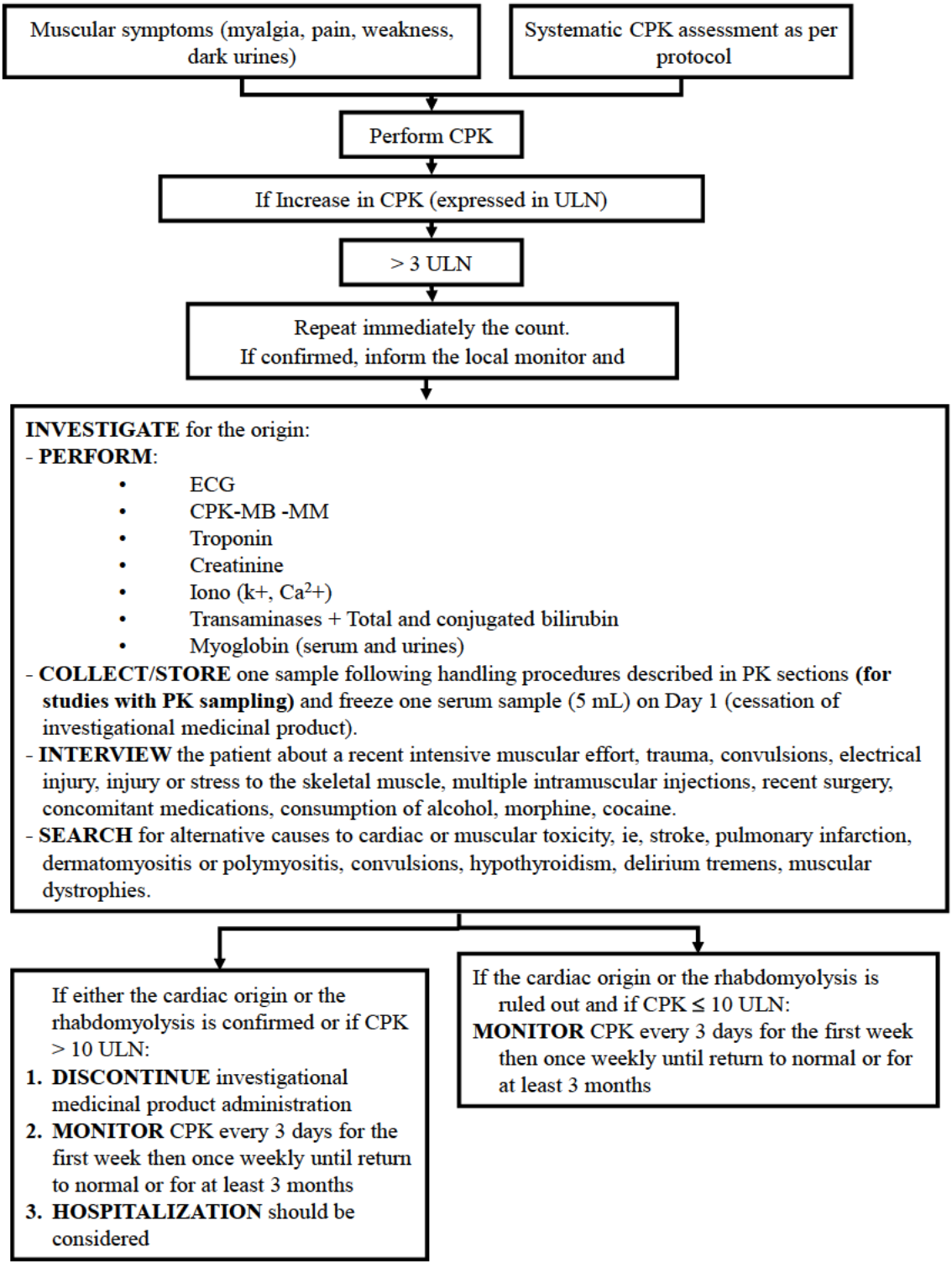
NOTE: ALT >3 ULN (IF BASELINE ALT < ULN) OR ALT ≥2 TIMES THE BASELINE VALUE (IF BASELINE ALT ≥ ULN) SHOULD BE NOTIFIED WITHIN 24 HOURS TO THE MONITORING TEAM (SEE SECTIONS 10.4.1.3, 10.4.5, AND 10.4.6). IN ADDITION, IF ALT <3 ULN MEETS A SERIOUSNESS CRITERION, THE EVENT SHOULD BE NOTIFIED WITHIN 24 HOURS 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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efc14643-16-1-1-amended-protocol03

NCT03510884

STATISTICAL ANALYSIS PLAN

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

SAR236553/RGN727-EFC14643

STATISTICIAN: [redacted]

Statistical Project Leader: [redacted]

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACTH:	adenocorticotrophic hormone
ADA:	anti-alirocumab antibody
AE:	adverse event
AESI:	adverse event of special interest
ALP:	alkaline phosphatase
ALT:	alanine aminotransaminase
ANCOVA:	analysis of covariance
Apo A-1:	apolipoprotein A-1
Apo B:	apolipoprotein B
AST:	aspartate aminotransferase
ATC:	anatomic therapeutic chemical
BMI:	body mass index
BW:	body weight
CMQ:	customized MedDRA queries
CPK:	creatine phosphokinase
CV:	cardiovascular
DBP:	diastolic blood pressure
DET:	Detection test
DHEAS:	dehydroepiandrosterone sulfate
e-CRF:	electronic case report form
eDISH:	evaluation of drug-induced serious hepatotoxicity
eGFR:	estimated glomerular filtration rate
GML:	Groton maze learning task test
HbA1c:	glycated haemoglobin A1c
HDL-C:	high density lipoprotein cholesterol
heFH:	heterozygous familial hypercholesterolemia
HLGT:	high level group term
HLT:	high level term
HR:	heart rate
IDN:	Identification test
IMP:	Investigational Medicinal Product
ITT:	intent-to-treat
LDH:	lactate dehydrogenase
LDL-C:	low-density lipoprotein cholesterol
LLN:	lower limit of normal
LLOQ:	lower limit of quantification
LLT:	lowest level term
LMT:	lipid modifyng therapy
LOCF:	last observation carried forward
Lp[a]:	lipoprotein (a)

LS:	least square
MedDRA:	medical dictionary for regulatory activities
MI:	myocardial infarction
NMAR:	not-missing-at-random
non-HDL-C:	non-high density lipoprotein cholesterol
OCL:	One card learning test
OL:	open-label
PCSK9:	proprotein convertase subtilisin/kexin type 9
PK:	pharmacokinetics
PT:	preferred term
Q1:	first quartile
Q2W:	every 2 weeks
Q3:	third quartile
Q4W:	every 4 weeks
QQ-plot:	Quantile Quantile plot
SAE:	serious adverse event
SBP:	systolic blood pressure
SC:	subcutaneous
SMQ:	standardised MedDRA queries
SOC:	system organ class
TGs:	triglycerides
Total-C:	total-cholesterol
ULN:	upper limit of normal
ULOQ:	upper limit of quantification
US:	United States of America
WHO-DD:	World Health Organization-Drug Dictionary
γGT:	gamma-glutamyl transferase

1 OVERVIEW AND INVESTIGATIONAL PLAN

This Statistical Analysis Plan (SAP) is intended to be a detailed description of the definitions and statistical techniques to be used for the analyses of data collected in the EFC14643 study. This SAP will be finalized prior to the first step analysis. This first step analysis would be conducted after the completion of the double-blind treatment period.

1.1 STUDY DESIGN AND RANDOMIZATION

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

Approximately 150 children and adolescents 8 to 17 years of age with heterozygous familial hypercholesterolemia (heFH) and low-density lipoprotein cholesterol (LDL-C) ≥130 mg/dL (3.37 mmol/L) at the screening visit, despite stable lipid modifying therapies (LMTs), are randomized to alirocumab or placebo using a 2:1 ratio (alirocumab: placebo). Two dosing regimens, administration every 2 weeks (Q2W) and every 4 weeks (Q4W), will be evaluated with approximately 75 patients in each dosing regimen cohort. Recruitment in the Q4W dosing regimen cohort started once recruitment in the Q2W dosing regimen cohort was completed and the protocol amendment was approved.

A Flow Mediated Dilation (FMD) exploratory sub-study is also planned to involve a subset of 30-39 patients at selected sites.

Note: Patients who had previously participated in the DFI14223 study and had received alirocumab administration during the open-label extension of the DFI14223 study required 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 had already met the LDL-C requirement of at least 130 mg/dL (3.37 mmol/L) when they were screened for the DFI14223 study, they were not excluded based on the LDL-C value obtained during the screening for the EFC14643 study.

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

The study is comprised of 4 periods as described below:

- 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 24-week double-blind treatment period.
- A 80-week open-label treatment period.

The total study duration may be up to 110 weeks (+7 days).

Double-blind treatment period:

Two dosing regimens will be evaluated, Q2W and Q4W. Patients will be included in them in a sequential manner, ie, the first half of the patients in the Q2W dosing regimen cohort then the second half of patients in the Q4W dosing regimen cohort. Patients will be blinded to study treatment and randomized to either alirocumab or placebo using a 2:1 ratio for each dosing regimen cohort.

Q2W dosing regimen cohort:

The first half of the total patient population (approximately 75 patients) will be randomized to receive Q2W subcutaneous (SC) injections of either alirocumab or placebo, starting at the randomization Visit (Week 0) and continuing up to the end of the double-blind period.

For patients randomized to receive alirocumab the following doses based on 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, in a blinded manner:

- Continue alirocumab 40 mg or 75 mg Q2W, if the Week 8 LDL-C is <110 mg/dL (2.85 mmol/L) OR
- Have a dose up-titration to alirocumab 75 mg Q2W (for patients initially on 40 mg Q2W) or 150 mg Q2W (for patients initially on 75 mg Q2W) if the Week 8 LDL-C is ≥110 mg/dL (2.85 mmol/L).

Q4W dosing regimen cohort:

The second half of the patient population (ie, approximately 75 patients) will be enrolled in a Q4W dosing regimen cohort. During the first 12 weeks of the double-blind period, all patients will receive SC injection(s) Q4W of alirocumab or placebo. After Week 12, with regard to the possible dose-adjustment in some patients and the need for maintaining the double-blind until the end of the double-blind period, all patients will receive SC injection(s) Q2W.

For patients randomized to alirocumab the following doses based on 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, in a blinded manner:

- Continue alirocumab 150 mg or 300 mg Q4W, if the Week 8 LDL-C is <110 mg/dL (2.85 mmol/L) alternating with Q4W placebo injection (“sham” Q2W regimen) OR

- Have a dose adjustment to 75 mg Q2W (for patients on 150 mg Q4W) or 150 mg Q2W (for patients on 300 mg Q4W) if the Week 8 LDL-C is ≥110 mg/dL (2.85 mmol/L) ("actual" Q2W regimen).

Note: participants enrolled in the placebo Q4W group will receive injection of placebo of alirocumab Q4W for the first 12 weeks, then injection of placebo of alirocumab Q2W until the end of the double-blind period.

Open-label treatment period

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

At the first open-label treatment period visit (corresponding to Week 24 of the double-blind period), depending on whether subjects were randomized in the Q2W or Q4W dosing regimen cohort, both alirocumab and placebo treated patients will receive alirocumab either 40 mg Q2W or 150 mg Q4W if BW <50 kg, and 75 mg Q2W or 300 mg Q4W if BW ≥50 kg, based on the weight obtained at the Week 24 visit (dosing frequency assigned at the start of the open-label treatment period was to maintain the same dosing frequency to which the patient was randomized for the double-blind treatment period).

After Week 24, change in the dose and dosing regimen can be based on either change in BW or LDL-C levels.

Therefore, the Investigator can manage, based on his/her own judgment, adjustment of alirocumab dose based on changes in BW:

- If the patient is currently on 40 mg Q2W but the BW has changed from <50 kg to ≥50 kg, then the Investigator can adjust the dose to 75 mg Q2W.
- If the patient is currently on 150 mg Q4W but the BW has changed from <50 kg to ≥50 kg, then the Investigator can adjust the dose to 300 mg Q4W.

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

Lipid levels will be communicated to the Investigator during the OL treatment period from the second visit (ie, Week 32) onwards. From this visit, the Investigator is responsible, 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:

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

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.

For 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.

Note: A patient for whom the dose has been adjusted to a Q2W dosing regimen can only have subsequently a dose modification following the rule that applies for the Q2W dosing regimen cohort.

Approximately 150 patients (approximately 75 patients in each dosing regimen cohort) from approximately 70 sites will be randomized.

1.2 OBJECTIVES

1.2.1 Primary objectives

To evaluate the efficacy of alirocumab administered Q2W and Q4W versus placebo after 24 weeks of double-blind treatment on LDL-C levels in patients with heFH 8 to 17 years of age on optimal stable daily dose of statin therapy ± other LMTs or a stable dose of non-statin LMTs in case of intolerance to statins.

1.2.2 Secondary objectives

- 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.

1.2.3 Other Objectives

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

1.2.4 Exploratory objective of the FMD sub-study

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

1.3 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% in any comparison between each alirocumab dosing regimen group and its contemporaneously randomized placebo dosing regimen group with a 0.025 two-sided significance level 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 of the placebo dosing regimen group). The enrollment of 150 patients will allow for a safety assessment over 2 years in approximately 128 patients, assuming a discontinuation rate of 15%.

Calculations were made using nQuery 7.0 Advisor software.

Sample Size Determination for the FMD sub-study:

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 in the sub-study, the statistical power to demonstrate superiority of alirocumab versus placebo at a 0.05 two-sided significance level is provided in Table 1. This sample size calculation is based on several assumptions for the mean difference and standard deviation (SD) of the absolute change from baseline to Week 24 in flow mediated dilatation of the brachial artery that are enumerated in Table 1.

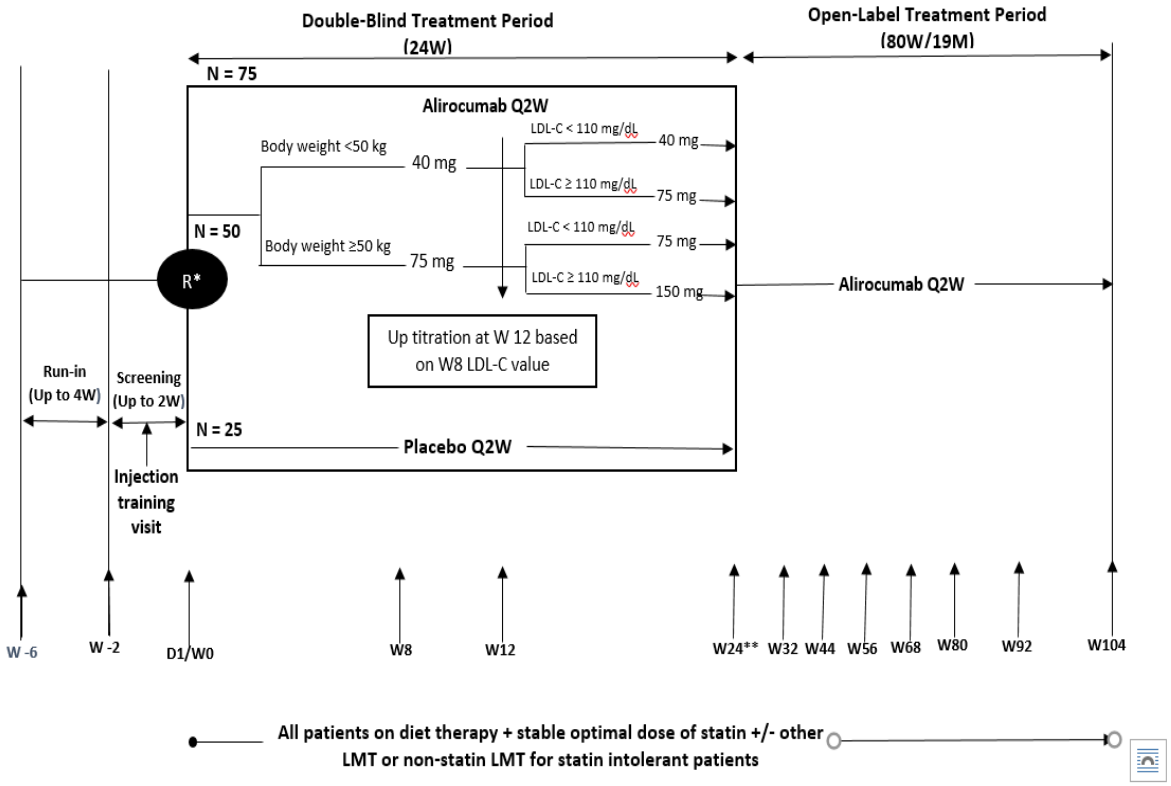
Table 1 - Statistical power according to mean difference and SD of the FMD absolute change from baseline to Week 24

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%

1.4 STUDY PLAN

The following figures present the graphical study design:

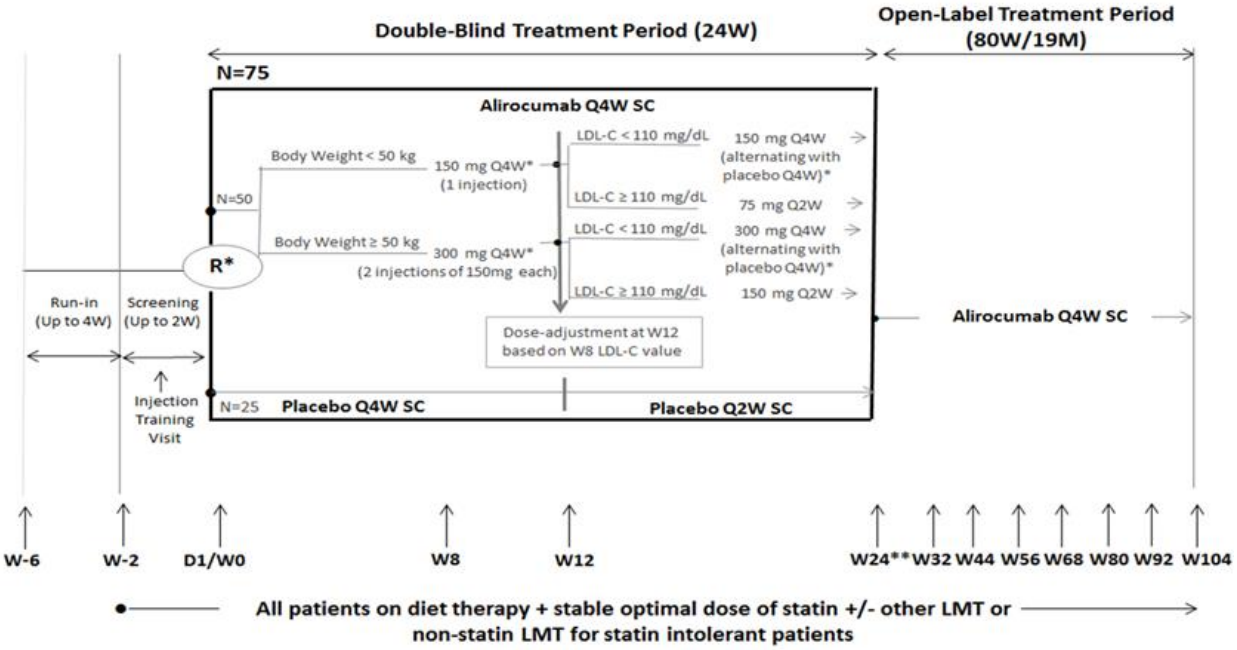
Figure 1 - Graphical study design for Q2W dosing regimen cohort



*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

Figure 2 - Graphical study design for 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 "sham Q2W*" regimen, with alirocumab Q4W alternating with placebo Q4W.

** Primary endpoint at W24.

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

This section summarizes major changes to the protocol statistical section with emphasis on changes after study start (after the first patient was enrolled).

The protocol history table below gives the timing, rationale, and key details of major changes to the protocol statistical section.

Table 2 - Protocol amendment statistical changes

Amendment Number	Rationale	Description of statistical changes
2	Revision of the statistical section in accordance with the addition of the Q4W regimen	- Sample size considerations adapted to the addition of the Q4W regimen - In the efficacy analyses, addition of alirocumab Q4W and placebo Q4W to the treatment groups used in the statistical modelling, as well as description of the main comparison (each alirocumab regimen compared to the combined placebo group) - Addition of an analysis exploring the difference in terms of percent change from baseline in LDL-C between the 2 alirocumab dosing regimens - Safety analyses: the summary of safety results will be presented in each alirocumab regimen, in the combined alirocumab group (ie, regardless of the regimen), and in the combined placebo group. - Description of the duration of exposure added for the Q4W dosing regimen - Revision of the handling of multiplicity.
3	Revision of the statistical sections in order to specify analyzing each of the two randomized dosing regimen cohorts separately	- Revision of the 2 main comparisons: in each dosing regimen cohort, the alirocumab group will be compared to its contemporaneously randomized placebo group (ie, of the same dosing regimen cohort). The study power has been updated accordingly. Revision of the statistical models (a separate model will be run for each dosing regimen cohort) Revision of the treatment groups to be displayed in result summaries for safety and other endpoints: alirocumab and placebo within each dosing regimen cohort, and regardless of the dosing regimen cohort (pooled across cohorts)
	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.
	Information omitted by error in the previous version	- Addition of the definition of the treatment period for the Q4W dosing regimen cohort - For the FMD sub-study: addition of the dosing regimen cohort and the treatment-by-dosing regimen cohort effects in the statistical model.
	Revision of the statistical analysis for the FMD sub-study due to its very exploratory nature	- Removal of the multiple imputations process

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

Changes already incorporated in a protocol amendment are listed in Table 2. The statistical analysis plan history table below gives the timing, rationale, and key details for major changes to the statistical analysis features in this amended version of the statistical analysis plan (version 2) compared to the initial version (version 1) of 8 January 2021.

Table 3 - Statistical analysis plan statistical changes

SAP version number	Date approved	Rationale	Description of statistical changes
2	This version	Per protocol, safety assessments (laboratory data, vital signs etc..) at Week 24 are measured on the same day as the administration of first open-label injection (just before)	For patients proceeding into the open-label period, the double-blind TEAE period is truncated at the first open-label injection and not the day before (Section 2.1.4)
2	This version	As per regulatory agency's feedback	Unequal variances by treatment group will be implemented for ANCOVA analyses (Section 2.4.4.1.4, Section 2.4.4.4 and Section 2.4.5.7). Consistently, a correlation matrix by treatment group to model within-patients error will be used for the MMRM models (Section 2.4.4.1.1)
2	This version	As per regulatory agency's feedback	In the pattern mixture model (Section 2.4.4.1.4), post-treatment missing values for patients who discontinued the treatment due to the COVID-19 pandemic will be imputed under missing at random assumption, ie. based on on-treatment values in the same treatment group
2	This version	Simplification	Removal of a sensitivity analysis in Section 2.4.4.1.5 as a similar analysis is already included in Section 2.4.4.1.4
2	This version	As per regulatory agency's feedback	Pattern Mixture Model for key secondary continuous efficacy endpoints normally distributed will be implemented (Section 2.4.4.2.1)
2	This version	As per regulatory agency's feedback	For binary efficacy endpoints, in the situation of data dependent case, post-treatment missing values will be considered as failure (except for patients who discontinue due to the COVID-19 pandemic) (Section 2.4.4.2.3)

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline value is defined as the last available value obtained before or equal to the date and time of the first double-blind Investigational Medicinal Product (IMP) injection in the EFC14643 study. In case of missing time of the first double-blind IMP injection and/or time of assessment, the baseline value is defined as the last available value obtained before or equal to the date of the first double-blind IMP injection.

For patients randomized and not treated, the baseline value is defined as the last available value obtained before or equal to the date and time of randomization. In case of missing time of assessment, the baseline value is defined as the last available value obtained before or equal to the date of the randomization.

All baseline safety and efficacy parameters are presented along with the summary statistics in the safety and efficacy sections (Section 2.4.4 and Section 2.4.5).

Demographic characteristics

Demographic variables include:

- Gender (Male, Female).
- Age in years (quantitative and categorical variable: <12 and ≥12 to <18 years, as well as <10, ≥10 to <12, and ≥12 to <18 years).
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Island, other).
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino).
- Weight in kilograms (quantitative and categorical variable: <50 and ≥50 kg).
- Height in centimeters (quantitative variable).
- Body mass index (BMI) in kg/m² (quantitative and categorical variable: <P5: Underweight, ≥P5 to <P85: Healthy weight, ≥P85 to <P95: Overweight and ≥P95: Obesity, using the World Health Organization [WHO] growth reference 5-19 years (1, 2, 3).

Medical or surgical history

Medical or surgical history includes medical history of specific interest such as cardiovascular (CV) history and cardiovascular risk factors, subject medical allergic history and family medical allergic history, and relevant medical or surgical history other than hypercholesterolemia, CV/CV

Risk and allergies. Medical and surgical history will be described using all pre-printed terms collected in the dedicated medical history e-CRF pages.

CV history and CV Risk factors history will be based on items pre-listed in the dedicated medical history e-CRF page and include:

- Family history of Myocardial Infarction (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).
- Tendon xanthoma in family (in 1st or 2nd degree relative).
- Familial defective apo B-100.
- DNA-based evidence of an LDL receptor mutation (of the subject).
- Tendon xanthoma (of the subject).
- Subject history of raised Total-C: Total-C >6.7 mmol/l (260 mg/dL) in a child under 16 years of age OR >7.5 mmol/l (290 mg/dL) above 16; Levels either pre-treatment or highest on treatment.
- Subject history of raised LDL cholesterol: LDL cholesterol > 4.0 mmol/l (155 mg/dL) in a child under 16 years OR > 4.9 mmol/l (190 mg/dL) above 16; Levels either pre-treatment or highest on treatment.
- Hypertension (of the subject).
- Type 1 Diabetes (of the subject).
- Type 2 Diabetes (of the subject).

Subject medical allergic history and family medical allergic history will be described using all pre-printed terms collected in the dedicated medical history e-CRF page.

All medical history information pre-listed or not in the e-CRF, will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

Smoking status and alcohol habits

Smoking status and alcohol habits include:

- Smoking status (Never, Former and Current).
- Frequency of alcoholic drinks in the last 12 months (Never/Occasional/At least monthly/At least weekly/At least daily).
- Number of standard drinks (1 or 2/Greater than 2) per day when drinking alcohol.

Disease Characteristics and relevant medical data

Specific disease characteristic includes:

- Diagnosis of heFH made by Clinical Simon Broome Criteria (Definite/Possible).
- Diagnosis of heFH made by genotyping at any time prior to or during the study (Yes [Prior to screening/ At baseline with centralized genotyping], No).
- Time to diagnosis (in years).
- Statin intolerant status, as per protocol definition (Yes, No):
  - If Yes, reason the subject is statin intolerant: [Subject is not receiving a daily regimen of statin/Not tolerating daily dose, Subject unable to tolerate statins, having tried at least 2 statins: one statin at the lowest daily starting dose, AND another statin at any dose, due to skeletal muscle-related symptoms].
  - If Not statin intolerant: [Subject treated with maximal dose of statin he can tolerate due to adverse event (AE) at higher dose [Yes, No]].
  - If Yes, AE(s) encountered at higher doses: [Skeletal muscle related events, Liver function test abnormalities, Co-morbid conditions such as impaired glucose tolerance/impaired fasting glucose, Other].
  - If No, reason of no statin intensification: [Regional practice or local guideline, Patient/parent's refusal, Other].
- Subjects, age of 8 to less than 10 years, have had other available interventions to lower calculated LDL-C, but these have been insufficient [Yes, No, NA].
- Type of lipid-modifying therapy ever taken: Statin, fibrates, bile acid sequestrant, cholesterol absorption inhibitor, nicotinic acid and derivates, omega 3 fatty acids ≥1000 mg/day) as reported in the "History of Hyperlipoproteinemia" e-CRF page.
- Background LMT at randomization, as reported in the dedicated prior & concomitant medications e-CRF pages.
  - Any statin
    - Atorvastatin daily dose in mg (<10, 10, 20, 40, 80, Other),
    - Rosuvastatin daily dose in mg (<5, 5, 10, 20, 40, Other),
    - Simvastatin daily dose in mg (<10, 10, 20, 40, >40, Other),
    - Pravastatin daily dose in mg (<10, 10, 20, 40, >40, Other),
    - Lovastatin daily dose in mg (<10, 10, 20, 40, >40, Other),
    - Fluvastatin daily dose in mg (<20, 20, 40, 80, >80, Other),
    - Pitavastatin (at any dose)

- Any LMT other than statins:
  - Ezetimibe,
  - Any other LMT other than nutraceuticals (by chemical class and drug name). This includes fenofibrate and other non-Statin LMT eg, niacin.
  - Nutraceuticals (Omega 3 fatty acids (<1000mg/day), Phytosterols, Psyllium/plantago, Policosanol, Other nutraceuticals).

Other baseline characteristics

Other baseline characteristics include:

- Glycated haemoglobin A1c (HbA_{1c}) (quantitative and qualitative variable: <5.7%, ≥5.7% to <6.5%, ≥6.5%), and efficacy lipid parameters (quantitative variables for all efficacy parameters and the following categorical variables) will be also summarized at baseline (see definition in Section 2.1.3):
- LDL-C: <130, ≥130 to <160, ≥160 to <190, ≥190 mg/dL (ie, <3.37, ≥3.37 to <4.14, ≥4.14 to <4.91, ≥4.91 mmol/L).
- HDL-C: <40, ≥40 mg/dL (ie, <1.04, ≥1.04 mmol/L).
- Non-HDL-C: <160, ≥160 to <190, ≥190 to <220, ≥220 mg/dL (ie, <4.14, ≥4.14 to <4.91, ≥4.91 to 5.69, ≥5.69 mmol/L).
- Fasting TGs: <150, ≥150 to <200, ≥200 mg/dL (ie, <1.7, ≥1.7 to <2.3, ≥2.3 mmol/L).
- Lp(a): <30, ≥30 to <50, ≥50 mg/dL (ie, <0.3, ≥0.3 to <0.5, ≥0.5 g/L).
- Apo B: <75, ≥75 to <90, ≥90 mg/dL (ie, <0.75, ≥0.75 to <0.9, ≥0.9 g/L).

Any technical details related to computation, dates, and imputation for missing dates are described in Section 2.5.

2.1.2 Prior or concomitant medications and post-treatment medications

All medications taken within 12 weeks prior to screening and until the end of the study, including LMTs are to be reported in one of the following specific case report form pages:

- Previous and concomitant statin drugs.
- Previous and concomitant lipid lowering drugs (other than statins).
- Other Previous and concomitant medications (other than statin, lipid lowering drugs).
- Topical anesthetic for IMP injection.

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at Sanofi at the time of database lock.

- Prior medications are those the patient used within 12 weeks prior to screening visit and prior to first double-blind IMP administration. Prior medications can be discontinued before first administration or can be ongoing during treatment phase.
- Double-blind concomitant medications are any treatments received by the patient concomitantly with the IMP, from first double-blind IMP to the last double-blind IMP injection +70 days (for patients choosing not to continue into the OL period). For patients entering in the OL period, concomitant medications will be truncated at the day before first open-label IMP injection in the extension period. A given medication can be classified both as a prior medication and as a concomitant medication. Double-blind concomitant medications do not include medications started during the double-blind post-treatment period (as defined in the observation period in Section 2.1.4).
- Post-treatment double-blind medications are those the patient took in the period starting from 71 days after the last double-blind IMP injection and ending when the patient terminates the study (for patients choosing not to continue into the OL period).
- Open-label concomitant medications are defined as any treatments received by the patient concomitantly with the open-label IMP, from the first open-label IMP injection to the last open-label IMP injection +70 days.
- Post-treatment open-label medications are those the patient took in the period starting from 71 days after the last open-label IMP injection.

Any technical details related to computation, dates, imputation for missing dates are described in Section 2.5

2.1.3 Efficacy endpoints

Efficacy endpoints include lipid parameters (ie, Total-C, LDL-C, HDL-C, fasting TG, non-HDL-C, Apo B, Apo A-1, ratio Apo B/Apo A-1, Lp[a]). All these parameters are measured or calculated by a central laboratory, for both scheduled and unscheduled time points. Calculated LDL-C is obtained using the Friedewald formula. However if TG values exceed 400 mg/dL (4.52 mmol/L), the LDL-C should be measured by the Central Laboratory (via beta quantification method) and used as the reference value for LDL-C rather than calculated LDL-C. Non-HDL-C is calculated by subtracting HDL-C from the Total-C.

Unless otherwise specified, all lipid values (scheduled or unscheduled, fasting or not fasting) may be used to provide a value for the primary and secondary efficacy endpoints. All measurements, scheduled or unscheduled, fasting or not fasting, will be assigned to analysis windows defined in Section 2.5.4, Table 5 and Table 6 in order to provide an assessment for time points when the lipid values were to be collected as per protocol. For TG, only fasting measurements will be used and measurements with missing fasting status will be excluded from the analyses.

For all time points post-baseline, the value used for the analyses at a given time point (eg, at Week 24) is the value obtained within the corresponding analysis window.

The baseline definition described in Section 2.1.1 will be used for the analyses of the double-blind and OL periods.

The analysis of primary and key secondary endpoints consists of the comparison of each alirocumab dosing regimen group versus its contemporaneously randomized placebo group (ie, alirocumab Q2W versus placebo Q2W; alirocumab Q4W versus placebo Q4W) for endpoints listed in primary endpoint and secondary endpoints. A sequential inferential approach will be used within each regimen (refer to Section 2.4.4.3).

2.1.3.1 Primary efficacy endpoint(s)

The primary efficacy endpoint is the percent change in LDL-C from baseline to Week 24 in the intent-to-treat (ITT) population (defined in Section 2.3.1.1), using LDL-C values regardless of adherence to treatment (ITT estimand). Primary endpoint is defined as: 100x (LDL-C value at Week 24 - LDL-C value at baseline) / LDL-C value at baseline.

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 the above definition. In case both calculated and measured LDL-C values are provided for the same sampling, the measured LDL-C will be considered.

2.1.3.2 Secondary efficacy endpoint(s)

2.1.3.2.1 Key secondary efficacy endpoints

The key secondary efficacy endpoints are:

- 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).

2.1.3.2.2 Other secondary efficacy endpoints

- All primary and key secondary endpoints in the modified ITT (mITT) population (defined in Section 2.3.1.2), using 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).

2.1.3.2.3 Exploratory endpoint of the FMD sub-study

The exploratory endpoint of the FMD sub-study is 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. The analysis will consist of the comparison of alirocumab to placebo, regardless of the dosing regimen cohort.

On-treatment analysis will be also conducted.

2.1.4 Safety endpoints

The safety analysis will be based on the reported AEs and other safety information, such as clinical laboratory data, vital signs, Tanner stage and Cogstate battery (neurocognitive functions) test assessment.

Observation period for the Q2W dosing regimen cohort,

The observation of safety data will be as follows:

- The pre-treatment 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 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) as residual effect of alirocumab is possible until 10 weeks after the stop of treatment IMP injection. This period will be truncated at the first dose of open-label IMP for patients proceeding into the OL treatment period.

  The double-blind TEAE period will include:

  - The double-blind treatment period defined as the time from the first dose of double-blind IMP injection up to the day of last dose of double-blind IMP injection +21 days.
- The double-blind post-treatment period is defined as the time starting the day after the end of the double-blind TEAE period (truncated at the first dose of open-label IMP for patients proceeding into the open-label treatment period).
- The open-label TEAE period is defined as the time from the first dose of open-label IMP injection up to the day of last dose of open-label IMP injection +70 days.
  - The open-label TEAE period will include the open-label treatment period defined as the time from the first dose of open-label IMP injection up to the day of last dose of open-label IMP injection + 21 days.
- The open-label post-treatment period is defined as the time starting the day after the end of the open-label TEAE period (ie, 71 days after the day of last dose of open-label IMP injection).

Observation period for the Q4W dosing regimen cohort,

The observation of safety data will be as follows:

- The pre-treatment 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 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) as residual effect of alirocumab is possible until 10 weeks after the stop of treatment IMP injection. This period will be truncated at the first dose of open-label IMP for patients proceeding into the OL treatment period.

  The double-blind TEAE period will include:

  - The double-blind treatment period defined as the time from the first dose of double-blind IMP injection up to the day of last dose of double-blind IMP injection +35 days

for patients who stopped definitively the IMP before the switch to Q2W regimen (actual or sham) at Week 12

- The double-blind treatment period defined as the time from the first dose of double-blind IMP injection up to the day of last dose of double-blind IMP injection +21 days, otherwise.

- The double-blind post-treatment period is defined as the time starting the day after the end of the double-blind TEAE period (truncated at the first dose of open-label IMP for patients proceeding into the open-label treatment period).
- The open-label TEAE period is defined as the time from the first dose of open-label IMP injection up to the day of last dose of open-label IMP injection +70 days.

  The open-label TEAE period will include the open-label treatment period defined as:

  - the time from the first dose of open-label IMP injection up to the day of last dose of open-label IMP injection +35 days, for patients still under Q4W regimen at the end of the open-label treatment period.
  - the time from the first dose of open-label IMP injection up to the day of last dose of open-label IMP injection + 21 days, otherwise.
- The open-label post-treatment period is defined as the time starting the day after the end of the open-label TEAE period (ie, 71 days after the day of last dose of open-label IMP injection).

2.1.4.1 Adverse events variables

Adverse events (including serious adverse events (SAEs) and adverse events of special interest (AESIs) are recorded from the time of signed informed consent until the end of study (definition of AESIs is provided in the study protocol). All AEs diagnosed by the Investigator will be reported and described.

All AEs will be coded to a "lowest level term (LLT)", "preferred term (PT)", "high level term (HLT)", "high level group term (HLGT)" and associated primary "system organ class (SOC) using the version of MedDRA currently in effect at Sanofi at the time of database lock.

Adverse event observation period

- Pre-treatment AEs are AEs that developed or worsened or became serious during the pre-treatment period.
- For double-blind period:
  - Double-blind treatment-emergent adverse events are AEs that developed or worsened or became serious during the double-blind TEAE period.
  - Double-blind post-treatment AEs are AEs that developed or worsened or became serious during the double-blind post-treatment period.
- For open-label period:

- Open-label treatment-emergent adverse events are AEs developed or worsened or became serious during the open-label TEAE period.
- Open-label post-treatment AEs are AEs that developed or worsened or became serious during the open-label post-treatment period.

Groupings of adverse events

Grouping of adverse events include the following:

- Local injection site reactions (AESIs or not), selected using e-CRF specific tick box on the adverse event page.
- General allergic events (AESIs or not), selected using SMQ “hypersensitivity” (broad and narrow) excluding the preferred terms linked to local injection site reactions (ie, preferred terms containing “injection site” or “infusion site”).
- ALT >3 ULN (if baseline ALT < ULN), or ALT ≥2 times the baseline value (if baseline ALT ≥ ULN), selected using laboratory data.
- Neurologic events (AESIs or not), selected using a CMQ based on SMQs “demyelination” (broad and narrow), “peripheral neuropathy” (broad and narrow), and “Guillain-Barre syndrome” (broad and narrow) excluding the following preferred terms “acute respiratory distress syndrome”, “asthenia”, “respiratory arrest” and “respiratory failure” and including selected PTs from SMQ "optic nerve disorders" (see Table 8 for the list of terms).
- Neurocognitive events:
  - Selected using a CMQ, based on the following 5 HLGTs: “deliria (including confusion)”, “cognitive and attention disorders and disturbances”, “dementia and amnestic conditions”, “disturbances in thinking and perception”, and “mental impairment disorders”.
  - A second grouping of terms for neurocognitive events was defined based on Regulatory Agency request (see Table 9 for the list of terms).
- Symptomatic overdose of IMP selected using appropriate MedDRA codes and the tick boxes “Overdose of Alirocumab” and “Symptomatic Overdose” in the overdose adverse event form.
- Pregnancy (including male patient’s partner) selected using eCRF tick box.

In addition, the following additional grouping of events will be provided:

- Hepatic disorder events using SMQ “Hepatic disorder”.
- Diabetes mellitus or diabetic complications using 1/HLGT “diabetes complications” (including PTs pertaining to the secondary SOC included in the HLGT), 2/ the HLT “diabetes mellitus”, 3/ the HLT “carbohydrate tolerance analyses (including diabetes)” excluding PTs “blood glucose decreased” and “glycosylated haemoglobin decreased” and 4/ from the HLT "hyperglycaemic conditions NEC" only the following PTs “hyperglycaemia”, “hyperglycaemic unconsciousness” and “hyperglycaemic seizure”.

- Cataract using HLT “Cataract conditions”.

Of note, groupings are based on the version of MedDRA currently in effect at Sanofi at the time of this SAP version (Version 23.1) and may be updated if appropriate, based on a more recent version available at time of database lock.

2.1.4.2 Deaths

The deaths observation periods are per the observation periods defined above.

For double-blind period:

- Death on-treatment: deaths occurring during the double-blind TEAE period,
- Death post-treatment: deaths occurring during the double-blind post-treatment period

For open-label period:

- Death on-treatment: deaths occurring during the open-label TEAE period,
- Death post-treatment: deaths occurring during the open-label post-treatment period

2.1.4.3 Laboratory safety variables

Clinical laboratory data consist of blood analysis, including hematology and clinical chemistry. Clinical laboratory values will be analyzed into international units. International units will be used in all listings and tables. Clinical laboratory values converted into conventional (US) units will be also available in the database. Analyses can be provided upon request.

Unless otherwise specified below, blood samples for clinical laboratories (eg, hematology, clinical chemistry) were to be collected during:

- Screening at Visit 2 (up to Week -2).
- The double-blind period at Visit 4 (Week 0 / Day 1), Visit 6 (Week 12) and Visit 7 (Week 24) /or early termination.
- The OL period at Visit 8 (Week 32), Visit 9 (Week 44), Visit 11 (Week 68) and Visit 14 (Week 104)/or early termination, for patients proceeding into OL period.

Adrenal gland hormones, gonadal and pituitary hormones, fat soluble vitamins, were to be collected during:

- The double-blind period at Visit 4 (Week 0 / Day 1) and Visit 7 (Week 24)/or early termination
- The OL period at Visit 9 (Week 44), Visit 11 (Week 68) and Visit 14 (Week 104)/or early termination, for patients proceeding into OL period.

The following laboratory parameters (excluding those considered as efficacy parameters) will be classified as follows:

- Hematology:
  - Red blood cells and platelets: hemoglobin, hematocrit, red blood cell count, platelet count and hematocrit
  - White blood cells: white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils.
- Clinical chemistry:
  - Metabolism: glucose, total protein, albumin, creatine phosphokinase (CPK),
  - Electrolytes: sodium, potassium, chloride, calcium, phosphorus, bicarbonate,
  - Renal function: creatinine, eGFR, creatinine clearance, blood urea nitrogen, uric acid,
  - Liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase (γGT), lactate dehydrogenase (LDH), total bilirubin, and in case of total bilirubin values above the normal range, must include conjugated and non-conjugated bilirubin (used for describing individual cases only).
- Adrenal gland hormones: cortisol (with reflexive adrenocorticotrophic hormone (ACTH) levels if cortisol < lower limit of normal [LLN]) and dehydroepiandrosterone sulfate (DHEAS).
- Gonadal hormones: testosterone (males) and estradiol (females).
- Pituitary hormones: luteinizing hormone (LH) and follicle-stimulating hormone (FSH).
- Fat soluble vitamins: A (retinol), D (25 hydroxy vitamin D), E (alpha-tocopherol), and K (phylloquinone).
- Serum pregnancy test: blood test at screening visit and local urine pregnancy test for all other tests.

Technical formulas are described in Section 2.5.1.

2.1.4.4 Vital signs variables

Vital Signs parameters include Heart Rate (HR), Systolic and Diastolic Blood Pressure (SBP and DBP) in sitting position, as well as weight, height and BMI.

Body weight was to be measured during:

- Run-in (if applicable) at Visit 1 (up to Week -6) or Screening at Visit 2 (up to Week -2).
- The double-blind period at Visit 4 (Week 0/Day 1), Visit 6 (Week 12), Visit 7 (Week 24)/or early termination.

- The OL period at Visit 8 (Week 32), Visit 9 (Week 44), Visit 11 (Week 68), Visit 13 (Week 92) and Visit 14 (Week 104)/or early termination for patients proceeding into OL period.

Height was to be measured during:

- Run-in (if applicable) at Visit 1 (up to Week -6) or Screening at Visit 2 (up to Week -2).
- The double-blind period at Visit 7 (Week 24)/or early termination.
- The OL period at Visit 9 (Week 44), Visit 11 (Week 68) and Visit 14 (Week 104)/or early termination for patients proceeding into OL period.

BMI and height percentiles will be calculated (1, 2, 3).

Heart rate and blood pressure were to be measured during:

- Screening at Visit 2 (up to Week -2).
- The double-blind period at Visit 4 (Week 0/Day 1), Visit 6 (Week 12), Visit 7 (Week 24) /or early termination.
- The OL period at Visit 8 (Week 32), Visit 9 (Week 44), Visit 11 (Week 68) and Visit 14 (Week 104)/or early termination for patients proceeding into OL period.

2.1.4.5 Electrocardiogram variables

Not applicable

2.1.4.6 Tanner stage measurement

Tanner stages measurement include assessments of boys–development of external genitalia, girls breast development, boys/girls –pubic hair, performed if possible, by the same investigator/designee trained to assess pubertal development, during:

- Run-in (if needed) at Visit 1 (up to Week -6) or Screening at Visit 2 (up to Week -2).
- The double-blind period at Visit 7 (Week 24)/or early termination.
- The OL period at Visit 9 (Week 44), Visit 11 (Week 68) and Visit 14 (Week 104)/or early termination for patients proceeding into OL period.

In addition, a global Tanner puberty classification as Prepubescent [Tanner stage = 1], Pubescent

[Tanner stage ≥2 to 4] and Postpubescent [Tanner stage = 5]) will be derived, based on breast development stage for girls and external genitalia stage for boys as it is commonly reported in the literature that in most children the first signs of puberty is breast development for girls and external genitalia for boys (4, 5, 6).

2.1.4.7 Cogstate battery test

Cogstate battery test was to be administered during:

- The double-blind period at Visit 4 (Week 0/Day 1) and Visit 7 (Week 24)/or early termination
- The OL period at Visit 11 (Week 68) and Visit 14 (Week 104)/or early termination

Cogstate battery test consists of identification test (IDN), detection test (DET), one card learning test (OCL), and Groton maze learning test (GML). The results (ie, scores) will be automatically calculated. The change from baseline to Week 24 will be calculated for each score.

Z-scores will be also computed for each test based on patient's age at baseline for the 24-week DB period, or based on patient's age at the visit when the test is performed for the OL period (see Appendix E and Appendix F for details).

A composite score will be calculated as the mean of the Z-scores equally weighted, provided that at least three of the four tests are available AND if all the following cognitive domains are covered:

- Attention, through either DET or IDN
- Visual learning, through OCL
- Executive function, through GML

Then change from baseline to Week 24 will be computed for the composite score.

2.1.5 Other endpoints

Other endpoints listed below are defined using same definitions and rules as for LDL-C, when applicable (see Section 2.1.3) and include:

- The absolute change in HbA_{1c} (%) from baseline to Week 24 in the double-blind period, as well as change from baseline to Week 68 and Week 104 in the OL period. PCSA criteria for HbA_{1c} will be also used (see Appendix A).
- 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 each treatment period (double-blind or open-label) and the time to the first LDL-C <50 mg/dL (<25 mg/dL, <15mg/dL respectively) for these patients within the relevant treatment period.
- Cardiac function: CPK-MB and cardiac troponin (at Visit 4 [Week 0 / Day 1] and Visit 7 [Week 24]/or early termination) and in case of any clinically relevant cardiovascular effect observed in patients.
- The percent change in hs-CRP from baseline to Week 24 in the double-blind period. Hs-CRP values greater or equal to 10 mg/L will be excluded from analyses in a second approach, since these are suggestive of concurrent infections (1). PCSA (potentially

clinically significant abnormalities) criteria for hs-CRP will be also used (see Appendix A).

- Urine test at Visit 4 (Week 0 / Day 1) and Visit 7 (Week 24)/or early termination. Macroscopy will be performed at the central laboratory. If abnormal, then a standard microscope assessment will be conducted.

2.1.6 Anti-alirocumab antibodies variables

Anti-alirocumab antibodies (ADA) are assessed:

- During the double-blind period at Visit 4 (Week 0/Day 1, before the first IMP injection), at Visit 6 (Week 12) and Visit 7 (Week 24)/or early termination for patients not proceeding into OL period.
- During the OL period at Visit 11 (Week 68) and Visit 14 (Week 104) /or early termination for patients proceeding into OL period.

ADA measurements will be assigned to the same analysis windows as defined for efficacy endpoints (Table 5 and Table 6).The following variables will be described for both double-blind and open-label periods:

- ADA response (Positive or Negative).

  For ADA positive:

  - Titer levels.
  - Neutralizing status (Positive or Negative).
- Pre-existing positive ADA defined as patients with positive ADA response at baseline with less than 4-fold increase in titer in the post-baseline period.
- Treatment-emergent positive ADA response defined as:
  - Patients with no ADA positive response at baseline but with any positive response in the post-baseline period (for double-blind period: up to Visit 7 (Week 24)/ early termination visit for patients not proceeding into open-label period or first open-label IMP injection for patient proceeding into open-label period, for open-label period: up to Visit 14 (week 104)/early termination.

    OR
  - Patients with a positive ADA response at baseline and at least a 4-fold increase in titer in the post-baseline period (for double-blind period: up to Visit 7 (Week 24)/early termination for patients not proceeding into OL period or first open-label IMP injection for patient proceeding into OL period, for OL period: up to Visit 14 (week 104)/early termination.

For treatment-emergent positive ADA, the following categories for ADA duration will be applied:

- A persistent positive response is a treatment-emergent ADA positive response detected in at least 2 consecutive post-baseline samples separated by at least a 12-week period.
- An indeterminate duration positive response is defined as ADA present only at the last sampling time point.
- A transient positive response is defined as any treatment-emergent positive ADA response that is neither considered persistent nor indeterminate.

In addition, potential ADA samples to be collected for patients who do not enter into OL period or who prematurely discontinue the double-blind period and have a titer≥240 at their end of treatment visit will be listed.

2.1.7 Pharmacokinetic variables

Concentrations of total alirocumab, total and free PCSK9 in serum are assessed during the double-blind period at Visit 4 (Week 0/Day 1), Visit 5 (Week 8), Visit 6 (Week 12) and Visit 7 (Week 24).

Pharmacokinetic variable is the total alirocumab concentration at each time point. Depending on the timing of the sample versus the previous injection, C_{trough}, will be defined as follows:

- C_{trough} for Q2W regimen: alirocumab concentration sample taken between 8 and 21 days after previous injection of alirocumab (ie, just prior the next injection).
- C_{trough} for Q4W regimen: alirocumab concentration sample taken between 22 and 35 days after previous injection of alirocumab (ie, just prior the next injection).

Total alirocumab concentration and total and free PCSK9 concentration will be described following time windows as defined in Section 2.5.4 in Table 7.

Of note, for patients with a dose adjustment from Q4W dosing regimen to Q2W dosing regimen, the C_{trough} will be defined according to the regimen received at the time of the sample collection.

2.2 DISPOSITION OF PATIENTS

This section describes patient disposition for both patient study status and the patient analysis populations.

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 IVRS/IWRS database, regardless of whether the treatment kit was used or not. Patients treated without being randomized or treated with a double-blind treatment kit

before the randomization will not be considered as randomized and will not be included in any analysis population.

For patient study status in the double-blind period, the total number of patients in each of the following categories will be presented in the clinical study report using a flowchart diagram or summary table:

- Screened patients.
- Screen failure patients and reasons for screen failure.
- Non-randomized but treated patients, if any.
- Randomized patients.
- Randomized but not treated patients and reason for not being treated.
- Randomized and treated patients.
- Patients who completed the double-blind study treatment period as per protocol (as per eCRF end of double-blind treatment form).
- Patients who did not complete the double-blind study treatment period as per protocol (as per eCRF end of double-blind treatment form).
- Patients who discontinued the double-blind study treatment by main reason for permanent treatment discontinuation (as per eCRF end of double-blind treatment form).
- Status at last study contact for patients not entering in the open-label treatment extension.
- Patients participating in the open-label treatment extension period.

For all above categories of patients (except for the screened and non-randomized categories) percentages will be calculated using the number of randomized patients as denominator and summaries will be presented by treatment group as described in Section 2.4.

For patient study status in the open-label period, the total number of patients in each of the following categories will be presented in the clinical study report using a flowchart diagram or summary table:

- Patients treated during the OL period (all patients who received at least one open-label injection during the OL period).
- Patients who completed the OL treatment period as per protocol (as per eCRF end of open-label treatment form).
- Patients who did not complete the OL treatment period as per protocol (as per eCRF end of open-label treatment form).
- Patients who discontinued OL treatment by main reason for permanent treatment discontinuation.

For patient study status in the open-label period, percentages will be calculated using the number of patients in the OL population (defined in Section 2.3.5) as denominator and summaries will be presented by treatment group as described in Section 2.4.

Reasons for treatment discontinuation will be supplied in tables giving numbers and percentages.

The incidence of premature treatment discontinuation during the double-blind period (irrespective of the reason) and premature treatment discontinuation due to AEs will be presented graphically on randomized and treated patients (as randomized), using Kaplan-Meier method.

Any critical or major protocol deviations (automatic or manual) will be summarized by deviation category in the randomized population for the double-blind period and in the OL population for open-label period. This description will also be performed distinguishing patients with trial impact due to Covid-19 from those who were not (see definition in Section 2.3). In addition, the number (%) of patients by country/site and the listing of patients with at least one critical or major deviation will be provided.

Additionally, the following populations will be summarized:

- Randomized population.
- Efficacy populations: ITT and mITT populations.
- Exploratory efficacy population: FMD sub-study population.
- Safety population.
- Pharmacokinetics population.
- Anti-alirocumab antibody population.
- Open-label population.
- Population without trial impact/disruption due to COVID-19.

Definitions of the study populations are provided in Section 2.3.

2.2.1 Randomization and drug dispensing irregularities

Randomization and drug-dispensing irregularities occur whenever:

1. A randomization is not in accordance with the protocol-defined randomization method, such as a) a patient is randomized based on an incorrect stratum, or b) a patient is randomized twice.

   OR

2. A patient is dispensed an IMP kit not allocated by the protocol-defined randomization, such as a) a patient at any time in the study is dispensed a different treatment kit than as randomized (which may or may not contain the correct-as-randomized IMP), or b) a non-randomized patient is treated with IMP reserved for randomized patients.

Randomization and drug-dispensing irregularities will be monitored throughout the study and reviewed on an ongoing basis.

All randomization and drug-dispensing irregularities will be documented in the clinical study report. These irregularities will be summarized on the randomized population. Non-randomized, treated patients will be described separately.

2.3 ANALYSIS POPULATIONS

Patients treated without being randomized will not be considered randomized and will not be included in any analysis population. The safety experience of patients treated and not randomized will be reported separately, and these patients will not be in the safety population.

The randomized population includes any patient who has been allocated to a randomized treatment regardless of whether the treatment kit was used.

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.

2.3.1 Efficacy populations

The primary efficacy analysis population will be the ITT population.

2.3.1.1 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 group).

2.3.1.2 Modified Intent to treat population

The mITT population is defined as all randomized patients who took at least one dose or part of a dose of the double-blind IMP injection.

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

2.3.1.3 FMD sub-study population

The analysis of the FMD will be performed on randomized patients included in the sub-study with a baseline and a post-baseline FMD assessment available. Patients in the FMD sub-study population will be analyzed according to the treatment group allocated by randomization (ie, as-randomized treatment group).

2.3.2 Safety population

The Safety population considered for safety analyses will be the randomized patients who actually received at least one dose or part of a dose of the double-blind IMP injection. Patients will be analyzed according to the treatment actually received (ie, as-treated treatment group).

In addition, randomized patients for whom it is unclear whether they took the study medication will be included in the safety population in the treatment group as randomized.

Within each dosing regimen cohort, for patients receiving mistakenly both placebo and alirocumab (regardless of the dose) IMP injection during the double-blind period (cases reported as protocol deviation), the treatment group used for as-treated analysis will be defined according to the treatment (alirocumab or placebo) of which the patient received highest number of injections. In case of the same number of injections of each treatment is received, the as-treated treatment group will be the as-randomized group. Of note, placebo injections allocated by IVRS/IWRS to maintain the blind for the alirocumab Q4W group ("sham Q2W") will not be taken into account in the derivation of the "as-treated treatment group".

2.3.3 Anti-alirocumab antibody population

The ADA analysis will be performed on all randomized and treated patients (safety population) with an available ADA sample at Week 0 (baseline) and at least one non-missing ADA sample post first double-blind IMP injection and up to Week 24/early termination or up to first open-label IMP injection for patient proceeding into open-label period.

2.3.4 Pharmacokinetics population

The PK analysis will be performed on all randomized and treated patients (safety population) with at least one non-missing drug concentration value (including BLQ values) post first double-blind IMP injection and up to Week 24/early termination visit or up to first injection in the open-label period, for patients proceeding into the open-label period.

2.3.5 Open-label population

The OL population considered for all analyses in the OL treatment period will be all randomized patients who received at least one dose or part of dose of IMP during the OL treatment period.

2.3.6 Population without trial impact/disruption due to COVID-19

The population without trial impact/disruption due to COVID-19 will be defined as any patient without any of the following:

- Major or critical deviation related to COVID-19
- Permanent treatment discontinuation related to COVID-19
- Permanent study discontinuation related to COVID-19.

2.4 STATISTICAL METHODS

General rules

Analyses will be performed separately for the double-blind and the OL periods, unless otherwise noted.

Double-blind period

Unless otherwise specified, the analyses will be performed by treatment group (placebo, alirocumab) within each dosing regimen cohort.

In addition, for disposition, populations, demographic/baseline characteristics, safety and other endpoints (refer to Section 2.1.5), analyses will be provided by treatment group (placebo, alirocumab) regardless of the dosing regimen cohorts (pooled across cohorts).

Of note, an Overall column will be displayed for populations, demographics and baseline characteristics.

OL period

The summaries will be displayed according to the treatment group (placebo, alirocumab) received in the double-blind period and Overall within each dosing regimen cohort (dosing regimen initiated at the randomization).

For disposition, populations, demographic/baseline characteristics, safety and other endpoints, analyses will be also provided by treatment group received in the double-blind period regardless of the dosing regimen cohorts, and Overall.

2.4.1 Demographics and baseline characteristics

Parameters described in Section 2.1.1 will be summarized using descriptive statistics.

Continuous data will be summarized using the number of available data, mean, SD, median, minimum and maximum for each treatment group. First quartile (Q1) and third quartile (Q3) will be also provided for baseline lipid parameters and HbA_{1c}. Categorical and ordinal data will be summarized using the number and percentage of patients.

Parameters will be summarized on the randomized population analyzed in the as-randomized treatment group. Similar analyses will be done on safety population in the as-treated treatment group and will be included in the appendices if the size of the safety population is different (>10%) from the size of the randomized population for any dosing regimen/treatment group. In the randomized population, parameters will also be summarized within each randomization stratum as per IVRS/IWRS.

All reported patient's medical and surgical history will be presented by primary SOC and HLT. The tables will be sorted by SOC internationally agreed order and decreasing frequency of HLT

based on the overall incidence across treatment groups. In addition, all medical history of specific interest (see Section 2.1.1) will be summarized.

These parameters will be also summarized in the OL population.

P-values on demographic and baseline characteristic data will not be calculated.

No specific description of safety parameters will be provided at baseline. If relevant, the baseline values will be described along with each safety analysis.

2.4.2 Prior or concomitant medications

Double-blind period

The prior, concomitant and post-treatment medications will be presented for the safety population. Medications will be summarized according to the WHO-DD dictionary, considering the first digit of the anatomical therapeutic chemical (ATC) class (anatomic category) and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized, and patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore, patients may be counted in several categories for the same medication.

The table for prior medications will be sorted by decreasing frequency of ATC followed by therapeutic class based on the overall incidence across treatment groups. In case of equal frequency across anatomic or therapeutic categories, alphabetical order will be used.

The tables for concomitant and post-treatment medications will be sorted by decreasing frequency of ATC followed by therapeutic class based on the incidence in the combined alirocumab group. In case of equal frequency across anatomic or therapeutic categories, alphabetical order will be used.

In addition, concomitant LMT medications will be summarized by pre-specified categories, chemical class or therapeutic class and standardized medication name.

OL period

All concomitant and post-treatment medications recorded during the OL period will be summarized in the OL population according to the WHO-DD dictionary.

2.4.3 Extent of investigational medicinal product exposure and compliance

The extent of IMP exposure and compliance for the double-blind period will be assessed and summarized for the safety population; for the OL period, it will be assessed on the OL population.

In addition, a description will be performed distinguishing patients with trial impact due to COVID-19 from those who were not.

2.4.3.1 Extent of investigational medicinal product exposure

Double-blind period

- Q2W dosing regimen cohort

The exposure during the double-blind period will be assessed using descriptive statistics for:

- The total number of double-blind IMP administrations by patient.
- Duration of IMP exposure in weeks defined as (last dose of double-blind IMP injection date – first dose of double-blind IMP injection date + 14 days)/7, regardless of unplanned intermittent discontinuations (see Section 2.5.3 for calculation in case of missing or incomplete data).

- Q4W dosing regimen cohort

The exposure during the double-blind period will be assessed using descriptive statistics for:

- The total number of double-blind IMP administrations by patient.
- Duration of IMP exposure in weeks defined as:
  - (last dose of double-blind IMP injection date – first dose of double-blind IMP injection date + 28 days)/7, for patients who stopped definitively the IMP before the switch to Q2W regimen (actual or sham) at Week 12, regardless of unplanned intermittent discontinuations (see Section 2.5.3 for calculation in case of missing or incomplete data).
  - (last dose of double-blind IMP injection date – first dose of double-blind IMP injection date + 14 days)/7, otherwise, regardless of unplanned intermittent discontinuations (see Section 2.5.3 for calculation in case of missing or incomplete data).

Non-integer values will be rounded to one decimal place.

All quantitative parameters above will be summarized using number, mean, SD, median, minimum and maximum. In addition, the durations of treatment exposure will be summarized according to the following categories: ≥1 day and <4 weeks, ≥4 weeks and <8 weeks, ≥8 weeks and <12 weeks, ≥12 weeks and <16 weeks, ≥16 weeks and <22 weeks, ≥22 weeks.

OL period

- Q2W dosing regimen cohort

The duration of IMP exposure (in weeks) during the OL period will be defined as (last dose of open-label IMP injection date – first dose of open-label IMP injection date + 14 days)/7, regardless of unplanned intermittent discontinuations.

- Q4W dosing regimen cohort

The duration of IMP exposure (in weeks) during the OL period will be defined as:

- (last dose of open-label IMP injection date – first dose of open-label IMP injection date + 28 days)/7, for patients still under Q4W regimen at the end of the open-label treatment period, regardless of unplanned intermittent discontinuations.
- (last dose of open-label IMP injection date – first dose of open-label IMP injection date + 14 days)/7, otherwise, regardless of unplanned intermittent discontinuations.

Duration of IMP exposure will be summarized using number, mean, SD, median, minimum and maximum and according to the following categories: ≥1 day and <24 weeks, ≥24 weeks and <52 weeks, ≥ 52 weeks and <78 weeks, ≥ 78 weeks.

Combined period (double-blind and OL periods)

In each dosing regimen cohort, study treatment exposure variables combining double-blind and open-label periods are listed below for all patients who received alirocumab in the double-blind period and entered in the OL period:

- Combined duration of alirocumab exposure in weeks, regardless of unplanned intermittent discontinuations.
- The following categories will be used for treatment exposure intervals: ≥1 day and <24 weeks, ≥24 weeks and <52 weeks, ≥ 52 weeks and <78 weeks, ≥ 78 weeks and <102 weeks, ≥ 102 weeks.

Titration/dose-adjustment

For the double-blind period, the number and percentage of patients with an up-titration/dose-adjustment in the alirocumab group during the double-blind period will be described for each dosing regimen cohort.

- In the Q2W dosing regimen cohort, patients with an up-titration are defined as up-titrated patients according to IVRS/IWRS Week 12 transaction with at least 1 injection of alirocumab 75 mg Q2W for patients with baseline BW<50 kg and 150 mg Q2W for patients with baseline BW≥50 kg afterwards.
- In the Q4W dosing regimen cohort, patients with a dose-adjustment are defined as dose-adjusted patients according to IVRS/IWRS Week 12 transaction with at least 1 injection of alirocumab 75 mg Q2W for patients with baseline BW<50 kg and 150 mg Q2W for patients with baseline BW≥50 kg afterwards.

For the OL period, the number and percentage of patients with an up-titration/dose-adjustment at Week 32 or thereafter will be described for each dosing regimen cohort, as well as the number and percentage of patients down-titrated at least once. A summary of titration status will be provided by visit. Reasons for up- or down-titration and LDL-C used to up/down-titrate will be summarized, overall and by visit. LDL-C will be summarized quantitatively and with the following categories: <25, ≥25 and <50, ≥50 and <110, ≥110 and <130, ≥ 130 mg/dL.

2.4.3.2 Compliance

For the Q2W dosing regimen cohort, compliance for the double-blind period will be assessed using the following parameters:

- The mean administration frequency of IMP double-blind injections will be defined for each patient as the average number of days between 2 consecutive double-blind administrations, that is: (last double-blind administration date – first double-blind administration date)/ (number of double-blind administrations -1) for patients receiving at least 2 administrations.
- The overall compliance for double-blind injections will be defined for each patient as: 100-(%days with under-planned dosing + %days with above-planned dosing). Under-planned and above-planned dosing will be defined as follows, considering that administrations should be performed every 2 weeks (±3 days as per protocol):
  - The % days with under-planned dosing will be defined for each patient as the number of days with no IMP administration within the previous 17 days divided by the duration of IMP exposure in days. For example, if a patient takes a dose 18 days after his/her previous administration, then 1 day is counted as a day under-planned dosing.
  - The % days with above-planned dosing will be defined for each patient as the number of days with more than one administration within the 11 days before divided by the duration of IMP exposure in days. For example, if a patient takes a dose 9 days after his/her previous administration, then 2 days are counted as days above-planned dosing.

For the Q4W dosing regimen cohort, compliance for the double-blind period will be assessed using the following parameters:

- The mean administration frequency of IMP double-blind injections will be defined for each patient as the average number of days between 2 consecutive double-blind administrations, that is: (last double-blind administration date – first double-blind administration date)/ (number of double-blind administrations -1) for patients receiving at least 2 administrations.
- The overall compliance for double-blind injections will be defined for each patient as: 100-(% days with under-planned dosing + %days with above-planned dosing). Under-planned and above-planned dosing will be defined as follows, considering that administrations should be performed every 4 weeks (±3 days as per protocol) during the first 12 weeks and every 2 weeks (±3 days) afterwards:
  - The % days with under-planned dosing will be defined for each patient as:
    - the number of days with no IMP administration within the previous 31 days divided by the duration of IMP exposure in days, for the first 12 weeks.
    - the number of days with no IMP administration within the previous 17 days divided by the duration of IMP exposure in days, after the first 12 weeks.
  - The % days with above-planned dosing will be defined for each patient as:

- the number of days with more than one administration within the 25 days before divided by the duration of IMP exposure in days within the first 12 weeks.
- the number of days with more than one administration within the 11 days before divided by the duration of IMP exposure in days after the first 12 weeks.

If appropriate, for the Q4W dosing regimen cohort, mean administration frequency and compliance could be also provided separately for the first 12 weeks and the period after.

For the OL period, only mean administration frequency will be assessed for compliance.

- The mean administration frequency of IMP open-label injections will be defined for each patient as the average number of days between 2 consecutive open-label administrations, that is: (last open-label administration date – first open-label administration date)/(number of administration -1) for patients receiving at least 2 administrations (or partial administration)

These parameters will be summarized descriptively (N, Mean, SD, Median, Minimum and Maximum).

The percentage of patients whose overall compliance for injections is <80% will be also summarized as well as numbers and percentages of patients with 0%, >0% and ≤5%, >5% and ≤10%, >10% and ≤20%, and >20% days with above-planned dosing and numbers and percentages of patients with 0%, >0% and ≤5%, >5% and ≤10%, >10% and ≤20%, and >20% days with under-planned dosing.

According to protocol, cases of overdose are reported in the AE e-CRF pages and will be described in the AE analysis (see Section 2.1.4.1 and Section 2.4.5.1). More generally, dosing irregularities will be listed in Section 2.2.1.

2.4.4 Analyses of efficacy endpoints

For statistics where international and conventional units do not impact the results (eg, means and least square (LS) means for percent changes from baseline, p-values for both percent and absolute changes from baseline, rates of patients below a threshold), derivations will be done and statistical models will be run using conventional units. For other statistics (eg, descriptive statistics at baseline and over time, absolute changes from baseline), derivations will be done with both international and conventional units.

Double-blind period

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

- 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.

OL period

With respect to efficacy data collected during the OL period, only descriptive summaries for each lipid parameter will be provided in the OL population.

Formal testing is not planned due to the absence of control group in the OL period.

Combined period (double-blind and OL periods)

For patients receiving alirocumab in the double-blind period, a combined summary including both the double-blind and open-label period assessments may be considered, referencing the double-blind baseline for variable calculations.

2.4.4.1 Analysis of primary efficacy endpoint

2.4.4.1.1 Primary efficacy analysis

Within each dosing regimen cohort, the percent change from baseline in LDL-C to Week 24 as defined in Section 2.1.3.1 will be analyzed in the ITT population using a mixed-effect model with repeated measures (MMRM) model. 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. Model assumptions for normality will be explored prior to the analysis testing.

For the Q4W dosing regimen cohort, the model will include the fixed categorical effects of treatment group (alirocumab, placebo), randomization strata (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. Model assumptions for normality will be explored prior to the analysis testing.

Of note, the stratum related to the previous participation in the DFI14223 Phase 2 study will not be included in the model for the Q4W dosing regimen cohort, as too few patients from this Phase 2 study are enrolled in this cohort due to the late start of enrollment in the Q4W regimen.

These 2 separate models will be run using SAS Mixed procedure with an unstructured correlation matrix by treatment group (in case of convergence issue, a common unstructured correlation matrix for both groups will be used) 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 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.

LS means difference at Week 24 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) as follows:

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

with the SE, 97.5% confidence intervals (CI) and p-value, using appropriate contrasts. Statistical testing will be evaluated at a 2-sided significance level of 0.025 per comparison.

Within group least-squares means and standard errors will be provided, using weights equal to the observed proportion of patients in strata variable levels in the study population (ie, "population weight") rather than equal weights. Population weights are considered more appropriate than equal coefficients due to unbalances observed in the study population between levels of the randomization stratification factors.

Let $\mu 0$, $\mu 1$ be the population means of the percent change from baseline in calculated LDL-C at Week 24 under placebo and alirocumab in the Q2W dosing regimen cohort, and respectively $\mu 0'$, $\mu 1'$ the corresponding population means in the Q4W dosing regimen cohort. The hypotheses that will be tested are:

- For Q2W dosing regimen cohort: "H0: $\mu 0 = \mu 1$ versus "H1: $\mu 0 \neq \mu 1$
- For Q4W dosing regimen cohort: "H0: $\mu 0' = \mu 1'$ versus "H1: $\mu 0' \neq \mu 1'$

The MMRM models relies on the "missing-at-random" (MAR) assumption. As we can never exclude the possibility for a not-missing-at-random (NMAR) missingness mechanism, sensitivity analyses to explore the impact of non-ignorable missingness on the primary efficacy analysis will be conducted (pattern mixture model approach using mixed imputation defined in Section 2.4.4.1.4).

2.4.4.1.2 Model assumption checks

Homogeneity of treatment effect across baseline LDL-C levels

In order to check the homogeneity of treatment effect versus baseline LDL-C, the following interaction terms will be added in the two primary MMRM models:

- Treatment group * baseline LDL-C.

- Treatment group * time-point * baseline LDL-C.

Within the framework of this model with interaction terms, for each dosing regimen cohort, a graph presenting the LS means difference versus the placebo group at Week 24 and the corresponding 97.5% CI will be provided by baseline LDL-C value.

Analysis of residuals:

The analysis of the residuals of the MMRM (for each dosing regimen cohort separately) will be primarily based on studentized residuals. It will include:

- Normality of studentized residuals, presented graphically using histogram and QQ-plot.
- Plot of studentized residuals versus predicted values.
- Distribution of studentized residuals, presented graphically using boxplots, within each category of the fixed categorical effects of the MMRM:
  - treatment group (alirocumab and placebo).
  - time point (Week 8, Week 12, Week 24).
  - treatment-by-time point interaction.
  - randomization strata.
  - randomization strata-by time point interaction.

2.4.4.1.3 Sensitivity to randomization strata

In order to assess the robustness of the primary analysis to randomization stratum mistakes (ie, the stratum recorded in IVRS differs from the actual one), the MMRM model for each dosing regimen cohort for the primary efficacy endpoint will be re-run including the actual stratum as per the eCRF instead of the stratum recorded in IVRS.

In addition, for each dosing regimen cohort, a sensitivity analysis excluding patients who previously participated in the Phase 2 DFI14223 study will be conducted for the primary efficacy endpoint.

2.4.4.1.4 Sensitivity to handling of missing data

Sensitivity analyses will be conducted to assess the robustness of primary efficacy analysis with regards to handling of missing data (7) (for each dosing regimen cohort separately).

Visual examination:

- In order to explore the missing data pattern, post-baseline LDL-C observations (in the ITT population) will be described by visit according to the following groups:

1. LDL-C available at Week 24* (ie, primary efficacy endpoint available),
2. LDL-C available at Week 12* but missing at Week 24*,

3. LDL-C available at Week 8* but missing from Week 12*,
4. LDL-C missing from Week 8

(*): as defined in Section 2.5.4 in Table 5

- Then, a graph of mean LDL-C levels (respectively percent change from baseline in LDL-C) ± SE at baseline, Week 8, Week 12 and Week 24 will be provided by missing data pattern, for each treatment group.

In the ITT population, demographic and baseline characteristics will be described within the missing data pattern number 1 versus the pooled others. P-values from Fisher exact test for categorical data and from asymptotic one-way ANOVA test for Wilcoxon scores (Kruskal-Wallis test) for continuous data, will be also provided, for descriptive purposes.

Multiple Imputations (under MAR assumption):

In addition to the MMRM method, for each dosing regimen cohort separately, the multiple imputation method will be used to address missing values, in the randomized population, followed by the testing of alirocumab versus placebo group, using an analysis of covariance (ANCOVA) model, with unequal variances by treatment group (except if convergence issue), with the intent to evaluate the robustness of the primary analysis using a different statistical method. The imputation model described in Section 2.4.4.2.2 will be used but without log transformation. In addition, for each simulation leading to negative imputed value, another value will be redrawn using MINIMUM option of MI SAS procedure.

Pattern mixture model (see Appendix C for more details)

For the Q2W dosing regimen cohort, multiple imputations will be used with different imputation strategies applied to LDL-C values missing during the on-treatment period (ie, within the time period from the first double-blind IMP injection up to the day of last double-blind injection +21 days) versus LDL-C values missing after treatment discontinuation (ie, after the day of last double-blind injection +21 days) based on the following assumptions:

- Patients within 21 days of their last double-blind IMP injection would continue to show benefit from treatment similar to that observed at the scheduled time point. Therefore, LDL-C values missing during the on-treatment period (eg, samples obtained out-side the specified window, no blood sample available although visit was performed, etc.) should be considered “Missing At Random” and imputed based on other on-treatment measurements.
- Patients who stopped taking their study treatment no longer benefited from it after discontinuation, and thus tended to have LDL-C values returning to baseline. Therefore, LDL-C values missing more than 21 days after treatment discontinuation should be imputed based on patient’s own baseline value.

For patients who permanently discontinued the treatment due to the COVID-19 pandemic, missing post-treatment data will be considered “Missing at Random” and imputed based on other on-treatment measurements in the same treatment group.

Missing LDL-C values will be imputed 100 times to generate 100 complete data sets. The percent change from baseline to Week 24 will be derived from observed and imputed LDL-C at this time point. The completed data sets will be analyzed using an ANCOVA model, with unequal variances by treatment group (except if convergence issue), with treatment group (alirocumab, placebo) and randomization strata (previous participation [yes or no] to DFI14223 study, baseline body weight [<50 or ≥50 kg]) as fixed effects, and the baseline LDL-C value as continuous covariate. The results from the 100 analyses will be combined using Rubin's formulae (8).

For the Q4W dosing regimen cohort, the same approach will be taken with the following differences:

- The on-treatment period will be defined as the time period from the first IMP injection up to the day of the last double-blind injection +35 days for patients with a last double-blind injection before the switch to Q2W regimen (actual of sham), +21 days otherwise.
- The ANCOVA model will include treatment group (alirocumab, placebo) and randomization strata (baseline body weight [<50 or ≥50 kg]) as fixed effects, and the baseline LDL-C value as continuous covariate.

2.4.4.1.5 Sensitivity to the impact of COVID-19

To estimate what would have been the treatment effect had the COVID-19 pandemic not occurred, the MMRM model used for the primary analysis will be executed on the population without trial impact/disruption due to COVID-19 (See definition in Section 2.3.6).

2.4.4.1.6 Subgroup analyses

To assess the homogeneity of the treatment effect across various subgroups, treatment-by-subgroup factor, time point-by-subgroup factor and treatment-by time point-by subgroup factor interaction terms and a subgroup factor term will be added in the two primary MMRM models (except for the subgroup "Body weight").

LS means difference at Week 24 will be provided, as well as the corresponding SE and 97.5% CIs, within each subgroup for each alirocumab dosing regimen group versus its contemporaneously randomized placebo dosing regimen group (ie, of the same dosing regimen cohort):

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

The significance level of the treatment-by-subgroup factor interaction term for each alirocumab dosing regimen group versus its contemporaneously randomized placebo group (ie, of the same dosing regimen cohort) at Week 24 will be also provided for each factor group for descriptive purpose. Forest plots will be provided. In order to handle unbalances between randomization stratification factors levels, population weights will be used as for the primary analysis model.

Only subgroups for which we anticipate having enough patients in each level are evaluated.

Subgroups of interest are:

- Body Weight stratum as par IVRS/IWRS (<50 kg, ≥50 kg),
- Gender (Female, Male),
- Age (<12 years, ≥12 years),
- Baseline LDL-C: < 160 mg/dl; ≥160 mg/dL.

2.4.4.2 Analyses of secondary efficacy endpoints

2.4.4.2.1 Continuous endpoints anticipated to have a normal distribution

Continuous secondary efficacy endpoints defined in Section 2.1.3.2 analyzed with the ITT estimand and anticipated to have a normal distribution [ie, lipids other than TG and Lp(a)] will be analyzed using the same MMRM models as for the primary endpoint with the corresponding baseline and post-baseline values in the ITT population.

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 but only including on-treatment values in the mITT population.

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

In addition, key continuous secondary efficacy endpoints anticipated to have a normal distribution will be analyzed using the same ITT estimand and Pattern Mixture Model for missing data as described for the primary efficacy endpoint in Section 2.4.4.1.4.

2.4.4.2.2 Continuous endpoints anticipated to have a non-normal distribution

Continuous secondary efficacy endpoints defined in Section 2.1.3.2 analyzed with the ITT estimand and anticipated to have a non-normal distribution (ie, TG and Lp(a)), will be analyzed using multiple imputation approach for handling of missing values in the ITT population. The percent change from baseline at time point of interest will be derived from observed and imputed lipid values at this time point.

For the Q2W dosing regimen cohort, multiple imputation will be followed by robust regression model (9) with endpoint of interest as response variable using M-estimation (using SAS ROBUSTREG procedure) with treatment group (alirocumab, placebo), randomization strata (previous participation [yes or no] to DFI14223 study, baseline body weight [<50 or ≥50 kg]) and corresponding baseline value(s) as effects to compare treatment effects. Combined means

estimates for each treatment group will be provided. The differences of these estimates with their corresponding SEs, 97.5% CIs and p-value will be provided through the SAS MIANALYZE procedure for the comparison of the alirocumab group versus the placebo group.

For the Q4W dosing regimen cohort, the same strategy will be conducted, using a robust regression model with endpoint of interest as response variable using M-estimation with treatment group (alirocumab, placebo) and randomization strata (baseline body weight [<50 or ≥50 kg]) as main effects and corresponding baseline value as covariate.

For both dosing regimen cohorts, continuous secondary efficacy endpoints analyzed with the on-treatment estimand and anticipated to have a non-normal distribution will be analyzed using the same imputation and analysis models but only including on-treatment values (see Section 2.4.4.2.1) in these models in the mITT population.

Multiple imputation model

Since in general the missing pattern is anticipated to be not monotone, a two-step approach will be used:

- Step 1: The MCMC method will be used in conjunction with the IMPUTE=MONOTONE option to create an imputed data set with a monotone missing pattern;
- Step 2: Using the monotone data set from step 1, missing data will be imputed using the regression method.

The imputation model for step 1 will include the treatment group and the values of the analyzed parameter at baseline and time-points up to Week 24.

The imputation model for step 2 will include the same variables as in step 1 with the following additional variables:

- the randomization strata;
- age and gender (age included as continuous variables).

Data will be log-transformed before imputation process and then back-transformed to create the imputed data sets using the TRANSFORM statement of SAS MI procedure.

2.4.4.2.3 Binary endpoints

Binary secondary efficacy endpoints defined in in Section 2.1.3.2 (ie, proportion of patients achieving at least 30% reduction, 50% reduction in LDL-C at Week 12 or Week 24) will be analyzed using multiple imputation approach for handling of missing values as described for non-normally distributed endpoints but without log-transformation (see Section 2.4.4.2.2 for details about multiple imputation).

For each simulation leading to negative imputed value, another value will be redrawn using MINIMUM option of MI SAS procedure.

For the Q2W dosing regimen cohort, the binary endpoint at time point of interest will be derived from observed and imputed lipid values at this time point. Multiple imputation will be followed by stratified logistic regression with treatment group (alirocumab, placebo) as main effect and corresponding baseline value(s) as covariate, stratified by randomization factors (as per IVRS, previous participation [yes or no] to DFI14223 study, baseline body weight [<50 or ≥50 kg]) Combined estimates of odds ratio 97.5% CIs, and p-value will be obtained through the SAS MIANALYZE procedure, for the alirocumab group versus the placebo group.

For the Q4W dosing regimen cohort, the same strategy will be conducted using a stratified logistic regression with treatment group (alirocumab, placebo) as main effect and corresponding baseline value(s) as covariate, stratified by randomization factors (as per IVRS, baseline body weight [<50 or ≥50 kg]).

In the data dependent case such logistic regression is not applicable (eg, the response rate is zero in one treatment arm and thus the maximum likelihood estimate may not exist), a stratified exact conditional logistic regression would be performed to compare treatment effects. LDL-C values missing during the on-treatment period will be imputed using the last observation carried forward (LOCF) approach, as well as post-treatment missing values for patients who discontinued due to the COVID-19 pandemic. The LOCF imputation method will consist of using the last value obtained up to the Week 24 analysis window (Week 12 respectively) to impute the missing Week 24 value (Week 12 respectively). Other post-treatment missing values will be considered as failure.

In case of computing issues with exact logistic regression, the baseline level(s) will be entered in the model as a categorical variable(s) using quartiles. In case the model would not converge with stratification variables, an unstratified exact logistic regression will be performed. Exact odds ratio versus placebo, 97.5% CIs, and p-value will be provided.

Binary secondary efficacy endpoints analyzed with the on-treatment estimand will be analyzed using the same imputation model, but only including on-treatment values (see Section 2.4.4.2.1) in this model in the mITT population.

2.4.4.2.4 Summary of results per time point

Double-blind period

Central laboratory values (in conventional (US) and international units), percent change from baseline, and/or when appropriate absolute change from baseline (in conventional and international units), for LDL-C, Total-C, HDL-C, fasting TG, non-HDL-C, at Week 8, Week 12 and Week 24 time points, for Lp(a), Apo-B, Apo-A1 and ratio Apo-B/Apo-A1 (absolute change from baseline) at Week 12 and Week 24 time points will be summarized in the ITT population and in the mITT population using:

- For lipids other than TG and Lp(a): LS mean and SE, obtained from the same MMRM models as used for endpoints above and including planned time points (see

Section 2.4.4.2.1) and with raw values, changes from baseline, or percent change from baseline as response variable in the model as appropriate.

- For TG and Lp(a): mean and SE obtained from multiple imputation approach followed by the robust regression models as used for endpoints above and including planned time points (see Section 2.4.4.2.2) and with raw values or percent changes from baseline as response variable in the model as appropriate.

In addition, quantitative descriptive summaries by time point (value at visit and % change from baseline) will be presented for all lipids using observed (ie, non-missing) data. In addition, binary variables for LDL-C will be also described by time point. For LDL-C, these summaries will be also provided according to BW stratum as per IVRS/IWRS, and according to up-titration/dose adjustment status at Week 12.

OL period

Quantitative descriptive summaries by time point will be presented for LDL-C, Total-C, HDL-C, fasting TG, and non- HDL-C, Lp(a), Apo-B, Apo-A1 and ratio Apo-B/Apo-A1 using observed data in the OL population. LDL-C will be also described by category over time.

Combined period

In each dosing regimen cohort, for patients receiving alirocumab in the double-blind period, central laboratory values (in conventional (US) and international units) including both the double-blind and open-label period assessments, percent change from baseline, and/or when appropriate absolute change from baseline (in conventional and international units), LDL-C, Total-C, HDL-C, fasting TG, and non- HDL-C, Lp(a), Apo-B, Apo-A1 and ratio Apo-B/Apo-A1 (absolute change from baseline) at all planned time points (Week 8 to Week 104) will be summarized by patient counts, mean and SD by all patients.

2.4.4.3 Multiplicity issues

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 Q2W versus placebo Q2W; alirocumab Q4W versus placebo Q4W) for the primary efficacy endpoint (two-sided 0.025 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 two-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 2.1.3.2.1. 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 at the two-sided 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).

In addition, no further multiplicity adjustment is needed for multiple analyses (ie, first step and second step analyses, if applicable, see Section 3). All primary and key secondary efficacy endpoints will be fully evaluable at the time of the first step analysis. Analyses of lipid parameters beyond Week 24 will be descriptive.

2.4.4.4 Exploratory efficacy analyses

Difference in percent change in LDL-C between the 2 alirocumab Q2W and Q4W dosing regimen cohorts

The difference in terms of percent change in LDL-C between the 2 alirocumab dosing regimen groups will be explored in the ITT population and in the mITT population.

FMD sub-study

The absolute change from baseline in FMD at Week 24 in the FMD sub-study population will be analyzed using an ANCOVA model, with unequal variances by treatment group (except if convergence issue). The model will include the fixed categorical effects of treatment group (alirocumab, placebo), the dosing regimen cohort (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, regardless of the dosing regimen cohort, for the alirocumab group and the placebo group. LS means difference will be provided for the comparison of the alirocumab group versus the placebo group regardless of the dosing regimen cohorts 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.

In addition, the same statistical approach as described above will be applied but only including on-treatment values in the model (on-treatment analysis).

2.4.5 Analyses of safety data

No formal inferential testing will be performed for either study period. Summaries will be descriptive in nature. All summaries of safety results described below will be presented for each study period respectively, unless otherwise noted.

General common rules

All safety analyses will be performed on the safety population for the double-blind period and on the OL population for the OL period, as defined in Section 2.3.2 unless otherwise specified, using the following common rules:

- Safety data in patients who do not belong to the safety population (ie, exposed but not randomized) will be listed separately.
- The baseline value for both double-blind and OL periods is defined as the last available value obtained up to the date and time of the first double-blind IMP injection in EFC14643 study, except otherwise specified.
- 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 in children [Appendix A] and PCSA in adults version dated May 2014 [Appendix B]). Considering that the threshold defined in the PCSA list for monocytes and basophils can be below the ULN, the following PCSA criteria will be used for the PCSA analysis of monocytes and basophils:
  - PCSA criterion for monocytes: >0.7 Giga/L or > ULN (if ULN ≥0.7 Giga/L)
  - PCSA criterion for basophils: >0.1 Giga/L or > ULN (if ULN ≥0.1 Giga/L)
- 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 nonscheduled or repeated evaluations.
- The treatment-emergent PCSA denominator by group for a given parameter will be based on the number of patients assessed for that given parameter at least once during the TEAE period.
- All measurements, scheduled or unscheduled, fasting or not fasting, will be assigned to analysis windows defined in Section 2.5.4, Table 5 and Table 6 in order to provide an assessment for Week 4 to Week 104 time points.
- In both the double-blind and the OL periods, for quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results and change from baseline values by visit using analysis windows. Summaries will also include the last on-treatment value and the worst on-treatment value. The last on-treatment value is defined as the last value collected during the treatment period of each study period (see Section 2.1.4). The worst on-treatment value is defined as the nadir and /or the peak value during the treatment period of each study period according to the direction (minimum or maximum) of the abnormality as defined in the PCSA list.
- For exploratory purposes, key safety analyses for the double-blind period could also be provided according to up-titration/dose-adjustment status, ie, according to whether the patients remained on their initial dose or whether the dose was up-titrated/dose-adjusted. These analyses will be exploratory and descriptive (no formal comparison per dose) as it is expected that there could be inherent differences in the baseline characteristics between those patients up-titrating and those remaining on their initial dose. In order to reduce the

bias of this analysis, the period before the up-titration/dose-adjustment time point (planned at Week 12) will be analyzed separately since the early events occurring before Week 12 can only be attributed to the initial dose regimen (40 mg Q2W, 75 mg Q2W, 150 mg Q4W or 300 mg Q4W). Therefore the descriptive analysis per dose will include any safety events occurring from the first injection post Week 12 IVRS/IWRS transaction to the end of the TEAE period. Baseline characteristics of patients receiving each dose will be summarized.

2.4.5.1 Analyses of adverse events

Generalities

The primary focus of AE reporting will be on TEAEs. Pre-treatment and post-treatment AEs will be described separately.

If an AE date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the AE as pre-treatment, treatment-emergent, or post-treatment. The algorithm for imputing date/time of onset will be conservative and will classify an AE as treatment emergent unless there is definitive information to determine it is pre-treatment or post-treatment. Details on classification of AEs with missing or partial onset dates are provided in Section 2.5.3.

Adverse event incidence tables will present the number (n) and percentage (%) of patients experiencing an AE by SOC, HLGT (when applicable), HLT (when applicable), and PT. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. For tables presenting severity of events, the worst severity will be chosen for patients with multiple instances of the same event.

Sorting within tables ensures the same presentation for the set of all AEs within the observation period (pre-treatment, treatment-emergent, and post-treatment). For that purpose, the table of all TEAEs presented by SOC and PT sorted by the internationally agreed SOC order and decreasing frequency of PTs within SOCs (in the overall population) will define the presentation order for all other tables unless otherwise specified. The tables of AEs by SOC, HLGT, HLT and PT will be sorted by the SOC internationally agreed order and the other levels (HLGT, HLT, PT) will be presented in alphabetical order, unless otherwise specified.

Analysis of all treatment-emergent adverse events

The following TEAE summaries will be generated:

- Overview of TEAEs, summarizing number (%) of patients with any
  - TEAE.
  - Serious TEAE.
  - TEAE leading to death.
  - TEAE leading to permanent treatment discontinuation.

  - Treatment-related TEAE.

- All TEAEs by primary SOC, HLGT, HLT, and PT.
- Number (%) of patients experiencing common TEAE(s) presented by primary SOC, HLT and PT (HLT incidence ≥5 % in any treatment group), sorted by SOC internationally agreed order and by alphabetic order for the other levels (HLT and PT);
- All TEAEs by primary SOC and PT, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC (in the combined alirocumab group for the double-blind period and overall for the open-label period). This sorting order will be applied to all other tables by SOC and PT of TEAEs, unless otherwise specified.
- All TEAEs regardless of relationship in one column and, in the same table, a second column with TEAEs related to alirocumab according to investigator's opinion by primary SOC, HLGT, HLT and PT.
- All TEAEs by maximal intensity (ie, mild, moderate or severe), presented by primary SOC and PT, sorted by the sorting order defined above.

Analysis of all treatment emergent serious adverse event(s)

- All serious TEAEs by primary SOC, HLGT, HLT, and PT and by SOC/PT.
- All serious TEAEs by dose regardless of relationship in one column and, in the same table, a second column with TEAEs related to alirocumab according to investigator's opinion, by primary SOC, HLGT, HLT, and PT.

Analysis of all treatment-emergent adverse event(s) leading to treatment discontinuation

- All TEAEs leading to treatment discontinuation, by primary SOC, HLGT, HLT, and PT and by SOC/PT.

Analysis of groupings of adverse events including selected adverse events of special interest

All groupings of TEAEs including adverse events of special interest as listed in Section 2.1.4.1 will be analyzed using selections defined in Section 2.1.4.1 and will be presented by SMQ/CMQ and PT (when selection is based on SMQs/CMQs) and by SOC and PT (when selection is based on the e-CRF tick box or HLGT/HLT). The summaries will be sorted by decreasing incidence of PT within each SOC/SMQ (in the alirocumab group) for the double-blind period and overall for the open-label period.

In addition, the following variables will be tabulated for the local injection site reactions TEAEs:

- Intensity of the event (mild, moderate, severe).
- Number of events divided by the number of IMP injections.
- Time from first IMP injection to first injection site reaction.
- Description of the highest intensity of each symptom recorded in the specific e-CRF page.
- The use of the topical anesthetic will be assessed with regards to the occurrence of pain.

Besides, description of symptoms and possible etiologies for General Allergic Reaction TEAE reported by investigator (using the tick box), will be presented.

Analysis of pre-treatment and post-treatment adverse events

- All pre-treatment AEs by primary SOC and PT, sorted by the internationally agreed SOC order and decreasing incidence of PTs (in the alirocumab group) within each SOC;
- All pre-treatment AEs leading to treatment discontinuation by primary SOC and PT, sorted by the sorting order defined above;
- All post-treatment AEs by primary SOC and PT, sorted by the internationally agreed SOC order and decreasing incidence of PTs (in the alirocumab group) within each SOC;
- All post-treatment SAEs by primary SOC and PT, sorted by the sorting order defined above;

Analysis of treatment emergent adverse events related to COVID-19

The number of patients who experienced at least one TEAE related to COVID-19 will be described by primary SOC and PT (terms selected using the SMQ "COVID-19" narrow).

Analysis according to patients' status with regards to trial impact/disruption due to COVID-19

All TEAEs by primary SOC and PT will be presented according to trial impact/disruption due to COVID-19.

Subgroup of patients with two consecutive LDL-C <50 mg/dL or two consecutive LDL-C <25 mg/dL or two consecutive LDL-C <15 mg/dL

If applicable, summaries of TEAEs by SOC and PT and by SOC,HLGT,HLT and PT will be also provided on the safety subgroup population of patients with two consecutive results of LDL-C <50 mg/dL (and also those respectively <25 mg/dL, <15 mg/dL) (as defined in Section 2.1.5). Only TEAE for which it will be confirmed or unclear that they occurred, worsened or became serious the day or after the first level of LDL-C <50 mg/dL (respectively <25 mg/dl, <15 mg/dL) will be considered.

Analysis according to IVRS/IWRS BW strata

A summary of TEAEs, serious TEAE, TEAE leading to treatment discontinuation and local injection site reaction will be provided according to the baseline BW stratum (as per IVRS/IWRS) for the double-blind period.

Analysis according to previous participation to the Phase 2 DFI14223 study

A summary of TEAEs by SOC and PT and General allergic events will be provided on the safety population according to previous participation to the Phase 2 DFI14223 study.

Additional analysis for the OL period

The following summary tables will be added:

- The event rate per patient year (the number of patients with an event in question divided by total patient-years) will be provided for all TEAEs by SOC and PT. For a patient with event, patient year is censored at time of first event; for patient without event, it corresponds to length of the open-label TEAE period

2.4.5.2 Deaths

The following summaries of deaths will be generated separately for double-blind and OL periods:

- Number (%) of patients from the safety population who died by period (on-treatment, post-treatment).
- TEAEs leading to death (death as an outcome on the AE as reported by the Investigator) by primary SOC, HLGT, HLT, and PT sorted by internationally agreed SOC order, with HLGT, HLT, and PT presented in alphabetical order within each SOC. TEAEs leading to death are TEAEs that led to death regardless of timing of death in relation to IMP injection (ie, death occurring in the TEAE period or during the post-treatment period).
- In addition, deaths in nonrandomized patients or randomized but not treated patients will be summarized.

2.4.5.3 Analyses of laboratory variables

The summary statistics (including number, mean, median, Q1, Q3, SD, minimum and maximum) of all laboratory variables (central laboratory values and changes from baseline) will be calculated for each visit or study assessment (baseline, each post-baseline value of the treatment period, last on-treatment and worst on-treatment value). In addition, for some parameters of interest, mean changes from baseline with the corresponding SE could be plotted over time (at same time points). This section will be organized by biological function as specified in Section 2.1.4.3. For glucose, only fasting samples will be summarized.

The incidence of PCSAs (list provided in Appendix A and Appendix B), as well as ALT increase as defined as AESI, at any time during the TEAE period will be summarized by biological function irrespective of the baseline level and/or according to the following baseline status 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.

For clinical laboratory parameters during the OL period, summary tables as described for the double-blind period above will be used with the exceptions of the analyses by visit (unless data warrants further investigation)

Drug-induced liver injury

The liver function tests, namely AST, ALT, ALP, and total bilirubin, are used to assess possible drug-induced liver toxicity. The proportion of patients with PCSA values or ALT increase as defined in the section grouping of adverse events (see Section 2.1.4.1) during TEAE period by baseline status will be displayed for each parameter.

An evaluation of drug-induced serious hepatotoxicity (eDISH) with the graph of distribution of peak values of ALT versus peak values of total bilirubin will also be presented using post-baseline values during TEAE period. 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.

Listing of possible Hy's law cases identified by treatment group (ie, patients with any elevated ALT>3 x ULN, and associated with an increase in bilirubin >2 x ULN, concomitantly or not) with ALT, AST, ALP, total bilirubin, and if available direct and indirect bilirubin will be provided.

The incidence of liver related TEAEs will be summarized. The selection of PTs will be based on SMQ Hepatic disorder (see Section 2.1.4.1).

Gonadal hormones and pituitary hormones

Girls and boys will be described separately.

- For girls

  The following analyses will be provided only in post-menarchal girls for at least 1 year at baseline and without receiving any oral contraceptive throughout the study.

  - Changes from baseline will be tabulated by time point for estradiol and pituitary hormones (FSH and LH) during treatment period.
  - Similar table as for PCSA will be provided using normal range during the TEAE period. The number (%) of patients with at least one estradiol value <LLN and LH >ULN, estradiol value<LLN and FSH >ULN, estradiol value <LLN and LH>ULN and FSH >ULN) during the TEAE period will be presented.

  In addition, a listing of estradiol, LH, FSH values over time along with the tanner stage and date of last menses (if any) will be displayed for all girls.

- For boys

  The following analyses will be provided only in boys with at least a Tanner stage 2

  - Changes from baseline will be tabulated by time point for testosterone and pituitary hormones (FSH and LH) during treatment period.
  - Similar table as for PCSA will be provided using the normal range. The number (%) of patients with at least one testosterone value <LLN and LH >ULN, testosterone

value<LLN and FSH >ULN, testosterone value<LLN and LH>ULN and FSH >ULN) during the TEAE period will be presented.

In addition, a listing of testosterone, LH, FSH values over time along with the tanner stage will be displayed for all boys.

Adrenal gland hormones

DHEAS:

Girls and boys will be described separately.

- Changes from baseline will be tabulated by time point.
- Similar table as for PCSA will be provided using the normal range during the TEAE period.

These summaries will be provided in post-menarchal girls for at least 1 year at baseline and without receiving any oral contraceptive throughout the study, and in boys with at least a tanner stage 2.

In addition, a listing of all values over time along with normal range will be provided.

Cortisol and ACTH

Girls and boys will be analyzed together. Samples not drawn between ≥6:00 AM and <11:00 AM will be excluded.

- Changes from baseline will be tabulated by time point for cortisol during treatment period.
- Similar table as for PCSA will be provided using the normal range during the TEAE period. The number (%) of patients with at least one cortisol <LLN, cortisol <LLN and ACTH >ULN will be presented.

Although the summaries for gonadal and pituitary hormones and DHEA will be provided as planned for safety endpoints (ie, by treatment groups within each dosing regimen cohort, and by treatment groups regardless of the dosing regimen cohorts), the analyses by treatment regardless of the dosing regimen cohorts (ie, pooled across the cohorts) appears the most relevant, due to the restriction of the population involved in those analyses (post-menarchal girls for at least 1 year at baseline and without receiving any oral contraceptive throughout the study, and in boys with at least a tanner stage 2).

2.4.5.4 Analyses of vital sign variables

The summary statistics (including number, mean, median, standard deviation, minimum and maximum) of all vital signs variables (heart rate, diastolic and systolic blood pressure in sitting position) , height, height percentile, weight, BMI and BMI percentile (value and change from baseline) will be calculated for each visit or study assessment (baseline, each post-baseline value of the treatment period, last on-treatment, worst on-treatment value). For weight, percent change

from baseline will also be presented. In addition, summaries by gender will be provided for height, weight and BMI. Heart rate and blood pressure without position filled in will only be used for the PCSA analysis described below.

The incidence of PCSAs for heart rate and blood pressure at any time during the TEAE period will be summarized.

For OL vital signs parameters, summary tables as described for the double-blind period above will be used with the following exceptions:

- Analyses by visit (unless data warrants further investigation)

2.4.5.5 Analyses of electrocardiogram variables

Not Applicable.

2.4.5.6 Analysis of Tanner stages measurement

Boys–development of external genitalia, girls-breast development, boys/girls –pubic hair stages as well as a global Tanner puberty classification (Prepubescent, Pubescent and Postpubescent) will be described by analysis visit using count and percentage.

The change from baseline in Tanner stage based on development of external genitalia for boys, and breast development for girls by analysis visits will be assessed (No change in Tanner stage, change in Tanner stage $\geq$1).

In addition, number of post-menarchal girls at baseline and during the study will be summarized.

2.4.5.7 Analyses of Cogstate Battery test

Cognitive scores (including by domains: DET [Psychomotor Function], IDN [Attention]; [OCL; Visual Learning]; GML [Executive Function]) and composite score will be described on the safety population by treatment for the double-blind period.

The change from baseline will be described for each score and the composite score.

The absolute change from baseline in the composite score at Week 24 will be analyzed using an ANCOVA model, with unequal variances by treatment group (except if convergence issue). The model will include the fixed categorical effects of treatment group (alirocumab, placebo), the dosing regimen cohort (Q2W, Q4W), the treatment-by-dosing regimen cohort interaction, the randomization strata and the continuous fixed covariate of baseline composite score 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 (placebo, alirocumab) regardless of the dosing regimen cohorts. LS means difference will be provided for the comparison of the alirocumab group versus the placebo group regardless of the dosing regimen cohorts, with the SE, 95% confidence intervals (CI) for descriptive purpose, using

appropriate contrasts. The corresponding effect sizes will be computed using Cohen's formulae (see Appendix G).

For the OL period, the results will be described overall in the OL population.

2.4.6 Analyses of other endpoints

All analyses/summaries for other endpoints will be performed on the safety population for the double-blind period and on the OL population for the OL period.

All measurements, scheduled or unscheduled, fasting or not fasting, will be assigned to analysis windows defined in Section 2.5.4, Table 5 and Table 6 in order to provide an assessment for Week 4 to Week 104 time points.

HsCRP and HbA_{1c}

Hs-CRP and HbA_{1c} parameters will be summarized by analysis visit using number of available data, mean, SD, median, minimum, and maximum (for hs-CRP, Q1 and Q3 will be also provided) during the treatment period. The time profile of each parameter will be also plotted with the means and the corresponding SEs for HbA_{1c} and the medians with (Q1-Q3) for hs-CRP. The incidence of PCSA at any time during the TEAE period will be also summarized using descriptive statistics.

Patients with low LDL-C

Binary endpoints defined in Section 2.1.5 will be described using count and percentage. Kaplan-Meier curves will be provided for the "Time to" variables in the double-blind treatment period. Patient without event will be censored at the end of the treatment period. For the analysis of the time to the first of the two consecutive LDL-C as defined in Section 2.1.5, patients without post-baseline LDL-C result or with only one post-baseline LDL-C result will not be included.

Creatine phosphokinase-MB and cardiac troponin

Creatine phosphokinase-MB parameter will be summarized at Week 24 on the safety population using number of available data, mean, SD, median, Q1, Q3, minimum, and maximum. In addition, similar tables as for PCSA will be provided using the normal range. This table will summarize the number (%) of patients with value >ULN during the TEAE period irrespective of the baseline level and/or according to the following baseline status categories ≤ULN, >ULN.

Cardiac troponin at Week 24 will be summarized on the safety population according to the following categories:

- <LLOQ;
- ≥LLOQ.

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 using descriptive statistics.

2.4.7 Analyses of anti-alirocumab antibodies variables

The summary of ADA variables will be presented on the ADA population, taking into account all samples regardless of timing in relation to injections but within each study period separately.

Within each dosing regimen cohort, the double-blind period will be presented by treatment group, as well as, according to baseline body weight (as per IVRS/IWRS stratum) and by up-titration / dose-adjustment status.

The OL period will be presented also within each dosing regimen cohort, according to the treatment received in the double-blind period (placebo or alirocumab) and overall.

All summaries described below will be presented for each study period respectively.

ADA results (negative or positive) by time point;

- Neutralizing status (negative or positive) by time point for positive ADA;
- ADA titers using descriptive statistics (median, minimum and maximum) for positive ADA by time point;
- Number (%) of patients with pre-existing ADA and number (%) of patients with treatment-emergent ADA positive response;
- Number (%) of patients with persistent/indeterminate/transient treatment-emergent ADA positive response;
- Time to onset of treatment-emergent ADA positive response using descriptive statistics, beginning from the first IMP administration within the relevant period (double-blind or OL).
- Number (%) of patients with at least one neutralizing ADA.

If appropriate, correlations between ADA parameters (eg, titers, treatment-emergent ADA positive status, neutralizing status) and PK, safety and/or efficacy endpoints will be also explored (eg, scatter plot, summary of TEAEs for ADA positive patients).

In addition, the following summaries will be also presented on ADA population according to previous participation in the DFI14223 study:

- Number (%) of patients with pre-existing ADA and number (%) of patients with treatment-emergent ADA positive response;
- Number (%) of patients with persistent/indeterminate/transient treatment-emergent ADA positive response.

2.4.8 Analyses of pharmacokinetic and pharmacodynamic variables

Within each dosing regimen cohort, concentrations of total alirocumab in serum (C_{trough}), free and total PCSK9 concentrations will be summarized on the PK population by treatment group and up-titration/dose-adjustment status using descriptive statistics. These summaries will be also provided by baseline BW (as per IVRS/IWRS) in the treatment groups.

Time profiles for C_{trough} concentration, total and free PCSK9 will be also provided by group using graphs (mean ± SE or Median, as appropriate).

Additional plots will be prepared, as deemed necessary (eg, to explore the relationship with some safety or efficacy endpoints of interest).

Concentrations of total alirocumab in serum as well as concentrations of free and total PCSK9 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.

2.4.9 Analyses of quality of life variables

Not applicable.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

The following formulas will be used for computation of parameters:

Time from diagnosis of heFH

Time from diagnosis (years) = (Date of informed consent – Date of diagnosis*) / 365.25.

(*): In case the month of diagnosis would be missing, it will be put equal to 1st JANUARY if the year of diagnosis equals the year of informed consent; it will be put equal to 1st JUNE otherwise. In case only the day of diagnosis would be missing, it will be put equal to the 1st of the month.

Date of last dose of IMP (for double-blind and for open-Label)

The date of the last injection in the double-blind period is equal to the last date of administration reported on injection administration case report form page in double-blind period or missing if the last administration date is unknown.

The date of the last injection in the open-label period is equal to the last date of administration reported on injection administration case report form page in open-label period or missing if the last administration date is unknown.

Renal function formulas

Creatinine clearance value will be derived using the modified Schwartz equation presented in Appendix H.

Lipids variables, laboratory safety variables, Hs-CRP

For data below the lower limit of quantification (LLOQ) / limit of linearity, half of the lower limit value (ie, LLOQ/2) will be used for quantitative analyses. For data above the upper limit of quantification (ULOQ) / limit of linearity, the upper limit value (ie, ULOQ) will be used for quantitative analyses.

The above rules will not be applied for the calculated LDL-C and non-HDL-C when HDL-C value is below the LLOQ. The value of LLOQ/2 for HDL-C will be used to obtain the non-HDL-C and calculated LDL-C used for quantitative analyses.

Below is an example of data for a "dummy" patient, with the values that will be used in quantitative analyses for each parameter.

Table 4 - Example of lipid data for a "dummy" patient

Parameter	Value recorded in the database	Value used in the analysis
TC	255 mg/dL	255 mg/dL
HDL-C	<10 mg/dL	5 mg/dL
Calculated LDL-C[a]	<221 mg/dL	216 mg/dL
NON-HDL-C	<255 mg/dL	250 mg/dL
TG	172 mg/dL	172 mg/dL

a Friedewald formula for calculated LDL-C (when lipid expressed in mg/dL: LDL-C=NON-HDL-C-0.2*TG)

Pharmacokinetic variables

Data below the LLOQ are set to zero.

2.5.2 Data handling conventions for secondary efficacy variables

See Section 2.1.3.2.

2.5.3 Missing data

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

Handling of baseline definition if time of first double-blind administration or time of assessment at Week 0 visit is missing

If the time of the first double-blind administration or the time of assessment at Week 0 visit is missing, then the baseline value is defined as the last available value obtained before or on the day of the first double-blind IMP administration

Handling of computation of treatment duration and compliance if investigational medicinal product first or end of treatment date is missing

If the last or first injection date is missing, the exposure duration and compliance will be left as missing.

Handling of safety and efficacy analysis periods and survival analysis if investigational medicinal product end of treatment date is missing

If the last injection date of double-blind period or open-label period is missing, then this date is imputed to the earliest between:

- the last day of the month and year, when applicable or else the 31st of December of the year,
- the date of the end of treatment visit of the period (Double-blind period: Week 24 visit for patients who completed the double-blind study treatment period as per protocol, early end of treatment visit for patients who prematurely discontinued the IMP; open-label period: Week 104 for patients who completed the open-label study treatment period as per protocol, early end of treatment visit for patients who prematurely discontinued the IMP),
- and the date of the last contact,

for the purpose of safety and efficacy analysis period start and/or end.

Handling of medication missing/partial dates

No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior, concomitant, and post-treatment medication.

Handling of adverse events with missing or partial date/time of onset

Missing or partial AE dates and times will be imputed so that if the partial AE date/time information does not indicate that the AE started prior to treatment or after the TEAE period, the AE will be classified as treatment emergent. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of AE resolution.

Handling of adverse events when date and time of first investigational medicinal product administration is missing

When the date and time of the first IMP administration is missing, all AEs that occurred on or after the day of randomization will be considered as TEAEs.

When the time of the first double-blind IMP administration is missing, all AEs that occurred on the day of the first double-blind IMP administration will be considered as treatment-emergent AEs.

Handling of missing assessment of relationship of adverse events to investigational medicinal product

If the assessment of the relationship to IMP is missing, then the relationship to IMP has to be assumed and the adverse event considered as such in the frequency tables of possibly related adverse events, but no imputation should be done at the data level.

Handling of missing severity of adverse events

If the severity is missing for 1 of the treatment-emergent occurrences of an AE, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, a "missing" category will be added in the summary table.

Handling of potentially clinically significant abnormalities

If a patient has a missing baseline he will be grouped in the category "normal/missing at baseline."

For PCSAs with 2 conditions, one based on a change from baseline value or a normal range and the other on a threshold value, with the first condition being missing, the PCSA will be based only on the second condition.

For a PCSA defined on a threshold and/or a normal range, this PCSA will be derived using this threshold if the normal range is missing; eg, for eosinophils the PCSA is >0.5 GIGA/L or >ULN if ULN ≥0.5 GIGA/L. When ULN is missing, the value 0.5 should be used.

Measurements flagged as invalid by the laboratory will not be summarized or taken into account in the computation of PCSA values.

2.5.4 Windows for time points

Data analyzed by time point (including efficacy, laboratory safety data, vital signs, ADA) will be summarized using the analysis windows given in Table 5, Table 6 and Table 7. These analysis windows will be applicable for all analyses, and they are defined to provide more homogeneous data for time point-specific analyses.

Table 5 - Analysis windows definition for double-blind period

Time point	Targeted study day	Analysis window in study days
Week 8	57	43 to 70
Week 12	85	71 to minimum (98; study day corresponding to the first injection with IMP from kit allocated at Week 12 re-supply IVRS contact)
Week 24	169	155 to 182[a]

Time point	Targeted study day	Analysis window in study days

Study days are calculated from the day of first double-blind IMP injection, the day of first double-blind IMP injection being Day 1. For randomized but not treated patients, Day 1 is the day of randomization.
[a] 155 to 182 for patients not entering the OL period or minimum of 182 or study day corresponding to the first OL injection for patients entering the open-label extension

Table 6 - Analysis windows definition for OL period

Time point	Targeted study day	Analysis window in study days
Week 32	57	36 to 77
Week 44	141	120 to 161
Week 56	225	204 to 245
Week 68	309	288 to 329
Week 80	393	372 to 413
Week 92	477	456 to 497
Week 104	561	540 to 581

Study days are calculated from the day of first OL IMP injection, the day of first OL IMP injection being Day 1.

If multiple valid values of a variable exist within an analysis window, the value collected at the scheduled visit will be used if within the analysis window. Otherwise the nearest from the targeted study day or time will be selected. If the difference is a tie, the value after the targeted study day or time will be used

For all endpoints except PK, if multiple valid values of a variable exist within a same day, then the first value of the day will be selected when time is available, else the scheduled visit will be selected.

PK Concentration will be analyzed following time windows as defined below in Table 7. If the date of the previous injection is unknown, the alirocumab concentration will not be considered for the analysis.

Table 7 Time windows for PK variables definition

PK variables	Time window (D1 = day of previous injection or day of last injection for $C_{follow-up}$)	
	Q2W regimen	Q4W regimen
C_{trough}	Day 9 to Day 22	Day 23 to Day 36

If multiple valid values satisfy the C_{trough} criteria, the nearest from the targeted study day (ie, Day 15/32 for $C_{through}$, Day 1 being the day of previous injection) will be selected. If the difference is a tie, the value after the targeted study day will be used.

2.5.5 Unscheduled visits

For all parameters, unscheduled visit measurements may be used to provide a measurement for a time point, a baseline, a last or a worst value, if appropriate according to their definitions. The measurements may also be used to determine abnormal/PCSA.

2.5.6 Pooling of centers for statistical analyses

Not Applicable.

2.5.7 Statistical technical issues

Not Applicable.

3 INTERIM ANALYSIS

The analyses will be conducted in 2 steps. The first analysis will not be conducted before completion of the double-blind treatment period. Since analysis of double-blind primary and key secondary efficacy endpoints will have been concluded at the time of the first step analysis described below, no multiplicity adjustment for multiple analyses is needed (see Section 2.4.4.3), and the overall significance level remains at 0.05 for the study.

- First step analysis: Analysis of the completed double-blind treatment period and first step analysis of the open-label treatment period
  - This analysis will be conducted when all patients have been randomized and have at least all their lipid data up to Week 24 analysis window (double-blind period) collected and validated.
  - The efficacy analyses of the double-blind period will consist in the final analysis of the primary and secondary efficacy endpoints (except those measured during open-label period). Analysis of lipid data collected during the OL period will be descriptive.
  - The safety analyses of the double-blind period will not be fully final at the time of this analysis since the double-blind TEAE period will be truncated at the cut-off date for some patients. The safety analyses of the double-blind and open-label treatment periods will be performed on all safety data collected up to the common cut-off date. The common cut-off date is defined as date of the last patient included completed Week 24 visit.
- Final analysis of the open-label treatment period
  - This analysis will be conducted at the end of the study with the data of the open-label treatment period and will consist in the final analysis of the safety and efficacy measures of the open-label treatment period.

Analyses methods and conventions described in the other sections of this SAP will be applied for all analyses as applicable. The following additional rules will apply for analyses performed at first analysis:

- Any lipid assessments within analysis windows up to Week 24 will be taken into account (may include few unscheduled lipid data soon after the cut-off date).
- Open-label period: Patients without end of treatment visit performed at the time of the cut-off date will be considered as ongoing and exposed up to the cut-off date. Therefore:
  - Patients who did not complete treatment period nor prematurely discontinued the study treatment at cut-off date will be analyzed as “ongoing” in the disposition summary.
  - Their open-label TEAE period, open-label treatment period and open-label on-study observation period will end at the cut-off date.
  - Their treatment duration for the open-label period will be derived by considering date of cut-off as last injection date.

- Open-label period: Analyses of number of injections, mean injection frequency, percentage of days with under/above-planned dosing and compliance will be performed up to the last injection reported in the e-CRF up to the cut-off date.
- Double-blind period and open-label period: AEs occurring, worsening or becoming serious after the cut-off date will not be included in the analyses. However, any available outcome before database lock, regardless of timing in relation to the cut-off date, of an adverse event starting prior to the cut-off date will be taken into account. Medications, treatment discontinuations/completions and deaths occurring after the cut-off date will not be included in the analyses.
- Open-label period: Post-treatment period and post-study period are not applicable for ongoing patients. Analyses of post-treatment AEs, post-study deaths and post-treatment medications will be performed for patients who either completed or prematurely discontinued the treatment before or at the cut-off date.
- Analysis of status at last study contact will be provided for patients who prematurely discontinued the study treatment before or at the cut-off date.

4 DATABASE LOCK

As the analysis will be conducted in two-steps, two database locks will be done:

- First database lock (for first step analysis): will include all available data on all randomized patients up to the common cut-off date as defined in Section 3. This database lock is planned to be done approximately 4 weeks after the common cut-off date.
- Final database lock (for final analysis): will include all data of the open-label treatment period, for all patients entered in the OL period. This database lock is planned to be done approximately 4 weeks after last patient last visit.

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS version 9.4 or higher.

6 REFERENCES

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7 LIST OF APPENDICES

Appendix A: Potentially clinically significant abnormalities for children

Appendix B: Potentially clinically significant abnormalities for adults

Appendix C: Detailed statistical methodology for pattern mixture model

Appendix D: List of MedDRA terms for CMQs

Appendix E: Z-score calculation formula for Cogstate Battery test

Appendix F: Cogstate normative data

Appendix G: Effect size calculation formula for Cogstate data

Appendix H: Pediatric formula for eGFR and creatinine clearance

Appendix A Potentially clinically significant abnormalities for children

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For studies in children

Parameter	Age range	PCSA	Comments
ECG parameters			Ref.: Rijnbeek P.R. et al., Eur Heart J 2001; Davignon A. et al., Ped Cardiol 1979/1980; Semizel E.et al., Cardiol Young 2008; Mulberg AE et al. Pediatric Drug Development Concepts and applications. John Wiley & sons, Inc. 2009
HR	Birth/0 to 27 days old (Neonates)	≤90 bpm and decrease from baseline ≥20 bpm ≥190 bpm and increase from baseline ≥20 bpm	
	28 days/1 month to 23 months old (Infants)	≤80 bpm and decrease from baseline ≥20 bpm ≥175 bpm and increase from baseline ≥20 bpm	
	24 months/2 years to <6 years old (Children)	≤75 bpm and decrease from baseline ≥20 bpm ≥140 bpm and increase from baseline ≥20 bpm	
	6 to <12 years old (Children)	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	
	12 to 16/18 years old (Adolescents)	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	
PR	Birth/0 to 27 days old (Neonates)	≥120 ms	
	28 days/1 month to 23 months old (Infants)	≥140 ms	
	24 months/2 years to <6 years old (Children)	≥160 ms	
	6 to <12 years old (Children)	≥170 ms	
	12 to 16/18 years old (Adolescents)	≥180 ms	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For studies in children

Parameter	Age range	PCSA	Comments
QRS	Birth/0 to 27 days old (Neonates)	≥85 ms	
	28 days/1 month to 23 months old (Infants)	≥85 ms	
	2 to <6 years old (Children)	≥95 ms	
	6 to <12 years old (Children)	≥100 ms	
	12 to 16/18 years old (Adolescents)	≥110 ms	
QTc	Birth/0 to <12 years old (Neonates, Infants, Children)	Absolute values (ms) Borderline: 431-450 ms Prolonged*: >450 ms Additional: ≥500 ms AND Increase from baseline Borderline: Increase from baseline 30-60 ms Prolonged*: Increase from baseline >60 ms	To be applied to QTcF *QTc prolonged and ΔQTc >60 ms are the PCSA to be identified in individual subjects/patients listings.
	12 to 16/18 years old (Adolescents)	Borderline: 431-450 ms (Boys); 451-470 ms (Girls) Prolonged*: >450 ms (Boys); >470 ms (Girls) Additional: ≥500 ms AND Increase from baseline Borderline: Increase from baseline 30-60 ms Prolonged*: Increase from baseline >60 ms	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For studies in children

Parameter	Age range	PCSA	Comments
Vital Signs			Ref.: Kidney Disease Outcomes Quality Initiatives (KDOQI) Guideline 13; 1996; The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents, Pediatrics 2004; Bowman E & Fraser S Neonatal Handbook 2012; Mulberg AE et al. Pediatric Drug Development Concepts and applications. John Wiley & sons, Inc. 2009; Pediatric respiratory rates http://www.health.ny.gov/
SBP	Birth/0 to 27 days old (Neonates)	≤60 mmHg and decrease from baseline ≥20 mmHg ≥85 mHg and increase from baseline ≥20 mmHg	Based on definition of Hypertension as average SBP or DBP ≥95th percentile for gender, age, and height on ≥3 occasions
	28 days/1 month to 23 months old (Infants)	≤70 mmHg and decrease from baseline ≥20 mmHg ≥98 mmHg and increase from baseline ≥20 mmHg	
	24 months/2 years to <6 years old (Children)	≤70 mmHg and decrease from baseline ≥20 mmHg ≥101 mHg and increase from baseline ≥20 mmHg	
	6 to <12 years old (Children)	≤80 mmHg and decrease from baseline ≥20 mmHg ≥108 mmHg and increase from baseline ≥20 mmHg	
	12 to 16/18 years old (Adolescents)	≤90 mmHg and decrease from baseline ≥20 mmHg ≥119 mmHg and increase from baseline ≥20 mmHg	
DBP	Birth/0 to 27 days old (Neonates)	≤34 mmHg and decrease from baseline ≥10 mmHg ≥50 mHg and increase from baseline ≥10 mmHg	
	28 days/1 month to 23 months old (Infants)	≤34 mmHg and decrease from baseline ≥10 mmHg ≥54 mHg and increase from baseline ≥10 mmHg	
	24 months/2 years to <6 years old (Children)	≤34 mmHg and decrease from baseline ≥10 mmHg ≥59 mHg and increase from baseline ≥10 mmHg	
	6 to <12 years old (Children)	≤48 mmHg and decrease from baseline ≥10 mmHg ≥72 mHg and increase from baseline ≥10 mmHg	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For studies in children

Parameter	Age range	PCSA	Comments
	12 to 16/18 years old (Adolescents)	≤54 mmHg and decrease from baseline ≥10 mmHg ≥78 mHg and increase from baseline ≥10 mmHg	
Orthostatic hypotension	All age ranges	SBP: St − Su ≤ -20 mmHg DBP: St − Su ≤ -10 mmHg	
Temperature	All age ranges	Rectal, ear or temporal artery: >100.4°F/38.0°C Oral or pacifier: >99.5°F/37.5°C Axillary or skin infrared: >99°F/37.2°C	Ear temperature not accurate below 6 months of age
Respiratory rate	Birth/0 to 27 days old (Neonates)	<30 per minutes >60 per minutes	Based on normal range
	28 days/1 month to 23 months old (Infants)	<24 per minutes >40 per minutes	
	24 months/2 years to <6 years old (Children)	<22 per minutes >34 per minutes	
	6 to <12 years old (Children)	<18 per minutes >30 per minutes	
	12 to 16/18 years old (Adolescents)	<12 per minutes >20 per minutes	
Sa02	All age ranges	<95%	
Weight	All ranges	>5% weight loss from baseline	Based on identification of trends in the child's growth with a series of visits WHO Multicentre Reference Study Group, 2006; Center for Disease Control. Growth chart 2007

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For studies in children

Parameter	Age range	PCSA	Comments
Clinical Chemistry			Ref Molleston JP et al. JPGN 2011; Moritz et al., Pediatrics 1999; Moritz et al., Pediatr Nephrol 2005; Sedlacek et al., Seminars in Dialysis 2006) Gong G et al. Clinical Biochemistry 2009; Masilamani et al. Arch Dis Children 2012; Mulberg AE et al. Pediatric Drug Development Concepts and applications. John Wiley & sons, Inc. 2009
ALT/SGPT	All age ranges	By distribution analysis: >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
AST/SGOT	All age ranges	By distribution analysis: >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
Alkaline Phosphatase	All age ranges	>1.5 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For studies in children

Parameter	Age range	PCSA	Comments
Total Bilirubin	All age ranges	>1.5 ULN >2 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Conjugated Bilirubin	All age ranges	>35% Total Bilirubin and TBILI>1.5 ULN	Conjugated bilirubin dosed on a case-by-case basis.
ALT and Total Bilirubin	All age ranges	ALT >3 ULN and Total Bilirubin > 2 ULN	Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. To be counted within a same treatment phase, whatever the interval between measurement.
CPK	All age ranges	>3 ULN >10 ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
Creatinine	Birth/0 to <6 years old (Neonates, Infants, Children)	>53 µmol/L or 0.6 mg/dL	CF = mg x 8.8 = µmol Based on normal ranges: <0.6 mg/dL (0-1 year), 0.5 to 1.5 mg/dL (1 to 16/18 years)
	6 years to <12 years old (Children)	≥ 90 µmol/L or 1.1 mg/dL	
	12 years to 16/18 years old (Adolescents)	≥ 132 µmol/L or 1.5 mg/dL	
Creatinine Clearance	All age ranges	50% of normal <60 mL/min/1.73 m^2 (After 1 year old)	Based on GFR Bedside Schwartz Formula Based on normal ranges: 20 to 50 (<8 days), 25 to 80 (8 days to 1 month), 30 to 90 (1-6 months), 40 to 115 (6-12 months), 60 to 190 (12-23 months), 90 to 165 (2-12 years), 80-120 (After 12 years)

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For studies in children

Parameter	Age range	PCSA	Comments
Uric Acid	All age ranges	≤ 2.0 mg/dL or 119 µmol/L ≥ 8.0 mg/dL or 476 µmol/L	CF = mg x 5.95 = µmol Based on normal ranges: 2.4 to 6.4 mg/dL
Blood Urea Nitrogen (BUN)	Birth/0 to 27 days old (Neonates)	≥4.3 mmol/L or 12 mg/dL	CF = g x 16.66 = mmol Based on normal ranges: 3 to 12 mg/dL (NN; 5 to 18 mg/dL (other classes of age)
	28 days/1 month to 16/18 years old (Infants, Children, Adolescents)	≥6.4 mmol/L or 18 mg/dL	
Chloride	All age ranges	≤80 mmol/L or 80 mEq/L ≥115 mmol/L or 115 mEq/L	CF = 1 Based on normal range: 98 to 106
Sodium	All age ranges	≤129 mmol/L or 129 mEq/L ≥150 mmol/L or 150 mEq/L	CF = 1 Based on normal range: 134 to 146
Potassium	Birth/0 to 27 days old (Neonates)	≤3.0 mmol/L or 3.0 mEq/L ≥7.0 mmol/L or 7.0 mEq/L	CF = 1 Based on normal ranges: 3.0 to 7.0 (NN); 3.5 to 6.0 (Infants); 3.5 to 5.0 (> Infants)
	28 days/1 month to 23 months old (Infants)	≤3.5 mmol/L or 3.5 mEq/L ≥6.0 mmol/L or 6.0 mEq/L	
	24 months/2 years to 16/18 years old (Children, Adolescents)	≤3.5 mmol/L or 3.5 mEq/L ≥5.5 mmol/L or 5.5 mEq/L	
Bicarbonate	All age ranges	≤16 mmol/L or 16 mEq/L >ULN	CF = 1 Based on normal range: 18 to 26
Calcium total	All age ranges	≤2.0 mmol/L or 8.0 mg/dL ≥2.9 mmol/L or 11.6 mg/dL	CF = mg x 0.025 = mmol Based on normal range: 8.4 to 10.9 mg/dL
Calcium ionized	All age ranges	≤1.0 mmol/L or 4.0 mg/dL ≥1.4 mmol/L or 5.6 mg/dL	CF = mg x 0.025 = mmol Based on normal range: 4.0 to 5.1 mg/dL

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For studies in children

Parameter	Age range	PCSA	Comments
Total Cholesterol	All age ranges	≥6.20 mmol/L or 240 mg/dL	CF = g x 2.58 = mmol Based on normal ranges: 45 to 182 mg/dL (1-3 years), 109 to 189 mg/dL (4-6 years), 126 to 191 mg/dL (Boys 6-9 years), 122 to 209 mg/dL (Girls 6-9 years), 130 to 204 mg/dL (Boys 10-14 years), 124-217 mg/dL (Girls 10-14 years), 114 to 198 mg/dL (Boys 15-19 years), 125 to 212 mg/dL (Girls 14-19 years)
Triglycerides	All age ranges	≥4.0 mmol/L or 350 mg/dL	After >12 hours of fast) CF = g x 1.14 = mmol Based on normal ranges: 30 to 86 mg/dL (Boys 0-5 years), 32 to 99 mg/dL (Girls 0-5 years), 31-108 mg/dL (Boys 6-11 years), 35 to 114 mg/dL (Girls 6-11 years), 36 to 138 mg/dL (Boys 12-15 years), 43 to 138 mg/dL (Girls 12-15 years), 40 to 163 mg/dL (Boys 16-19 years), 40-128 mg/dL (Girls 16-19 years)
Lipasemia	All age ranges	≥2 ULN	Based on normal ranges: 3 to32 U/L (1-18 years)
Amylasemia	All age ranges	≥2 ULN	Based on normal ranges: 10 to 30 U/L (NN), 10 to 45 U/L (1-18 years)
Glucose	All age ranges	Hypoglycaemia <2.7 mmol/L or 50 mg/dL Hyperglycaemia >7 mmol/L or 120 mg/dL (fasted after >12 hours of fast); >10.0 mmol/L or 180 mg/dL (unfasted)	CF = g x 5.55 = mmol Based on normal ranges: 50 to 90 mg/dL (NN), 60 to 100 mg/dL (Child)
Albumin	All age ranges	≤25 g/L	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For studies in children

Parameter	Age range	PCSA	Comments
CRP	All age ranges	>2 ULN or >10 mg/L (if ULN not provided)	Based on normal ranges: <6 mg/L FDA Sept 2005.
Hematology			Common Terminology Criteria for Adverse Events v3.0 (CTCAE), 2006; Division of Microbiology and Infections Diseases Pediatric Toxicity Tables, 2007; Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, 2004; Mulberg AE et al. Pediatric Drug Development Concepts and applications. John Wiley & sons, Inc. 2009; Family Practice Notebook, LLC, 2012; Tietz NW et al. Clinical Guide to Laboratory Testing, 3rd edition 1995
WBC	Birth/0 to 27 days old (Neonates)	<4.0 GIGA/L or 4 000/mm^3 >25.0 GIGA/L or 25 000/mm^3	To be used if no differential count available
	28 days/1 month to 23 months old (Infants)	<4.0 GIGA/L or 4 000/mm^3 >20.0 GIGA/L or 20 000/mm^3	Based on normal ranges: 9 000 to 30 000/mm^3 (birth), 9 400 to 38 000/mm^3 (0-1 day), 5 000 to 21 000/mm^3 (1 day-1 month), 6 000 to 17 500/mm^3 (1 month-2 years), 5 000 to 17 000/mm^3 (2-6 years), 4 500 to 15 500/mm^3 (6-11 years), 4 500 to 13 500/mm^3 (11-18 years)
	24 months/2 years to <6 years old (Children)	<3.0 GIGA/L or 3 000/mm^3 >16.0 GIGA/L or 16 000/mm^3	
	6 to <12 years old (Children)	<5.0 GIGA/L or 5 000/mm^3 >17.0 GIGA/L or 17 000/mm^3	
	12 to 16/18 years old (Adolescents)	<4,5 GIGA/L or 5 000/mm^3 >13.5 GIGA/L or 17 000/mm^3	
Lymphocytes (ALC)	Birth/0 to 27 days old (Neonates)	<1.2 GIGA/L or 1 200/mm^3 >17.0 GIGA/L or 17 000/mm^3	Based on normal ranges: 2 000 to 11 500/mm^3 (0-1 days), 2 000 to 17 000 /mm^3 (2 days-1 month), 3 000 to 13 500 /mm^3 (1 month-2 years), 1,500 to 9 500/mm^3 (2-6 years), 1 500 to 8 000/mm^3
	28 days/1 month to 23 months old (Infants)	<2.0 GIGA/L or 2 000/mm^3 >13.5 GIGA/L or 13 500/mm^3	
	24 months/2 years to <6 years old (Children)	<1.0 GIGA/L or 1 000/mm^3 >9.5 GIGA/L or 9 500/mm^3	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For studies in children

Parameter	Age range	PCSA	Comments
	6 to <12 years old (Children)	<1.0 GIGA/L or 1 000/mm^3 >8.0 GIGA/L or 8 000/mm^3	(6-10 years), 1 200 to 5 200/mm^3 (10-18 years)
	12 to 16/18 years old (Adolescents)	<0.6 GIGA/L or 600/mm^3 >6.0 GIGA/L or 6 000/mm^3	
Absolute Neutrophil Count (ANC)	Birth/0 to 27 days old (Neonates)	<4.0 GIGA/L or 4 000/mm^3 (1 day old) <1.5 GIGA/L or 1 500/mm^3 (2-7 days old) <1.25 GIGA/L or 1 250/mm3 (>7 day-1month old) >1 ULN	Based on normal ranges: 5 000 to 28 000 /mm^3 (0-1 day), 1 000 to 10 000 (1 day-1 month), 1 000 to 8 500 (1-12 months), 1 500 to 8 500 (1 to 6 years), 1 500 to 8 000 (6 to 10 years), 1 800 to 8 000 (10 to 18 years)
	28 days/1 month to 23 months old (Infants)	<1.0 GIGA/L or 1 000/mm^3 (1-3 months) <1.2 GIGA/L or 1 200/mm^3 (3-24 months) >1 ULN	
	24 months/2 years to <6 years old (Children)	<1.2 GIGA/L or 1 200/mm^3 >1 ULN	
	6 to <12 years old (Children)	<1.2 GIGA/L or 1 200/mm^3 >1 ULN	
	12 to 16/18 years old (Adolescents)	<1.2 GIGA/L or 1 200/mm^3 >1 ULN	
Eosinophils	All age ranges	>0.5 GIGA/L or 500/mm^3 Or > ULN if ULN >0.5 GIGA/L or 500/mm^3	Based on normal ranges: 0 to 500 /mm^3 (0-1 month), 0 to 300 /mm^3 (1 month-18 years)
Hemoglobin	Birth/0 to 27 days old (Neonates)	<86 mmol/L or 12.0 g/dL or any decrease ≥0.31 mmol/L or 2 g/dL	CF = g x 1.55 = mmol Based on normal ranges: 15 to 20 g/dL (0-3 days), 12.5 to 18.5 g/dL (1-2 weeks), 10.0 to 13.0 g/dL (1-6 months), 10.5 to 13.0 g/dL (7 months-2 years), 11.5 to 13.0 g/dL (2-5 years), 11.5 to 14.5 (5-8 years), 12.0 to 15.2 g/dL (13-18 years)
	28 days/1 month to 23 months old (Infants)	<1.40 mmol/L or 9.0 g/dL or any decrease ≥0.31 mmol/L or 2 g/dL	
	24 months/2 years to <16/18 years old (Children, Adolescents)	<1.55 mmol/L or10.0 g/dL or any decrease ≥0.31 mmol/L or 2 g/dL	
Hematocrit	Birth/0 to 27 days old (Neonates)	<0.39 l/l or 40% >0.61 l/l or 47%	CF = % x 0.01 = l/l Based on normal ranges: 45% to 61% (0-3 days), 39% to 57% (1-2 weeks), 29% to 42% (1-6 months),
	28 days/1 month to 23 months old (Infants)	<0.29 l/l or 29% >0.42 l/l or 42%	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For studies in children

Parameter	Age range	PCSA	Comments
	24 months/2 years to <12 years old (Children)	<0.32 l/l or 32% >0.47 l/l or 47%	33% to 38% (7 months-2 years), 34% to 39% (2-5 years), 35% to 42% (5-8 years); 36% to 47% (13-18 years)
	≥12 years (Adolescents)	≤0.37 l/l or 37% (Male) ≤0.32 l/l or 32% (Female) ≥0.55 l/l or 55% (Male) ≥0.5 l/l or 50% (Female)	
Platelets	All age ranges	<100 GIGA/L or 100 000/mm^3 >700 GIGA/L or 700 000/mm^3	Based on normal ranges: 250 000 to 450 000/mm^3 (NN); 300 000 to 700 000/mm^3 (1-6 months), 250 000 to 600 00/mm^3 (7 months-2 years), 250 000 to 550 000/mm^3 (2-12 years), 150 000 to 450 000/mm^3 (13-18 years)
Urinalysis			Patel HP, Pediatr Clin N Am, 2006
Ketonuria	All age ranges	Presence	Semi-quantitative methods
Glycosuria	All age ranges	Presence	Semi-quantitative methods
Hematuria	All age ranges	≥1+	Semi-quantitative methods
Proteinuria	All age ranges	≥1+	Semi-quantitative methods
End of Document			

Appendix B Potentially clinically significant abnormalities for adults

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)

Parameter	PCSA	Comments
Clinical Chemistry		
ALT	By distribution analysis : >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
AST	By distribution analysis : >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
Alkaline Phosphatase	>1.5 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Total Bilirubin	>1.5 ULN >2 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Conjugated Bilirubin	>35% Total Bilirubin and TBILI>1.5 ULN	Conjugated bilirubin dosed on a case-by-case basis.
ALT and Total Bilirubin	ALT>3 ULN and TBILI>2 ULN	Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. To be counted within a same treatment phase, whatever the interval between measurement.
CPK	>3 ULN >10 ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)

Parameter	PCSA	Comments
CLcr (mL/min) (Estimated creatinine clearance based on the Cokcroft-Gault equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
eGFR (mL/min/1.73m2) (Estimate of GFR based on an MDRD equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
Creatinine	≥150 µmol/L (Adults) ≥30% change from baseline ≥100% change from baseline	Benichou C., 1994.
Uric Acid Hyperuricemia Hypouricemia	 >408 µmol/L <120 µmol/L	Harrison- Principles of internal Medicine 17th Ed., 2008.
Blood Urea Nitrogen	≥17 mmol/L	
Chloride	<80 mmol/L >115 mmol/L	
Sodium	≤129 mmol/L ≥160 mmol/L	
Potassium	<3 mmol/L ≥5.5 mmol/L	FDA Feb 2005.
Total Cholesterol	≥7.74 mmol/L	Threshold for therapeutic intervention.
Triglycerides	≥4.6 mmol/L	Threshold for therapeutic intervention.
Lipasemia	≥3 ULN	
Amylasemia	≥3 ULN	
Glucose Hypoglycaemia Hyperglycaemia	 ≤3.9 mmol/L and <LLN ≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)	 ADA May 2005. ADA Jan 2008.
HbA1c	>8%	
Albumin	≤25 g/L	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)

Parameter	PCSA	Comments
CRP	>2 ULN or >10 mg/L (if ULN not provided)	FDA Sept 2005.
Hematology		
WBC	<3.0 Giga/L (Non-Black); <2.0 Giga/L (Black) ≥16.0 Giga/L	Increase in WBC: not relevant. To be interpreted only if no differential count available.
Lymphocytes	>4.0 Giga/L	
Neutrophils	<1.5 Giga/L (Non-Black);<1.0 Giga/L (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
Monocytes	>0.7 Giga/L	
Basophils	>0.1 Giga/L	
Eosinophils	>0.5 Giga/L or >ULN (if ULN≥0.5 Giga/L)	Harrison- Principles of internal Medicine 17th Ed., 2008.
Hemoglobin	≤115 g/L (Male); ≤95 g/L (Female) ≥185 g/L (Male); ≥165 g/L (Female) Decrease from Baseline ≥20 g/L	Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
Hematocrit	≤0.37 v/v (Male) ; ≤0.32 v/v (Female) ≥0.55 v/v (Male) ; ≥0.5 v/v (Female)	
RBC	≥6 Tera/L	Unless specifically required for particular drug development, the analysis is redundant with that of Hb. Otherwise, consider FDA criteria.
Platelets	<100 Giga/L ≥700 Giga/L	International Consensus meeting on drug-induced blood cytopenias, 1991.
Urinalysis		
pH	≤4.6 ≥8	
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)

Parameter	PCSA	Comments
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Orthostatic Hypotension		
Orthostatic SDB	≤-20 mmHg	
Orthostatic DBP	≤-10 mmHg	
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.
ECG		Ref.: ICH E14 guidance (2005) and E14 Q&A (2012), and Cardiac Safety Research Consortium White Paper on PR and QRS (Nada et al. Am Heart J. 2013; 165(4) : 489-500)
HR	<50 bpm <50 bpm and decrease from baseline ≥20 bpm <40 bpm <40 bpm and decrease from baseline ≥20 bpm <30 bpm <30 bpm and decrease from baseline ≥20 bpm	Categories are cumulative
	>90 bpm >90 bpm and increase from baseline ≥20bpm >100 bpm >100 bpm and increase from baseline ≥20bpm >120 bpm >120 bpm and increase from baseline ≥20 bpm	Categories are cumulative
PR	>200 ms >200 ms and increase from baseline ≥25% > 220 ms >220 ms and increase from baseline ≥25% > 240 ms > 240 ms and increase from baseline ≥25%	Categories are cumulative
QRS	>110 ms >110 msec and increase from baseline ≥25% >120 ms >120 ms and increase from baseline ≥25%	Categories are cumulative
QT	>500 ms	

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)

Parameter	PCSA	Comments
QTc	Absolute values (ms)	To be applied to any kind of QT correction formula. Absolute values categories are cumulative
	>450 ms	
	>480 ms	QTc >480 ms and ΔQTc>60 ms are the 2 PCSA categories to be identified in individual subjects/patients listings.
	>500 ms	
	Increase from baseline	
	Increase from baseline]30-60] ms	
	Increase from baseline >60 ms	

Appendix C Detailed statistical methodology for pattern mixture model

For the Q2W dosing regimen cohort, as a sensitivity analysis of the primary efficacy endpoint (ie, percent change from baseline to Week 24 in LDL-C), a pattern-mixture model approach will be used, with a different imputation strategy applied for missing LDL-C values during the on-treatment period (ie, within the time period from the first IMP injection up to the day of the last double-blind injection +21 days) and missing LDL-C values after treatment discontinuation (ie, after the day of last double-blind injection +21 days as described above) based on the following assumptions:

- Patients within 21 days (see above) of their last double-blind IMP injection would continue to show benefit from treatment similar to that observed at the scheduled time point. Therefore, LDL-C values missing during the on-treatment period will be considered "Missing at Random" and imputed using a model estimated using all samples collected on treatment.
- Patients who stopped taking their study treatment no longer benefited from it in the future, and thus tended to have LDL-C values returning to baseline. Thus LDL-C values missing after treatment discontinuation will be imputed based on patient's own baseline value.

For patients who permanently discontinued the treatment due to the COVID-19 pandemic, missing post-treatment data will be considered "Missing at Random" and imputed based on other on-treatment measurements in the same treatment group.

For the Q4W dosing regimen cohort, the same approach will be taken except that the on-treatment period will be defined as the time period from the first double-blind IMP injection up to the day of the last double-blind injection +35 days for patients with a last double-blind injection before the switch to Q2W regimen (actual of sham), +21 days otherwise. The two assumptions made for the Q2W dosing regimen cohort prevail for the Q4W dosing regimen cohort as well.

The assumptions for this approach are based on the following considerations:

- Missing values during the on-treatment period are mostly consecutive to:
  - Visits performed outside of the pre-specified time-window,
  - No blood sample available although visit was done,
  - LDL-C not measurable due to technical reasons.

  In addition, these missing data are often intermittent, ie, followed by LDL-C values collected at subsequent visits. It is therefore considered reasonable to assume that these missing data were "At Random".
- Phase 2 studies DFI11565 and R727-CL-1003 included a prospective assessment of calculated LDL-C during the follow-up period after a 12-week treatment period. These studies showed that after treatment discontinuation, the average calculated LDL-C returned

to baseline level within 4 weeks after ceasing alirocumab treatment (See Figure 3 and Figure 4).

Figure 3 - Study DFI11565: calculated LDL-C mean (+/- SE) percent change from baseline

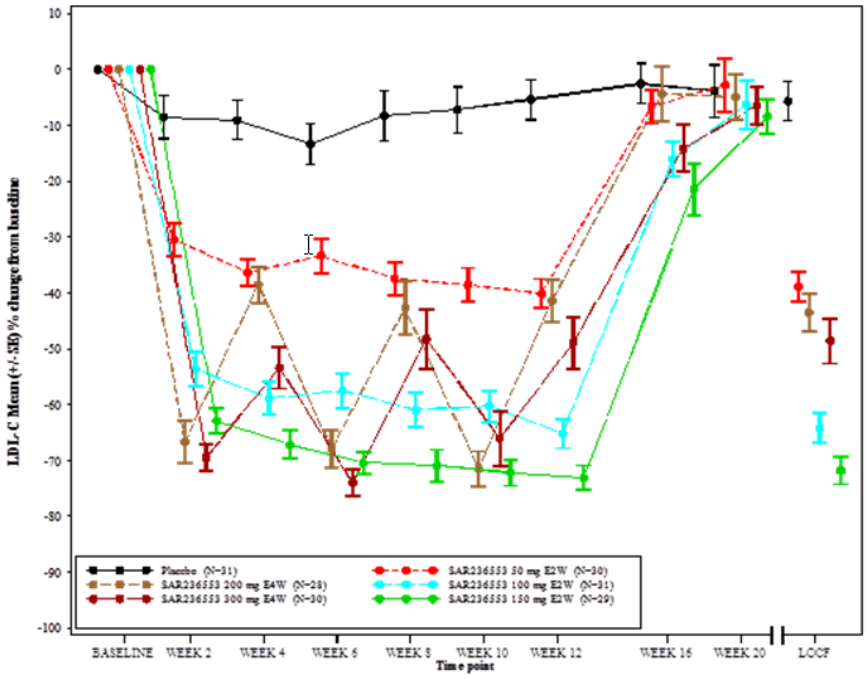
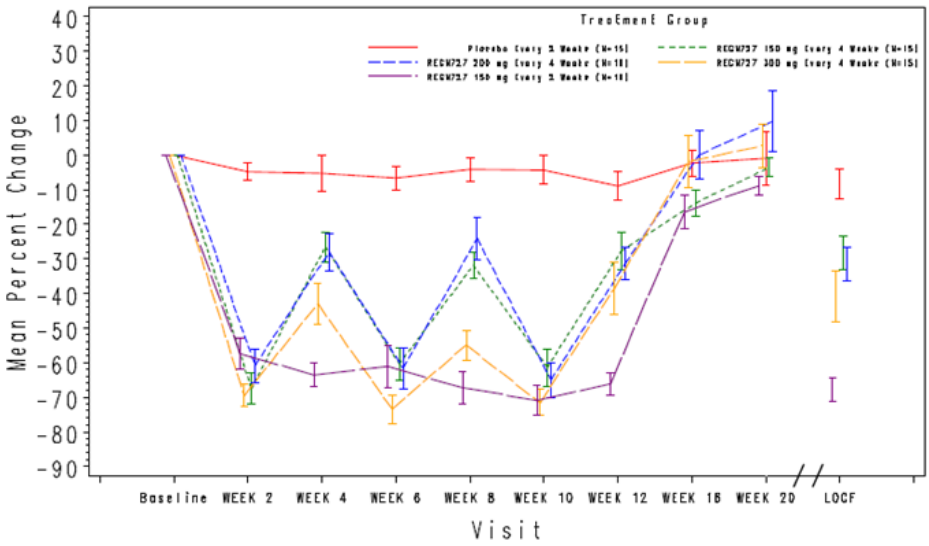


Figure 4 - Study R-727-CL-1003: calculated LDL-C mean (+/- SE) percent change from baseline



For each dosing regimen cohort, missing LDL-C values will be imputed 100 times to generate 100 complete data sets. The percent change from baseline to Week 24 will be derived from observed and imputed LDL-C at this time point. The completed data sets will be analyzed using a linear

regression model with the baseline LDL-C value as continuous covariate. Combined mean with their corresponding standard errors (SEs) and 97.5% CIs will be provided through the SAS MIANALYZE procedure using Rubin's formulae (8).

Imputation of missing data during the on-treatment period

Missing LDL-C values during the on-treatment period will be imputed from other on-treatment measurements assuming Missing At Random, using SAS MI procedure.

Only LDL-C values collected during the on-treatment period will be included in the imputation model. This way, missing LDL-C values during the on-treatment period will be imputed based solely on observed on-treatment LDL-C values.

The imputation model will include the baseline LDL-C value and all LDL-C values at pre-specified visits. Since the pattern of missing data is necessarily non-monotone, a Monte-Carlo Markov Chain (MCMC) method is used. A minimum value of 0 will be specified in order to avoid negative imputed LDL-C values.

A sample SAS code is provided below:

```
proc mi data=DATAIN out=DATAOUT nimpute=100 minimum=0;

        var LDL_BASE   LDL_W8   LDL_W12   LDL_W24  ;

run;
```

As stated above, the input dataset DATAIN will include only LDL-C values collected during the on-treatment period. Any LDL-C values collected during the post-treatment period will be excluded from the input dataset. In practice, the MI procedure generates imputed values for all missing values (whether on-treatment or post-treatment), but only imputed values during the-on-treatment period will be kept in the final datasets that will be described using means and their corresponding. Imputed values during the post-treatment period will be discarded and replaced by imputed values described in the next paragraph.

Imputation of missing data after treatment discontinuation

Missing LDL-C values during the post-treatment period will be imputed assuming LDL-C values would on average return to baseline values.

For each patient, missing post-treatment LDL-C values will be imputed 100 times, using a random draw from a normal distribution, with mean equal to patient's own baseline value and variance equal to the conditional variance at the specific time-point, given the baseline value.

Let Y_0 and Y_1 denote the LDL-C at baseline and at the specific time-point respectively. Since Y_0 and Y_1 are assumed to have a bivariate normal distribution, the conditional variance of Y_1 given Y_0 is:

$$Var(Y_1|Y_0 = y_0) = \sigma_1^2(1 - \rho^2)$$

Where σ_1^2 denotes the variance of Y1 and ρ the coefficient of correlation between Y_0 and Y_1.

The conditional variance will be estimated from observed data at the specific time-point.

During the random generation process, a minimum value of 0 will also be applied in order to avoid negative imputed LDL-C values.

Appendix D List of MedDRA terms for CMQs

Table 8 - Selected PTs from SMQ "Optic nerve disorders" including in the CMQ for neurologic events

MedDRA Term Label	Preferred Term Code
Benign neoplasm of optic nerve	10057424
Optic atrophy	10030910
Optic discs blurred	10030923
Optic nerve disorder	10061322
Optic nerve injury	10030938
Optic nerve neoplasm	10053645
Optic nerve operation	10053272
Optic neuropathy	10061323
Papillitis	10033708
Pseudopapilloedema	10037141
Subacute myelo-opticoneuropathy	10058009
Toxic optic neuropathy	10044245
Visual evoked potentials abnormal	10047549
Amaurosis fugax	10001903
Blindness	10005169
Blindness unilateral	10005186
Colour blindness acquired	10010051
Colour vision tests abnormal	10010056
Cranial nerve injury	10061094
Delayed myelination	10076456
Fundoscopy abnormal	10017520
Hemianopia	10019452
Hemianopia heteronymous	10019455
Hemianopia homonymous	10019456
Loss of visual contrast sensitivity	10064133
Neuro-ophthalmological test abnormal	10029256
Night blindness	10029404
Ophthalmological examination abnormal	10056836
Optic pathway injury	10030949
Optical coherence tomography abnormal	10073561

MedDRA Term Label	Preferred Term Code
Quadrantanopia	10077820
Visual acuity reduced	10047531
Visual acuity reduced transiently	10047532
Visual acuity tests abnormal	10047534
Visual field defect	10047555
Visual field tests abnormal	10047567
Visual impairment	10047571
Visual pathway disorder	10061411

Table 9 - CMQ "Neurocognitive disorders – FDA's recommendation"

MedDRA level	MedDRA Code	MedDRA Term Label
PTCD	10001949	Amnesia
PTCD	10061423	Amnestic disorder
PTCD	10002711	Anterograde Amnesia
PTCD	10078497	Neuropsychiatric symptoms
PTCD	10008398	Change in sustained attention
LLTCD	10009843	Cognitive Deterioration
PTCD	10057668	Cognitive Disorder
LLTCD	10010300	Confusion
LLTCD	10048321	Confusion Aggravated
PTCD	10010305	Confusional State
PTCD	10012218	Delirium
PTCD	10012267	Dementia
PTCD	10012271	Dementia Alzheimer's type
LLTCD	10012290	Dementia Nos
LLTCD	10012291	Dementia Nos Aggravated
LLTCD	10012292	Dementia of the Alzheimer's type NOS
PTCD	10067889	Dementia with Lewy Bodies
PTCD	10013395	Disorientation
PTCD	10013496	Disturbance in attention
PTCD	10070246	Executive dysfunction
PTCD	10068968	Frontotemporal Dementia
LLTCD	10058669	Global Amnesia
PTCD	10021402	Illogical Thinking

MedDRA level	MedDRA Code	MedDRA Term Label
PTCD	10071176	Impaired reasoning
PTCD	10021630	Incoherent
PTCD	10023236	Judgement impaired
PTCD	10027175	Memory Impairment
PTCD	10027374	Mental Impairment
LLTCD	10027376	Mental Impairment Nos
LLTCD	10048345	Mental State Abnormal Aggravated
PTCD	10048294	Mental Status Changes
PTCD	10065424	Mini Mental Status Examination Abnormal
PTCD	10036631	Presenile Dementia
PTCD	10038965	Retrograde Amnesia
PTCD	10039966	Senile Dementia
LLTCD	10039967	Senile Dementia Nos
LLTCD	10040602	Short-term Memory Loss
PTCD	10043431	Thinking Abnormal
LLTCD	10043438	Thinking Slowed
PTCD	10044380	Transient Global Amnesia
PTCD	10057678	Vascular Dementia

Appendix E Z-score calculation formula for Cogstate Battery test

Z-Score: Comparison of Individual Scores to Normative Data

- Performance on each Cogstate test can be standardized relative to age matched normative data (i.e., the score will be converted to a z-score by subtracting the age matched mean from Cogstate's normative sample and dividing by the age matched standard deviation (SD) from the same normative sample)
- The multiplicand equals 1 for tests for which a higher score is indicative of better cognitive performance (i.e., OCL) and -1 for tests where a lower score is indicative of better cognitive performance (i.e., DET, IDN, GML).
- The z-score will be calculated as follows:

$$z - Score\ (z_{ijt}) = \frac{(x_{ijt} - \bar{x}_{1t})}{\sigma_{1t}} * Multiplicand$$

Where:

t = is the test indicator

i = indexes subject i

j = indexes the jth assessment for subject i

x = cognitive score

$\bar{x}_{1t}$ = mean performance score of the age-matched normative sample for test t

σ_{1t} = Standard Deviation of the age-matched normative sample for test t

Appendix F Cogstate normative data

Cogstate

Table 1. Summary normative data for the Detection test. The primary outcome for this test is Reaction Time (Log10 transformation)

Age (Years)	N	Mean	SD	WSD
8	22	2.63129	0.13746	0.04997
9	32	2.58581	0.13506	0.04997
10	1,085	2.56241	0.08007	0.04997
11	1,548	2.53830	0.07896	0.04997
12	2,134	2.52938	0.07682	0.04997
13	2,785	2.51597	0.07535	0.04997
14	7,876	2.51298	0.08101	0.04997
15	7,708	2.50910	0.07674	0.04997
16	6,541	2.50538	0.07644	0.04997
17	5,986	2.50197	0.07528	0.04997

Table 2. Summary normative data for the Identification test. The primary outcome for this test is Reaction Time (Log10 transformation)

Age (Years)	N	Mean	SD	WSD
8	22	2.84589	0.11548	0.04210
9	32	2.80141	0.09222	0.04210
10	1,085	2.76101	0.07096	0.04210
11	1,548	2.73223	0.07068	0.04210
12	2,134	2.71368	0.06719	0.04210
13	2,785	2.69591	0.06782	0.04210
14	7,876	2.68636	0.06954	0.04210
15	7,708	2.67744	0.06687	0.04210
16	6,541	2.67182	0.06561	0.04210
17	5,986	2.66634	0.06456	0.04210

Cogstate

Table 3. Summary normative data for the One Card Learning test. The primary outcome for this test is Accuracy (Arcsine transformation)

Age (Years)	N	Mean	SD	WSD
8	15	0.91684	0.10775	-
9	16	0.94297	0.16884	-
10	1,085	0.96886	0.08819	0.11788
11	1,548	0.97218	0.08805	0.11788
12	2,134	0.97878	0.08754	0.11788
13	2,785	0.97863	0.08762	0.11788
14	7,876	0.97449	0.08567	0.11788
15	7,708	0.97758	0.08539	0.11788
16	6,541	0.98386	0.08588	0.11788
17	5,986	0.98932	0.08719	0.11788

Table 4. Summary normative data for the Groton Maze Learning Test. The primary outcome for this test is Total Errors

Age (Years)	N	Mean	SD	WSD
8	15	75.60	23.52	-
9	20	73.20	18.28	-
10	31	61.29	21.31	-
11	36	62.97	18.48	-
12	25	55.56	13.71	-
13	20	54.35	13.05	-
14	22	44.32	17.83	-
15	21	47.33	19.15	-
16	45	48.31	20.06	-
17	27	51.11	10.37	-

Appendix G Effect size calculation formula for Cogstate data

Effect Size

The magnitude of the differences between treatment groups and placebo, the effect size, can be assessed using Cohen's d (Cohen, 1988). The equations will be as follows:

$$d = \frac{(\bar{x}_t - \bar{x}_p) * Multiplicand}{Pooled\ SD}$$

$$Pooled\ SD = \sqrt{\frac{(n_t - 1)(SD_t)^2 + (n_p - 1)(SD_p)^2}{n_t + n_p - 2}}$$

Where:

- t = treatment group
- p = placebo group
- n = the sample size of each group
- $\bar{x}$ = descriptive sample mean of each group
- SD = descriptive standard deviation of each group
- The multiplicand equals 1 for tests for which a higher score is indicative of better cognitive performance (i.e., OCL) and -1 for tests where a lower score is indicative of better cognitive performance (i.e., DET, IDN, GML).

Effect size $|d|$: <0.2 considered as trivial, 0.2-0.5 considered as small, >0.5-0.8 considered as moderate, >0.8-1.1 considered as large, >1.1 considered as very large.

Appendix H Pediatric formula for eGFR and creatinine clearance

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

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