AMENDED CLINICAL TRIAL PROTOCOL NO. 02

COMPOUND: alirocumab

An 8-Week Open-Label, Sequential, Repeated Dose-Finding Study to Evaluate the Efficacy and Safety of Alirocumab in Children and Adolescents with Heterozygous Familial Hypercholesterolemia Followed by an Extension Phase

STUDY NUMBER: DFI14223

STUDY NAME: ODYSSEY KIDS

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CLINICAL TRIAL SUMMARY

COMPOUND: alirocumab	**STUDY No: DFI14223**
TITLE	An 8-Week Open-Label, Sequential, Repeated Dose-Finding Study to Evaluate the Efficacy and Safety of Alirocumab in Children and Adolescents with Heterozygous Familial Hypercholesterolemia Followed by an Extension Phase.
INVESTIGATOR/TRIAL LOCATION	Multi-center, multi-national.
PHASE OF DEVELOPMENT	Phase 2.
STUDY OBJECTIVE(S)	**Primary objective:** • To evaluate the effect of alirocumab administered every 2 weeks (Q2W) or every 4 weeks (Q4W) on low-density lipoprotein cholesterol (LDL-C) levels after 8 weeks of treatment in heterozygous familial hypercholesterolemia (heFH) patients aged of 8 to 17 years, with LDL-C ≥130 mg/dL (3.37 mmol/L) 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, for at least 4 weeks prior to the screening period. **Secondary objective(s):** • To evaluate the safety and tolerability of alirocumab. • To evaluate the pharmacokinetics profile of alirocumab. • To evaluate the effects of alirocumab on other lipid parameters (eg, Apolipoprotein B (Apo B), non-high density lipoprotein cholesterol (non-HDL-C), Total-Cholesterol (Total-C), high-density lipoprotein cholesterol (HDL-C), Lipoprotein (a) (Lp[a]), Triglycerides (TGs), Apolipoprotein A-1 (Apo A-1) levels after 8 weeks of treatment. • To evaluate the development of anti- alirocumab antibodies.
STUDY DESIGN	This study is an open-label, dose-finding, sequential group, multi-national, multi-center study with repeated dose of subcutaneous (SC) alirocumab injections administered every 2 weeks (Q2W) or every 4 weeks (Q4W) in children and adolescents aged of 8 to 17 years with heFH having LDL-C ≥130 mg/dL (3.37 mmol/L) despite 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, for at least 4 weeks prior to the screening period. There will be a sequential enrollment into the 4 separate and independent cohorts, Cohorts 1 to 4.The duration of this open-label, dose-finding treatment period will be 8 weeks for the first 3 cohorts, and 12 weeks for Cohort 4. Each independent cohort below will include approximately 10 patients with no less than 4 patients in each body weight (BW) category: • Cohort 1 will receive 30 mg Q2W for BW <50 kg and 50 mg Q2W for BW ≥50 kg. • Cohort 2 will receive 40 mg Q2W for BW <50 kg and 75 mg Q2W for BW ≥50 kg. • Cohort 3 will receive 75 mg Q4W for BW <50kg and 150 mg Q4W for BW ≥50 kg. • Cohort 4 will receive 150 mg Q4W for BW<50 kg and 300 mg Q4W for BW ≥50kg. For each cohort, the study consists of a main phase and an optional extension phase. The main phase is comprised of 3 periods: screening (including run-in, if applicable), open-label dose finding treatment, and follow-up only for Cohorts 1, 2, and 3, and 2 periods: screening (including run-in, if applicable), open-label dose

	finding treatment, but no follow-up period for Cohort 4. The extension period is an open-label extension period that will be offered to all patients, whatever the cohort.
STUDY DESIGN	**MAIN PHASE** **Screening Period:** • An up to 6 week (+1 week) screening period to allow eligibility to be established. Patients already on a stable LMT(s) (ie, stable optimal dose of statin ± other stable LMTs or stable dose of non-statin LMTs in statin-intolerant patients for at least 4 weeks prior to screening LDL-C being obtained) and with heFH diagnosis confirmed by previous genetic testing or meeting Simon Broome criteria can be enrolled within 2 weeks if meeting all other eligibility criteria. 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 on higher doses. For patients not receiving maximally tolerated dose of statin, statin intensification should be carefully considered prior to inclusion in this study in order to ensure that the addition of a non-statin LDL-C lowering therapy (ie, alirocumab) would be the next appropriate step in the management of the patient's hypercholesterolemia. The highest dose of statin should not exceed the maximum labeled dose of statin for pediatric patients as per the local prescribing information. Patients not already on a stable LMT(s), as defined above, for at least 4 weeks, will perform a "run-in" period as required to meet this eligibility criterion. 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 treated with statin *de novo* to avoid unstable LMT treatment during the screening period. Patients with suspected heFH but without confirmation by previous genetic testing and not meeting Simon Broome criteria will be asked to undergo genetic testing. If they do not consent to this testing, they will not be eligible to participate in this study. Laboratory testing and other assessments will be performed during this period, but not all assessments need to be completed at the same visit. • Of note, all patients who are successfully screened for Cohort 1 and are not included in Cohort 1, due to the appropriate Cohort 1 weight group being fully enrolled, may participate in Cohort 2, but only after eligibility, including all safety assessments, is reconfirmed. Patients who are successfully screened for Cohort 2 but are not enrolled, due to the appropriate Cohort 2 weight group being fully enrolled, may participate in Cohort 3, without the need to repeat the run-in/screening period. In such a circumstance, the run-in/screening period from Cohort 2 will substitute for the run-in/screening period for Cohort 3 if there is no more than 3 months between eligibility confirmation and inclusion. **Open-Label Dose Finding Treatment Period:** • An open-label dose finding treatment period of 8 weeks with alirocumab for Cohorts 1, 2 and 3, but 12 weeks for Cohort 4. Four independent cohorts (as described above) will be administered SC alirocumab injections Q2W or Q4W in a sequential enrollment. The DMC will review data on a regular basis during the dose finding treatment period. After Cohort 1 completes the open-label dose finding treatment period, the DMC will continue to review the safety data and make a recommendation on

	dose escalation to Cohorts 2 and 3. Cohort 2 will initially begin enrollment. Once enrollment is completed for Cohort 2, then this will immediately be followed by enrollment into Cohort 3 (ie, sequential enrollment). Cohort 4 is an independent cohort with a later start date. • Cohorts 1 and 2 (Q2W): Alirocumab injections will be prepared from vials by the pharmacist (or equivalent). Alirocumab injections will be administered at Weeks 0, 2, 4, and 6. The Weeks 0 and 4 alirocumab injections will be administered at the clinical site by the site staff. The Weeks 2 and 6 alirocumab injections will be administered at the clinical site by the site staff or at the patient's home by a health care professional, depending upon local arrangements and preferences of the investigator/patient. • Cohort 3 (Q4W): Alirocumab injections will be prepared from vials by the pharmacist (or equivalent). Alirocumab injections will be administered at Weeks 0 and 4 at the clinical site by the site staff. • Cohort 4 (Q4W): Alirocumab injections will be administered with pre-filled syringes by the site staff. Alirocumab injections will be administered at Week 0, Week 4, and Week 8 at the clinical site by the site staff. • The lipid results from specimens obtained during the open-label dose finding treatment period will be masked for the clinical site/Investigator and patients. No attempts should be made by the investigator or patient to routinely have the patient's lipid values independently evaluated after entry into the open-label dose finding treatment period and until the final follow-up visit for Cohorts 1 to 3, and the entry into the OLE period for Cohort 4 **Follow-Up Period, only for Cohort 1 to Cohort 3:** • A follow-up period (off treatment) of 6 (Cohort 3) or 8 weeks (Cohorts 1 & 2) after the end of open-label dose finding treatment period visit. For the first 3 cohorts, the final follow-up visit corresponds to 10 weeks after the last alirocumab injection administered during the open-label dose finding treatment period, since the last injection for Cohorts 1 & 2 is Week 6 and for Cohort 3 it is Week 4. The daily optimal dose of statin therapy or of other LMT (if applicable) should be stable from screening through the end of the follow-up visit unless there is a safety concern, as per the Investigator's judgment. At the end of the follow-up period of the main phase, patients enrolled in Cohorts 1-3 and who successfully completed the main phase will be offered entry into an optional extension phase. For Cohort 4, patients who successfully completed the open-label dose-finding treatment period will be offered entry into an optional extension phase with latest end date of December 2018 or direct entry into the Phase 3 study, depending on the time of site initiation.
STUDY DESIGN	**EXTENSION PHASE** **Open-label extension period:** • For Cohorts 1- 3, all doses / dose regimens of alirocumab administered during the open-label dose finding treatment period of the main phase are expected to be efficacious. Thus, the initial dose of alirocumab that will be administered Q2W or Q4W during the OLE period, will be a continuation of the same doses / dose regimens administered during the open-label dose finding treatment period of the main phase. However, once the final optimal doses of alirocumab for the Phase 3 study are selected and device is available, treatment will be adjusted as needed to these final optimal doses, based on each patient's body weight at the time of the dose

	change. • For Cohort 4: If patients enter the OLE phase, patients will continue on their doses from the main phase. If patients decline entry into the OLE phase, their treatment will stop. • For Cohorts 1 to 3, alirocumab injections may be prepared from vials by the pharmacist (or equivalent) or supplied as prefilled syringes (PFS) depending on availability and additional considerations. Vials used for extension phase will be switched to PFS when available. - If the PFS is available in the extension phase, then patients may either switch from alirocumab injections prepared from vials to PFS or directly initiate PFS (depending on patient's date of entry into the extension phase). After appropriate training, the parent/guardian or patient (if appropriate) will administer the PFS at home or another preferred location. In certain cases, alternative arrangements may be made for the administration of the PFS. - If the PFS is not available in the extension phase, then alirocumab injections prepared from vials will be administered at the clinical site (by the site staff) or at the patient's home or another preferred location contingent upon alternative arrangements being made for such an administration. • The alirocumab administration during the OLE period will continue until at least 10 weeks (corresponding to the wash out period) before initiation of the pediatric Phase 3 study in the site where the patient is potentially participating. Therefore, patients who consent to participate in the pediatric phase 3 study could have their alirocumab injection in the OLE period up to December 2018, depending on the time of initiation of the phase 3 study planned to be done no later than December 2018. All other patients enrolled in the OLE period who decline the participation in phase 3 study will have their last alirocumab injection in December 2018. • The lipid levels will be communicated to the investigator during the OLE period. If there is a need to adjust the degree of LDL-C lowering, the daily dose of statin should NOT be decreased, except in case of medical reason. The investigator has the option to discontinue alirocumab, or to adjust other LMT (if applicable). Increases in dose of any background LMT are allowed throughout the OLE, if needed. Patients will be instructed to follow a diet in accordance with the American Academy of Pediatrics (AAP) guidelines (1) or equivalent throughout the entire study (ie, both phases).
STUDY POPULATION **Main selection criteria**	**Inclusion criteria:** I 01. Children and adolescent male and female patients aged 8**** to 17 years at the time of signed informed consent. *For Russia only:* *Male and female patients aged ≥12 and ≤17 years at the time of signed informed consent* I 02. Patients with a diagnosis of heterozygous familial hypercholesterolemia (he FH) through genotyping or clinical criteria.* I 03. Patients treated with an optimal dose of statin** with or without other LMT(s) or non-statin LMT(s) if statin intolerant*** at stable dose for at least 4 weeks prior to screening lipid sampling. I 04. Patients with calculated LDL-C greater than or equal to 130 mg/dL (≥3.37 mmol/L) 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. I 05. Patients with body weight greater than or equal to 25 kg. I 06. Patients aged of 8 to 9 years to be at Tanner stage1 and patients aged of 10 to 17 years to be at least at Tanner stage 2 in their development. I 07. A signed informed consent indicating parental permission with or without patient assent, depending on capacity for understanding based on developmental maturity. In cases involving emancipated or mature minors with adequate decision-making capacity, or when otherwise permitted by law, a signed informed consent directly from patients. ** Diagnosis of heFH must be made either by previous genotyping, current 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 screening period with results supporting a diagnosis of heFH. The clinical diagnosis should be based on the Simon Broome criteria for possible or definite FH (*see Appendix F*). Once eligibility is confirmed based on prior genetic testing or Simon Broome criteria, results of elective genetic testing will not impact patient's eligibility.* *** 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 inclusion in this study in order to ensure that the addition of a non-statin LDL-C lowering therapy (ie, alirocumab) would be the next appropriate step in the management of the patient's hypercholesterolemia. The highest dose of statin should not exceed the maximum labeled dose of statin for pediatric patients as per the local prescribing information.* ****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.* *****Patients aged of 8 to less than 10 years have had other available interventions to lower calculated LDL-C but these have been insufficient.* **Key Exclusion criteria:** • Patient with secondary hyperlipidemia. • Diagnosis of homozygous familial hypercholesterolemia. • Patient who has received lipid apheresis treatment within 2 months prior to the screening period, or has plans to receive it during the study. • Known history of type 1 or type 2 diabetes mellitus. • Known history of thyroid disease. • Known history of hypertension. • Fasting triglycerides >350 mg/dL (3.95 mmol/L) at the screening visit. • Severe renal impairment (ie, eGFR <30 mL/min/1.73 m^2 at the screening visit. • ALT or AST >2 x ULN (1 repeat lab is allowed). • CPK >3 x ULN (1 repeat lab is allowed).

Total expected number of patients	40 patients Cohort 1 – 10 patients; no less than 4 patients with BW <50 kg and no less than 4 patients with BW ≥50 kg. Cohort 2 – 10 patients; no less than 4 patients with BW <50 kg and no less than 4 patients with BW ≥50 kg. Cohort 3 – 10 patients; no less than 4 patients with BW <50 kg and no less than 4 patients with BW ≥50 kg. Cohort 4 – 10 patients: no less than 4 patients with BW <50 kg and no less than 4 patients with BW ≥50 kg.
STUDY TREATMENT(s)	
Investigational medicinal product(s) **Formulation:**	**Alirocumab:** For Cohort 1 to Cohort 3, vials (during the dose finding treatment period and extension period if PFS not available): sterile alirocumab drug product supplied at a concentration of 150 mg/mL in histidine, pH 6.0, polysorbate 20, and sucrose. Cohorts 1 & 2 (Q2W): Prefilled syringes (if available during the extension period): sterile alirocumab drug product supplied at a concentration of 30, 40, 50 or 75 mg/ 0.5 mL in histidine, pH 6.0, polysorbate 20, and sucrose. Cohort 3 (Q4W): Prefilled syringes (if available during the extension period): sterile alirocumab drug product supplied at a concentration of 75 mg/1.0 mL or 150 mg/1.0 mL in histidine, pH 6.0, polysorbate 20, and sucrose. For Cohort 4 (Q4W): Prefilled syringes: sterile alirocumab drug product supplied at a concentration of 150 mg/1.0 mL in histidine, pH 6.0, polysorbate 20, and sucrose, with 1 injection of 1 mL for the 150 mg dose, and 2 injections of 1mL containing150 mg each to provide a total 300 mg dose. **Formulation for dilution**: Solvent for alirocumab vials (during the dose finding treatment period and extension period if PFS not available): sterile solution consisting of 10 mM histidine, pH 6.0, polysorbate 20, and sucrose.
Route(s) of administration:	Subcutaneous (SC) injections in the abdomen, thigh or outer area of upper arm.
Dose regimen:	Cohort 1: 30 mg Q2W for BW <50 kg and 50 mg Q2W for BW ≥50 kg; with possible change during the OLE period. Cohort 2: 40 mg Q2W for BW <50 kg and 75 mg Q2W for BW ≥50 kg; with possible change during the OLE period. Cohort 3: 75 mg Q4W for BW <50 kg and 150 mg Q4W for BW ≥50 kg; with possible change during the OLE period. Cohort 4: 150 mg Q4W for BW<50 kg and 300 mg Q4W for BW ≥50 kg throughout the entire study.
ENDPOINT(S)	**Primary endpoint:** Percent change in calculated LDL-C from baseline to Week 8. **Secondary endpoint(s):** • Absolute change in calculated LDL-C from baseline to Week 8. • Proportion of patients achieving a calculated LDL-C level lower than 130 mg/dL (3.37 mmol/L) at Week 8. • Proportion of patients achieving a calculated LDL-C level lower than 110 mg/dL (2.84 mmol/L) at Week 8. • Percent change in LDL-C from baseline to Week 12 only for Cohort 4. • Percent change in Apo B, non-HDL-C, Total-C, Lp(a), TG, HDL-C, Apo A-1 from baseline to Week 8.

	• Absolute change in Apo B, non-HDL-C, Total-C, Lp(a), TG, HDL-C, Apo A-1, ratio Apo B/Apo A-1 from baseline to Week 8. **Safety endpoint(s):** • Safety parameters: adverse events (AE)s, serious AEs (SAE), AESIs, laboratory data, vital signs, body weight, height, and Tanner stage assessed throughout the study. **Other endpoint(s):** • Anti- alirocumab antibodies assessed throughout the study. • Alirocumab and PCSK9 concentrations assessed throughout the study. • To evaluate the long-term efficacy and safety of alirocumab during the extension phase.
ASSESSMENT SCHEDULE	**MAIN PHASE** **Screening period:** The screening period is up to 6 weeks (+ 1 week), with 1 to 2 visits that are anticipated, depending on the duration of stable LMT dosing and the need for mandatory heFH genetic testing. Patients can be enrolled during this period as soon as eligibility is confirmed. **Open-label dose finding treatment period:** For Cohorts 1 to 3, visits schedule from entry into the open-label dose finding treatment period: baseline Visit (V2, Week 0) and then every 2 weeks (ie, Weeks 2, 4, 6) until the end of the open-label dose finding period (Week 8). The visits at Week 2 and Week 6 will take place either at the clinical site or patient's home, depending upon local arrangements and preferences of the investigator/patient. For Cohort 4, visits schedule from entry into the open-label dose finding treatment period: baseline, Visit (V2, Week 0), and then every 4 weeks (ie, Weeks 0, 4, and 8) until the end of the open-label dose finding period (Week 12) will take place at the clinical site. Visits at Week 2 and Week 6 will be a phone call and at Week 10 will be at the clinical site. **Follow-up period, only for Cohort 1 to Cohort 3:** Follow-up visits will take place 6 and 10 weeks after the last alirocumab injection administered during the open-label dose-finding treatment period. This corresponds to Week 12 and Week 16 for Cohorts 1 & 2 or Week 10 and Week 14 for Cohort 3. The Week 10 or Week 12 visit will be conducted through a phone call if there is no safety concern by the investigator. **EXTENSION PHASE** **Open-label extension (OLE) period:** After successful completion of Week 16 visit for Cohorts 1 & 2 or Week 14 visit for Cohort 3, patients will be offered entry into an optional OLE period. The first visit of the OLE period will overlap with the final follow-up visit of the main phase. Visits will take place at Week 20, Week 24, Week 28 and then every 12 weeks thereafter for assessments for Cohorts 1 & 2. Visits will take place at Week 18, Week 22, Week 26 and then every 12 weeks thereafter for assessments for Cohort 3. Depending on the clinical supplies and/or alternative contingency plans, more frequent visits such as every 2 weeks (for Cohorts 1 & 2) or every 4 weeks (for Cohort 3) may be required. Visits will continue until visit end of OLE at least 2 or 4 weeks after last alirocumab injection (with a follow-up phone call at least 10 weeks after the last alirocumab administration) before the initiation of the pediatric Phase 3 study in the site where the patient is potentially participating or December 2018, whichever comes first. A follow-up phone call will takes place at least 10 weeks after the last IMP of each cohort. All patients enrolled in Cohort 4 who successfully complete the open-label dose-finding treatment period will also be offered either entry into the extension phase at

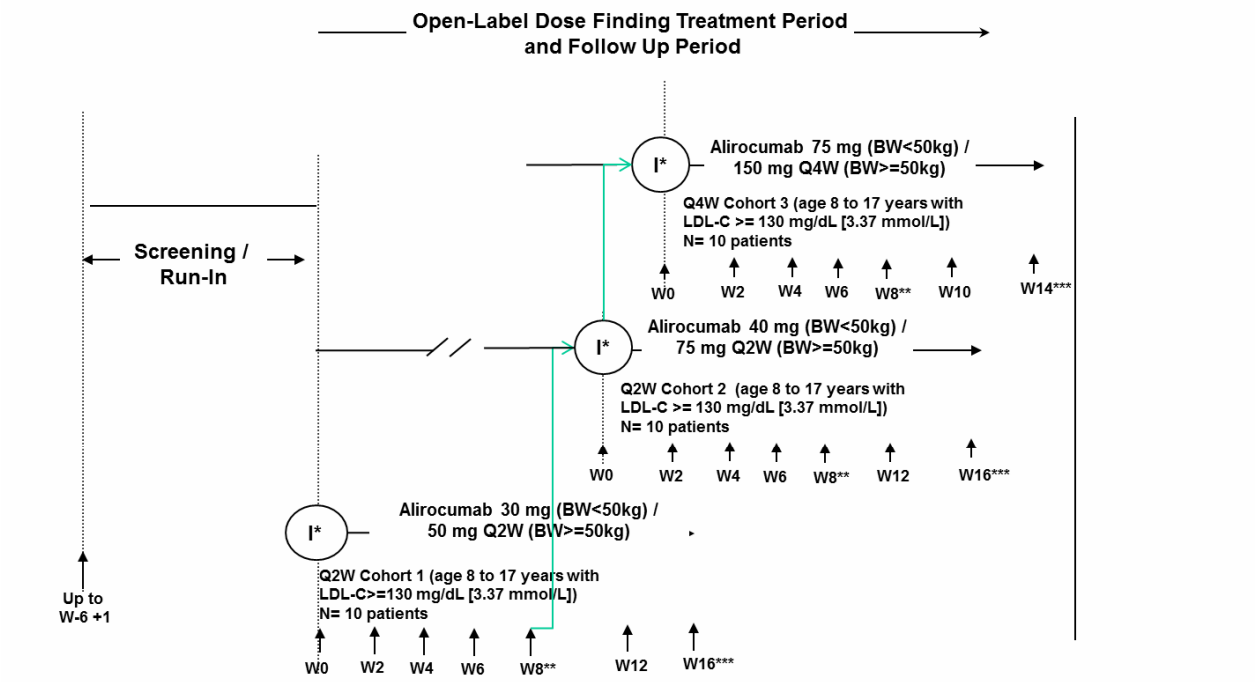
	Week 12 or direct entry into the phase 3 study, depending on the start date of phase 3 study in the site where patient is potentially participating.
STATISTICAL CONSIDERATIONS	**Sample size determination:** No power sample size calculations were performed for the main phase. A sample size of 10 patients per cohort is empirical and based on the sample size of the Phase 1 studies (R727-CL-904 and R727-CL-1001) conducted in adults. No less than 4 patients with BW <50 kg and no less than 4 patients with BW ≥50 kg will be enrolled in 4 independent cohorts (Cohort 1, Cohort 2, Cohort 3, and Cohort 4), which will allow the evaluation of the pharmacokinetics/pharmacodynamics (PK/PD) profile and safety of different alirocumab doses/dose regimen in each BW category and to compare with PK/PD profile and safety observed in adult patients. **Analysis population:** Efficacy analyses will be performed on the modified intent-to-treat (mITT) population defined as all patients receiving at least one dose or partial dose of alirocumab, with a baseline LDL-C available and with at least one LDL-C value available in the period from first alirocumab injection to last alirocumab injection + 21 days (for Cohorts 1 and 2) or + 35 days (for Cohorts 3 and 4) during the main phase. Safety analyses will be performed on Safety population which consists of patients receiving at least one dose or partial dose of alirocumab. **Primary analysis:** There will be no formal statistical test for the primary endpoint, efficacy analyses will be descriptive. The primary analysis will be based on an on-treatment approach, and will use LDL-C values collected during the efficacy treatment period. The efficacy treatment period is defined as the period from first alirocumab injection to last alirocumab injection + 21 days (for Cohorts 1 & 2) or + 35 days (for Cohorts 3 and 4) during the open-label dose finding treatment period. The percent change from baseline in calculated LDL-C at Week 8 will be analyzed in the mITT population using a mixed effect model with repeated measures (MMRM) approach. All on-treatment data available at Week 4 and Week 8 will be used and missing data will be accounted for by the MMRM model. The model will include the fixed categorical effects of alirocumab dose/dose regimen 30 mg Q2W (<50 kg), 40 mg Q2W (<50 kg), 50 mg Q2W (≥50 kg), 75 mg Q2W (≥50 kg), 75 mg Q4W (<50 kg) ,150 mg Q4W (≥50 kg), 150 mg Q4W (<50 kg) and 300 mg Q4W (≥50 kg), time point (Week 4, Week 8), dose-by-time point interaction, as well as, the continuous fixed covariates of baseline LDL-C value and baseline value-by-time point interaction. LS mean with 95% confidence intervals will be provided for each alirocumab dose. In addition, LS mean with 95% confidence intervals will be provided for each cohort using appropriate contrasts. Additionally, for Cohort 4 only, the percent change from baseline in calculated LDL-C at Week 12 will be analyzed in the mITT population using the same MMRM model as for the primary endpoint but including all on-treatment corresponding data available at Week 4, Week 8, Week 10, and Week 12. **Analysis of secondary endpoints:** Secondary endpoints will be analyzed using the same MMRM model as for the primary endpoint.

DURATION OF STUDY PERIOD (per patient)	**MAIN PHASE** For Cohorts 1 to 3, a study duration of approximately 16-23 weeks (screening period: up to 6 [+1] weeks, open-label dose finding treatment period: 8 weeks, follow-up period: 6-8 weeks). For Cohort 4, a study duration of approximately 14 -19 weeks (screening period: up to 6 [+1] weeks, open-label dose finding treatment period: 12 weeks). **EXTENSION PHASE** Patients who enroll in the open-label extension period will continue alirocumab administration until at least 10 weeks before the initiation of the pediatric Phase 3 study in the site where the patient is potentially participating. Therefore, patients who consent to participate to the pediatric phase 3 study could have their last alirocumab injection in the OLE period up to December 2018, depending on the timing of the phase 3 study. All other patients, enrolled in the OLE period, who decline participation in the phase 3 study, will have their last alirocumab injection in December 2018. For Cohorts 1 to 3, this corresponds to a maximum of approximately 24 months for first patients enrolled. For Cohort 4, this corresponds to a maximum of approximately 7 months for the first patients enrolled.

1 FLOW CHARTS

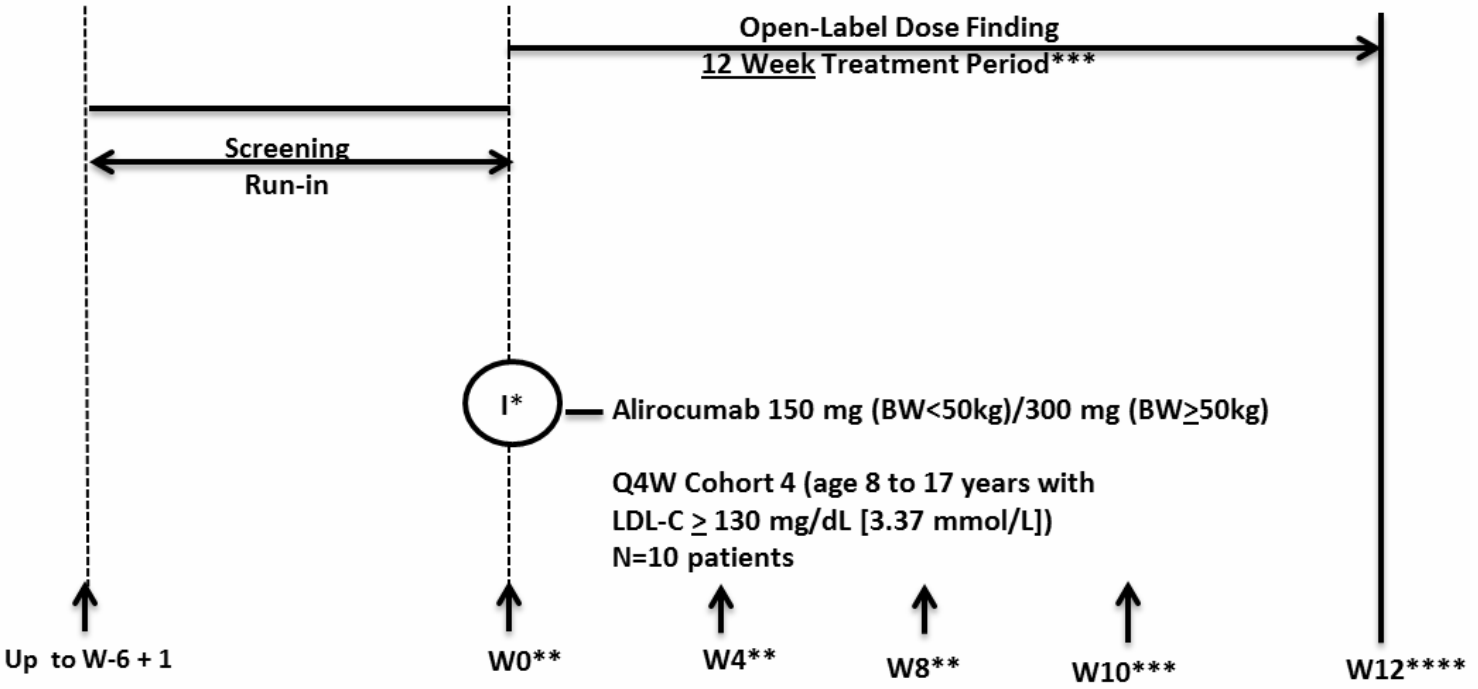
1.1 GRAPHICAL STUDY DESIGN (MAIN PHASE)

1.1.1 COHORTS 1 TO 3



* Inclusion (I): The inclusion or entry into the open-label dose finding treatment period is always Week 0 of the corresponding cohort. N: represent the number of patients to be included in each study cohort.
** Week 8 is the end of the open-label dose finding treatment period visit for the corresponding cohort.
*** Week 14 or 16 is the final follow up visit and the end of the main phase of the study.
Dose escalation will occur sequentially from Cohort 1 to both Cohorts 2 and 3, whereby the dose escalation to Cohorts 2 and 3 will commence after Cohort 1 completes 8 weeks of the open-label dose finding treatment period and the DMC reviews the ongoing safety data and renders a recommendation on dose escalation. Cohort 2 will initially begin enrollment. Once enrollment is completed for Cohort 2, then this will immediately be followed by enrollment into Cohort 3 (i.e., sequential enrollment).

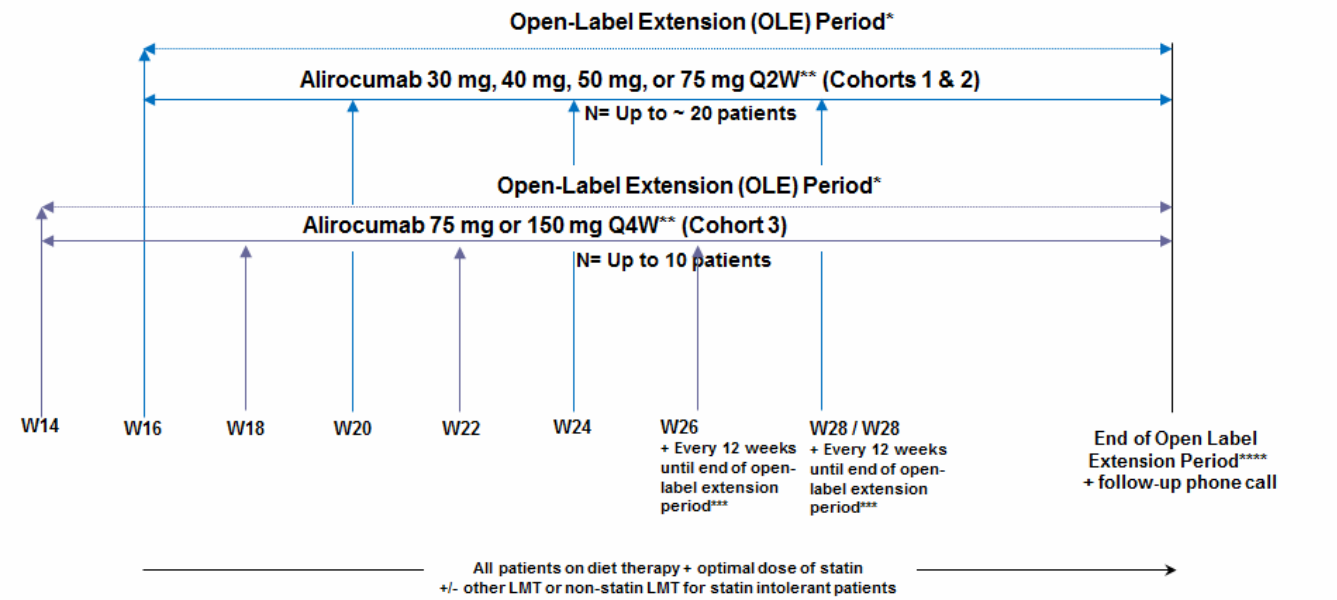
1.1.2 COHORT 4



*	Inclusion (I): The inclusion or entry into the open-label dose finding treatment period for Cohort 4.
**	The main phase for Cohort 4 will include 3 alirocumab injections (at W0, W4, and W8).
***	For Cohort 4, the study duration includes an extended 12 week treatment period, including a Week 10 visit, but will not have a follow up period, in contrast to the study design for Cohorts 1, 2, and 3.
****	Week 12 is the end of the open-label dose finding treatment period and possible entry point into the extension for Cohort 4.

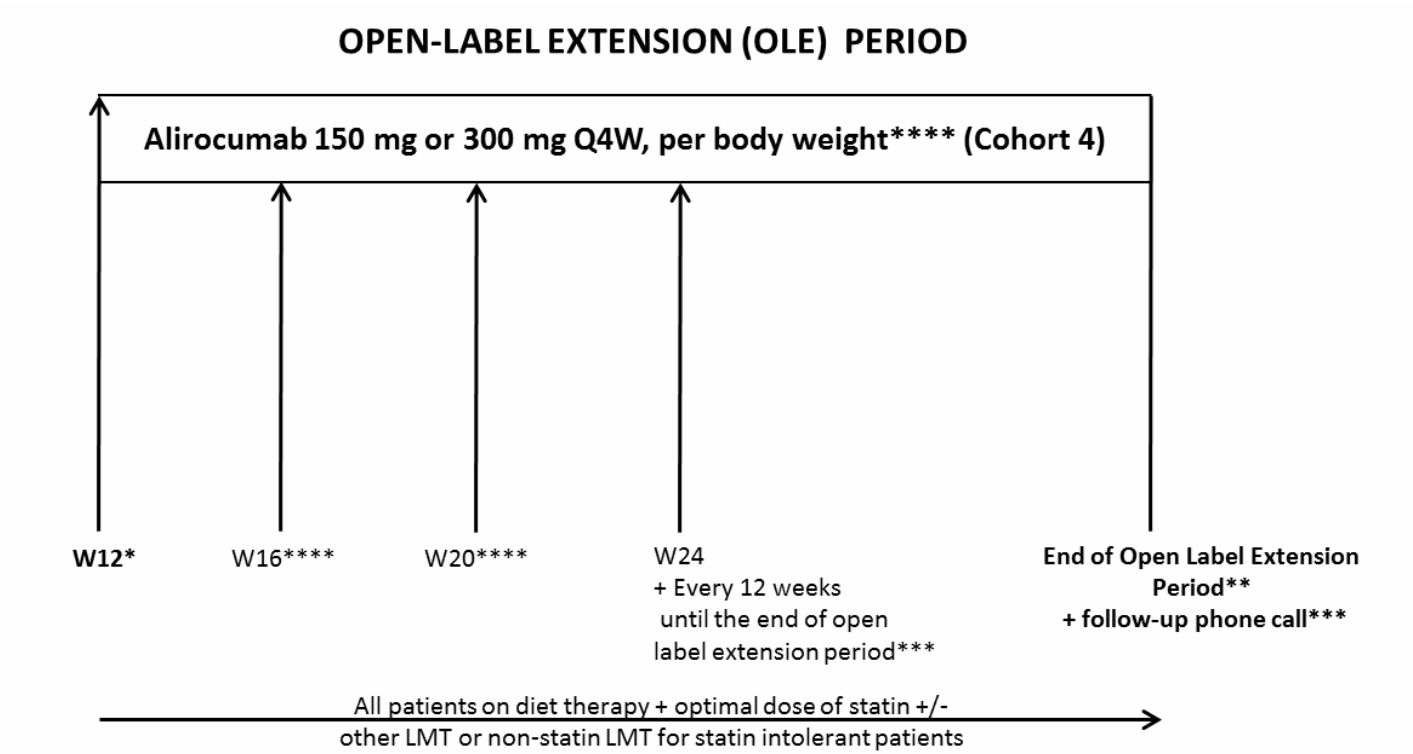
1.2 GRAPHICAL STUDY DESIGN (OPTIONAL EXTENSION PHASE)

1.2.1 COHORTS 1 TO 3



N: represent the number of patients.
* All patients enrolled in each cohort who successfully complete the main phase will be offered entry into the extension phase.
** The dose administered during the open-label dose finding treatment period of the main phase will initially be continued Q2W (cohorts 1 & 2) or Q4W (cohort 3) in the extension phase. Once the final doses for the phase 3 study are selected, then these final doses from the Q2W (cohorts 1 & 2) / Q4W (cohort 3) regimen will be administered to all patients during the OLE period, based on their body weight at the time of the dose change.
*** Alirocumab injections may be prepared from vials by the pharmacist (or equivalent) or supplied as prefilled syringes (PFS). If the PFS are not available in the OLE or for patients preceding the switch with the PFS, then alirocumab will be administered at the clinical site (by the site staff) every 2 weeks (cohorts 1 & 2) in addition to their scheduled visits or alirocumab will be administered at the patient's home or another preferred location contingent upon alternative arrangements being made for such an administration. For cohort 3 alirocumab will be administered with PFS every 4 weeks at the clinical site or at home if no visit is planned, or another preferred location contingent upon alternative arrangements being made for such an administration
**** Visits will continue until at least 6 or 8 weeks (corresponding to the wash out period of 10 weeks after the last alirocumab injection) before the initiation of the pediatric Phase 3 study in the site where the patient is potentially participating or December 2018, whichever comes first. A follow-up phone call will takes place at least 10 weeks after the last IMP of each cohort.

1.2.2 COHORT 4



* All patients enrolled in Cohort 4 who successfully complete the main phase will be offered entry into the extension phase at Week 12 or directly switch to the phase 3 study (EFC14643).

** Visits will continue until at least 6 weeks (corresponding to the wash out period of 10 weeks after the last alirocumab injection) before the initiation of the pediatric Phase 3 study in which the site where the patient is potentially participating where the latest end date for Cohort 4 will be December 2018.

*** A follow-up phone call will take place at least 10 weeks after the last IMP for all cohorts, except those patients who refuse phase 3.

**** The Q4W dose for Cohort 4 administered during the open label-dose finding treatment period of the main phase will initially be continued in the extension phase.

1.3 STUDY FLOWCHART (MAIN PHASE)

1.3.1 COHORTS 1 TO 3

Main Phase Cohorts 1 to 3	Screening Period (including run-in if applicable)	Open-Label Dose Finding Treatment Period					Follow-Up Period	
VISIT	1[c]	2	3	4	5	6	7	8
Week (W)	Up to W-6	W0/D1	W2	W4	W6	W8	W10 (Cohort 3) or W12 (Cohorts 1 & 2)	W14 (Cohort 3) or W16 (Cohorts 1 & 2)
Visit Window (+/- days)	+7		±3	±3	±3	±3	±7	±7
Visit Type	Clinical Site	Clinical Site	Clinical Site or Patient's Home[a]	Clinical Site	Clinical Site or Patient's Home[a]	Clinical Site	Clinical site or Phone Call[a]	Clinical Site
Informed Consent	X							
heFH Genotyping Informed Consent (if needed)	X							
Inclusion Criteria	X	X						
Exclusion Criteria	X	X						
Patient Demography	X							
Medical/Surgical/ Family medical History	X							
Alcohol/Smoking habits	X							
Prior Medication History[r]	X							
Physical Examination	X	X				X	X[d]	X[d]

Main Phase Cohorts 1 to 3	Screening Period (including run-in if applicable)	Open-Label Dose Finding Treatment Period					Follow-Up Period	
VISIT	1[c]	2	3	4	5	6	7	8
Week (W)	Up to W-6	W0/D1	W2	W4	W6	W8	W10 (Cohort 3) or W12 (Cohorts 1 & 2)	W14 (Cohort 3) or W16 (Cohorts 1 & 2)
Visit Window (+/- days)	+7		±3	±3	±3	±3	±7	±7
Visit Type	Clinical Site	Clinical Site	Clinical Site or Patient's Home[a]	Clinical Site	Clinical Site or Patient's Home[a]	Clinical Site	Clinical site or Phone Call[a]	Clinical Site
Measured Body Weight	X	X		X		X		X
Measured Height	X							X
Tanner Stages[p]	X							X
IVRS/IWRS contact	X	X	X	X	X			X
Inclusion		X						
Treatment:								
Alirocumab Administration Q2W (Cohorts 1 & 2)[e]		X	X	X	X			
Alirocumab Administration Q4W (Cohort 3 only)[e]		X		X				
Concomitant Medication	X	X	X	X	X	X	X	X
Review of diet[s]	X	X		X		X		
Check of stability of background LMT	X	X	X	X	X	X		

Main Phase Cohorts 1 to 3	Screening Period (including run-in if applicable)	Open-Label Dose Finding Treatment Period					Follow-Up Period	
VISIT	1[c]	2	3	4	5	6	7	8
Week (W)	Up to W-6	W0/D1	W2	W4	W6	W8	W10 (Cohort 3) or W12 (Cohorts 1 & 2)	W14 (Cohort 3) or W16 (Cohorts 1 & 2)
Visit Window (+/- days)	+7		±3	±3	±3	±3	±7	±7
Visit Type	Clinical Site	Clinical Site	Clinical Site or Patient's Home[a]	Clinical Site	Clinical Site or Patient's Home[a]	Clinical Site	Clinical site or Phone Call[a]	Clinical Site
Efficacy:								
Total-C, calculated LDL-C, HDL-C, TG, non-HDL-C[f]	X	X		X		X		
Apo B, Apo A-1, ratio Apo B / Apo A-1, and Lp(a)[f]	X	X				X		
Safety:								
AE /SAE recording (if any)	X	X	X	X	X	X	X	X
Vital Signs[f]	X	X		X		X		X

	Screening Period (including run-in if applicable)	Open-Label Dose Finding Treatment Period					Follow-Up Period	
VISIT	1[c]	2	3	4	5	6	7	8
Week (W)	Up to W-6	W0/D1	W2	W4	W6	W8	W10 (Cohort 3) or W12 (Cohorts 1 & 2)	W14 (Cohort 3) or W16 (Cohorts 1 & 2)
Visit Window (+/- days)	+7		±3	±3	±3	±3	±7	±7
Visit Type	Clinical Site	Clinical Site	Clinical Site or Patient's Home[a]	Clinical Site	Clinical Site or Patient's Home[a]	Clinical Site	Clinical site or Phone Call[b]	Clinical Site
Laboratory Testing[f]:								
heFH genotyping (Mandatory for consenting patients without documented heFH diagnosis; optional for documented heFH diagnosis patients wishing to undergo genotyping)[g]	X	X	X	X	X	X		
Hematology and chemistry[h]	X			X		X		X[q]
Creatine phosphokinase (CPK)	X			X		X		X[q]
Liver panel[i]	X			X		X		X[q]
Adrenal gland hormones[j]		X				X		
Gonadal and pituitary hormones[k]		X				X		
Fat soluble vitamins[l]		X				X		
Pregnancy test[m]	X	X				X		X
Anti-alirocumab antibodies (ADA)[n] [o]		X				X		X[o]
PCSK9 levels (free and total)/serum alirocumab concentration (PK) [n]		X		X		X		X

a The Week 2 and Week 6 visits will take place either at the clinical site or patient's home, depending upon local arrangements and preferences of the Investigator/patient. For Cohort 3, a phone call may be done instead of a home or office visit.
b The Week 10 or Week 12 visit will be conducted at clinical site or through a phone call if no safety concerns by the investigator
c Two site visits may be needed to complete eligibility confirmation.
d Physical examination at the follow-up visits should be performed only in case of clinically relevant abnormality at Week 8 visit.
e Alirocumab injections will be prepared from vials by the pharmacist (or equivalent). For Cohorts 1 & 2 the Weeks 0 and 4 alirocumab injections will be administered at the clinical site by the site staff. The Weeks 2 and 6 alirocumab injections will be administered at the clinical site by the site staff or at the patient's home by a health care professional, depending upon local arrangements and preferences of the Investigator/patient. For Cohort 3 the Weeks 0 and 4 alirocumab injections will be administered at the clinical site by the site staff, the Week 2 and
Week 6 visits could be done at the patient's home by a health care professional but without injections. Prior to each alirocumab administration, a local topical anesthetic may be utilized as per the Investigator.
f 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.
g 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 8-week dose-finding part of the trial.
h 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.
i Liver panel: ALT, AST, alkaline phosphatase (ALP), and total bilirubin.
j Adrenal gland hormones: cortisol (with reflexive ACTH levels if cortisol <LLN) and dehyroepiandrosterone sulfate (DHEAS).
k Pituitary hormones: luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Gonadal hormones: testosterone [males] and estradiol [females].
l Fat soluble vitamins: A (retinol), D (25 hydroxy vitamin D), E (alpha-tocopherol), and K (phylloquinone).
m Pregnancy test should be done on females of childbearing potential who are sexually active 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.
n ADA and PK samples should be collected before alirocumab administration.
o Only patients who prematurely discontinue the main phase or do not enter the optional extension phase and have a titer at or above 240 for ADA at follow-up 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.
p See Appendix E for Tanner stages evaluation.
q Only in case of clinically relevant abnormal values at the end of the treatment visit (Week 8).
r Document prior medication history within the previous 12 weeks, especially for lipid modifying therapy (including statin) and nutraceutical products that may affect lipids (eg, omega-3 fatty acids, plant stanols such as found in Benecol, flax seed oil, psyllium).
s Patients will be instructed to follow a diet in accordance with the American Academy of Pediatrics guidelines or equivalent throughout the entire study.
t Vital signs include: heart rate, systolic and diastolic BP in sitting position.

1.3.2 COHORT 4

Main Phase Cohort 4	Screening Period (including run-in if applicable)	Open-Label Dose-finding Treatment Period						
VISIT	1	2	3	4	5	6	7	8
Week (W)	Up to W-6	W0/D1[b]	W2	W4	W6	W8	W10	W12
Visit Window (+/- days)	+7		±3	±3	±3	±3	±7	±7
Visit Type	Clinical Site	Clinical Site	Phone Call	Clinical Site	Phone Call	Clinical Site	Clinical site[a]	Clinical Site
Informed Consent	X							
heFH Genotyping Informed Consent (if needed)	X							
Inclusion Criteria	X	X						
Exclusion Criteria	X	X						
Patient Demography	X							
Medical/Surgical/ Family medical History	X							
Alcohol/Smoking habits	X							
Prior Medication History[o]	X							
Physical Examination	X	X				X		
Measured Body Weight	X	X		X		X		X
Measured Height	X							X
Tanner Stages[n]	X							X
IVRS/IWRS contact	X	X						X
Inclusion		X						

Main Phase Cohort 4	Screening Period (including run-in if applicable)	Open-Label Dose-finding Treatment Period						
VISIT	1	2	3	4	5	6	7	8
Week (W)	Up to W-6	W0/D1[b]	W2	W4	W6	W8	W10	W12
Visit Window (+/- days)	+7		±3	±3	±3	±3	±7	±7
Visit Type	Clinical Site	Clinical Site	Phone Call	Clinical Site	Phone Call	Clinical Site	Clinical site[a]	Clinical Site
Treatment:								
Alirocumab Administration Q4W[c]		X		X		X		
Concomitant Medication	X	X	X	X	X	X	X	X
Review of diet[p]	X	X		X		X		X
Check of stability of background LMT	X	X	X	X	X	X		X
Efficacy:								
Total-C, calculated LDL-C, HDL-C, TG, non-HDL-C[d]	X	X		X		X	X	X
Apo B, Apo A-1, ratio Apo B / Apo A-1, and Lp(a)[d]	X	X				X		
Safety:								
AE /SAE recording (if any)	X	X	X	X	X	X	X	X
Vital Signs [q]	X	X		X		X		X

Main Phase Cohort 4	Screening Period (including run-in if applicable)	Open-Label Dose-finding Treatment Period						
VISIT	1	2	3	4	5	6	7	8
Week (W)	Up to W-6	W0/D1[b]	W2	W4	W6	W8	W10	W12
Visit Window (+/- days)	+7		±3	±3	±3	±3	±7	±7
Visit Type	Clinical Site	Clinical Site	Phone Call	Clinical Site	Phone Call	Clinical Site	Clinical Site[a]	Clinical Site
Laboratory Testing[d]:								
heFH genotyping (Mandatory for consenting patients without documented heFH diagnosis; optional for documented heFH diagnosis patients wishing to undergo genotyping)[e]	X	X		X		X		
Hematology and chemistry[f]	X			X		X		
Creatine phosphokinase (CPK)	X			X		X		
Liver panel[g]	X			X		X		
Adrenal gland hormones[h]		X				X		
Gonadal and pituitary hormones[i]		X				X		
Fat soluble vitamins[j]		X				X		
Pregnancy test[k]	X	X				X		X
Anti-alirocumab antibodies (ADA)[l m]		X				X		
PCSK9 levels (free and total)/serum alirocumab concentration (PK) [l]		X		X		X	X	X

a The Week 0, 4, 8, 10 and 12 visits will take place at the clinical site. For Week 2 and Week 6, a phone call may be done instead of a home or office visit.

b Two site visits may be needed to complete eligibility confirmation.

c The Week 0, 4 and 8 alirocumab injections will be administered at the clinical site by the site staff. Prior to each alirocumab administration, a local topical anesthetic may be utilized as per the Investigator, if at clinical site

d 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.

e 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 8-week dose-finding part of the trial.

f 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.

g Liver panel: ALT, AST, alkaline phosphatase (ALP), and total bilirubin.

h Adrenal gland hormones: cortisol (with reflexive ACTH levels if cortisol <LLN) and dehyroepiandrosterone sulfate (DHEAS).

i Pituitary hormones: luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Gonadal hormones: testosterone [males] and estradiol [females].

j Fat soluble vitamins: A (retinol), D (25 hydroxy vitamin D), E (alpha-tocopherol), and K (phylloquinone).

k Pregnancy test should be done on females of childbearing potential who are sexually active 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.

l ADA and PK samples should be collected before alirocumab administration.

m Only patients who prematurely discontinue the main phase or do not enter the optional extension phase and have a titer at or above 240 for ADA at follow-up 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.

n See Appendix E for Tanner stages evaluation.

o Document prior medication history within the previous 12 weeks, especially for lipid modifying therapy (including statin) and nutraceutical products that may affect lipids (eg, omega-3 fatty acids, plant stanols such as found in Benecol, flax seed oil, psyllium).

p Patients will be instructed to follow a diet in accordance with the American Academy of Pediatrics guidelines or equivalent throughout the entire study.

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

1.4 STUDY FLOW CHART (EXTENSION PHASE)

1.4.1 COHORTS 1 TO 3

	Open-Label Extension (OLE) Period[a]									
Extension Phase Cohorts 1 to 3	Cohort 3	Cohort 1 & 2	Cohort 3	Cohort 1 & 2	Cohort 3	Cohort 1 & 2	Cohort 3	Cohort 1 & 2	ALL Cohorts	ALL Cohorts Follow-up Phone contact at least 10 weeks after last IMP for each cohort
Week (W)	W14	W16	W18, W22	W20, W24	W26, W50, W74, W98, W120	W28, W52, W76, W100, W124 +	W38, W62, W86, W110 +	W40, W64, W88, W112+	W130 (End of OLE[c])	
Visit Number	8[b]		9, 10		11, 13, 15, 17, 19		12, 14, 16, 18		20	
Visit Window (+/- days)		±7		±7	±14		±14		±7	±7
Eligibility requirement[d]	X									
Physical Examination							X		X	
Body Weight							X		X	
Height							X		X	
Tanner Stages[q]	X						X		X	
IVRS/IWRS contact	X				X	X	X		X	
Treatment:										
Alirocumab Injection - VIALS (If Applicable)[e]	-----								→	
Injection Training (If Applicable)[f]	X									
Alirocumab Kit Dispensation (If Applicable)[g]	X				X		X			
Alirocumab Injection – PREFILLED SYRINGE (If Applicable)[h]	-----								→	
Concomitant Medication	X		X		X		X		X	X
Review of diet	X		X		X		X		X	
Compliance check of alirocumab injections (prefilled syringe – if applicable)			X		X		X		X	
Diary [r]	X		X		X		X		X	
Check of stability of background LMT	X		X		X		X		X	

	Open-Label Extension (OLE) Period[a]									
Extension Phase Cohorts 1 to 3	Cohort 3	Cohort 1 & 2	Cohort 3	Cohort 1 & 2	Cohort 3	Cohort 1 & 2	Cohort 3	Cohort 1 & 2	ALL Cohorts	ALL Cohorts Follow-up Phone contact at least 10 weeks after last IMP for each cohort
Week (W)	W14	W16	W18, W22	W20, W24	W26, W50, W74, W98, W120	W28, W52, W76, W100, W124 +	W38, W62, W86, W110 +	W40, W64, W88, W112+	W130 (End of OLE[c])	
Visit Number	8[b]		9, 10		11, 13, 15, 17, 19		12, 14, 16, 18		20	
Visit Window (+/- days)		±7		±7	±14		±14		±7	±7
Efficacy:										
Total-C, calculated LDL-C, HDL-C, TG, non-HDL-C[i]	X				X		X		X	
Apo B, Apo A-1, ratio Apo B / Apo A-1, and Lp(a)[i]	X				X		X		X	
Safety:										
AE /SAE recording (if any)			X		X		X		X	X
Vital Signs							X		X	
Laboratory Testing[i]:										
Hematology and chemistry[j]					X				X	
Creatine phosphokinase (CPK)					X				X	
Liver panel[k]					X				X	
Anti-alirocumab antibodies (ADA)					X				X	
Adrenal gland hormones[m]					X				X[l]	
Gonadal and pituitary hormones[n]					X				X	
Fat soluble vitamins[o]					X				X	
Pregnancy test[p]	X				X		X		X	

a Alirocumab injections may be prepared from vials by the pharmacist (or equivalent) or supplied as prefilled syringes (PFS) depending on availability and additional considerations. If the PFS is available in the extension phase, then patients may either switch from vials to PFS or directly initiate PFS (depending on patient's date of entry into the extension phase). If the PFS is not available in the extension phase, then alirocumab injections prepared from vials will be administered at the site (by the site staff) or at the patient's home or another preferred location contingent upon alternative arrangements being made for such an administration. Depending on the clinical supplies and/or alternative contingency plans, more frequent clinic visits such as every 2 weeks or every 4 weeks may be required for alirocumab administration in addition to the scheduled visits noted in the flowchart.

b The first visit of the OLE period from the extension phase will overlap with the final visit of the follow-up period from the main phase.

c The end of open-label extension period visit will take place at least 2 or 4 weeks after the last alirocumab administration (with a follow-up phone call at least 10 weeks after the last alirocumab administration) before the initiation of the pediatric Phase 3 study in the site where the patient is potentially participating or December 2018, whichever comes first.

d In order to enter into the extension phase, the patient must successfully complete the main phase including the 8 week open-label dose finding treatment period.

e Alirocumab administration will occur every 2 weeks or every 4 weeks. Prior to each alirocumab administration, a local anesthetic may be utilized (as per the Investigator). Alirocumab injections prepared from vials by the pharmacist (or equivalent) will be administered at the clinical site (by the site staff) or at the patient's home or another preferred location contingent upon alternative arrangements being made for such an administration. The last scheduled injection will take place 2 weeks or 4 weeks before the end-of-OLE visit for the Q2W regimen or Q4W regimen, respectively.

f Patients who will switch to or directly initiate prefilled syringes, will undergo training prior to alirocumab administration. The parent/guardian or patient (if appropriate) will be trained to administer the injections with the use of open-label alirocumab injection. Additional visits for training can take place at the discretion of the Investigator or parent/guardian. Other relevant training information will also be provided such as storage of device, etc. Patients will also have the option of dose administration at home by a health care professional, depending on local arrangements and preferences of the investigator/patient.

g Patients who will switch to or directly initiate prefilled syringes (PFS), should have a kit(s) dispensed containing alirocumab PFS. Along with kit dispensation, the treatment administration package should be given as well as the patient diary and injection instruction manual, as needed.

h Patients who will switch to or directly initiate prefilled syringes, will have alirocumab administration every 2 weeks or every 4 weeks at home or another preferred location. Prior to each alirocumab administration, a local anesthetic may be utilized that has been provided by the site.

i Prior to any laboratory testing, the site may utilize a local anesthetic as per the Investigator.

j 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.

k Liver panel: ALT, AST, alkaline phosphatase (ALP), and total bilirubin.

l Only patients who prematurely discontinue the extension phase or decide not to proceed to the Phase 3 study and have a titer at or above 240 for ADA at end-of-OLE 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.

m Adrenal gland hormones: cortisol (with reflexive ACTH levels if cortisol<LLN) and dehyroepiandrosterone sulfate (DHEAS).

n Pituitary hormones: luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Gonadal hormones: testosterone [males] and estradiol [females].

o Fat soluble vitamins: A (retinol), D (25 hydroxy vitamin D), E (alpha-tocopherol), and K (phylloquinone).

p Pregnancy test with a local urine pregnancy test should be done on females of childbearing potential who are sexually active or females who have experienced menarche.

q See Appendix E for Tanner stages evaluation.

r Diary completion starts from Pre-filled Syringe dispensation.

1.4.2 COHORT 4

Extension Phase Cohort 4	Open-Label Extension (OLE) Period					
Week (W)	**W12**	**W16, W20 [o]**	**W24**	**W36**	**W48 (EOS/End of OLE[b])**	**Follow-up Phone contact at least 10 weeks after last IMP**
Visit Number	**8 [a]**	**9, 10**	**11**	**12**	**13 (or Visit 20 for eCRF)**	**14**
Visit Window (+/- days)		**±7**	**±14**	**±14**	**±7**	**±7**
Eligibility requirement [c]	X					
Physical Examination				X	X	
Body Weight	X			X	X	
Height	X			X	X	
Tanner Stages [m]	X			X	X	
IVRS/IWRS contact	X		X	X	X	
Treatment:						
Alirocumab Injection – PREFILLED SYRINGE[d]	X	X	X	X		
Concomitant Medication	X	X	X	X	X	X
Review of diet	X	X	X	X	X	
Compliance check of alirocumab injections (prefilled syringe – if applicable)		X	X	X	X	
Diary[n]	X	X[o]	X	X	X	
Check of stability of background LMT	X	X	X	X	X	
Efficacy:						
Total-C, calculated LDL-C, HDL-C, TG, non-HDL-C[e]	X		X	X	X	

Extension Phase Cohort 4	Open-Label Extension (OLE) Period					
Week (W)	**W12**	**W16, W20 [o]**	**W24**	**W36**	**W48 (EOS/End of OLE[b])**	**Follow-up Phone contact at least 10 weeks after last IMP**
Visit Number	**8 [a]**	**9, 10**	**11**	**12**	**13 (or Visit 20 for eCRF)**	**14**
Visit Window (+/- days)		**±7**	**±14**	**±14**	**±7**	**±7**
Safety:						
AE /SAE recording (if any)	X	X	X	X	X	X
Vital Signs	X			X	X	
Laboratory Testing [e]:						
Hematology and chemistry[f]			X		X	
Creatine phosphokinase (CPK)			X		X	
Liver panel [g]			X		X	
Anti-alirocumab antibodies (ADA) [h]	X		X		X	
Adrenal gland hormones [i]			X		X[h]	
Gonadal and pituitary hormones [j]			X		X	
Fat soluble vitamins [k]			X		X	
Pregnancy test [l]	X		X	X	X	

a The first visit of the OLE period from the extension phase will overlap with the final visit of the 12-week dose-finding treatment period.

b The end of open-label extension period visit will take place at least 4 weeks after the last alirocumab administration (with a follow-up phone call at least 10 weeks after the last alirocumab administration) before the initiation of the pediatric Phase 3 study in the site where the patient is potentially participating or December 2018 at the latest.

c In order to enter into the extension phase, the patient must successfully complete the 12-week open-label dose-finding treatment period.

d Alirocumab administration will occur every 4 weeks. Prior to each alirocumab administration, a local anesthetic may be utilized (as per the Investigator). Alirocumab injections through PFS will be administered at the clinical site (by the site staff). The last scheduled injection will take place 4 weeks before the end-of-OLE visit.

e Prior to any laboratory testing, the site may utilize a local anesthetic as per the Investigator.

f 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.

g Liver panel: ALT, AST, alkaline phosphatase (ALP), and total bilirubin.

h Only patients who prematurely discontinue the extension phase or decide not to proceed to the Phase 3 study and have a titer at or above 240 for ADA at end-of-OLE 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.

i Adrenal gland hormones: cortisol (with reflexive ACTH levels if cortisol<LLN) and dehyroepiandrosterone sulfate (DHEAS).

j Pituitary hormones: luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Gonadal hormones: testosterone [males] and estradiol [females].

k Fat soluble vitamins: A (retinol), D (25 hydroxy vitamin D), E (alpha-tocopherol), and K (phylloquinone).

l Pregnancy test with a local urine pregnancy test should be done on females of childbearing potential who are sexually active or females who have experienced menarche.

m See Appendix E for Tanner stages evaluation.

n Diary completion.

o Phone Call Option

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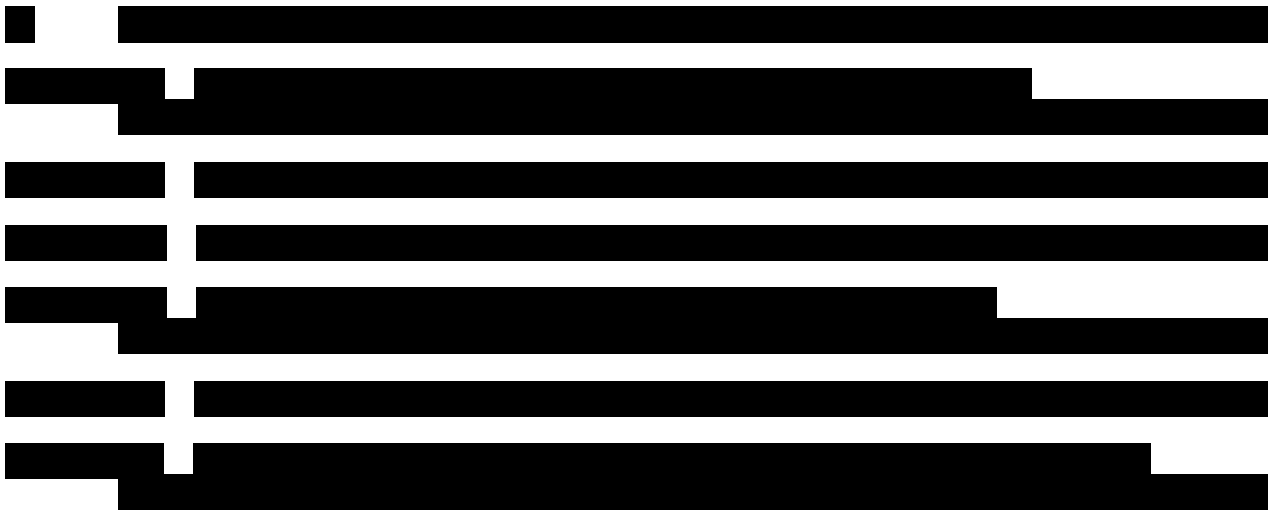

[redacted]

3 LIST OF ABBREVIATIONS

AAP:	American Academy of Pediatrics, American Academy of Pediatrics
AESI:	adverse events of special interest
ALP:	alkaline phosphatase, alkaline phosphatase
ALT:	alanine aminotransferase
Apo:	apolipoprotein
AST:	aspartate aminotransferase
BW:	body weight
CHD:	coronary heart disease
cIMT:	intima media thickness of the carotid artery
CPK:	creatinine phosphokinase
CSR:	clinical study report
CV/CVD:	cardiovascular/cardiovascular disease
DMC:	Data Monitoring Committee
DNA:	deoxyribonucleic acid
DRF:	discrepancy resolution form
e-CRF:	electronic case report form
eGFR:	estimated glomerular filtration rate
ELISA:	enzyme linked immuno-sorbent assay
FH:	familial hypercholesterolemia
GCP:	good clinical practice
HDL-C:	high density lipoprotein cholesterol
heFH:	heterozygous familial hypercholesterolemia
HLGT:	high level group term
ICF:	informed consent form
ICH:	International Conference on Harmonisation
IEC:	Independent Ethics Committee
IMP:	investigational medicinal product
IRB:	Institutional Review Board
IVRS:	interactive voice response system
IWRS:	interactive web response system
LDH:	lactate dehydrogenase
LDL-C:	low density lipoprotrein cholesterol
LDL-R:	low density lipoprotein receptor
LLN:	lower limit of normal range
LMT:	lipid modifying therapy
MedDRA:	Medical Dictionary for Regulatory Activities
mITT:	modified intent-to-treat
MMRM:	mixed-effect model with repeated measures
PCSA:	potentially clinically significant abnormality
PCSK9:	proprotein convertase subtilisin/kexin type 9
PD:	pharmacodynamics
PFS:	prefilled syringe

PK:	pharmacokinetics
PT:	preferred term
SAE:	serious adverse event
SAP:	statistical analysis plan
SOC:	system organ class
TG:	triglycerides
ULN:	upper limit of normal range
γGT:	gamma-glutamyl transferase

4 INTRODUCTION AND RATIONALE

Familial hypercholesterolemia (FH) is an inherited disorder of lipid metabolism, characterized by severely elevated levels of low-density lipoprotein cholesterol (LDL-C) that lead to premature atherosclerosis and cardiovascular disease (CVD) (2). 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 low density lipoprotein cholesterol (LDL-C) can cause FH. These include mutations in the gene coding for the low density lipoprotein receptor (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.

FH is the most clearly documented to have important cardiovascular consequences beginning in childhood (3). 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 of the brachial artery (4) 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 (3, 5). Both are surrogate markers for atherosclerotic vascular disease (6) 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 (7, 8). These findings strongly suggest that to be effective at preventing Coronary Heart Disease (CHD), prevention must begin decades prior to the onset of symptoms (9).

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 (3.4 mmol/L) is considered acceptable and <110 mg/dL (2.85 mmol/L) ideal for children with heFH (10, 11, 12, 1), or the achievement of ≥50% reduction in LDL cholesterol (10).

Recently, 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) (10). These revised recommendations were supported by the American Academy of Pediatrics (AAP) (1), 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 (13). The highest doses of statins tested in pediatric studies resulted in LDL-C reductions of 24% for pravastatin (14), 27% for lovastatin (15), 40% for atorvastatin (16), and 41% for simvastatin (17). 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 (16) 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 a 50% reduction in LDL-C with the highest dose of 20 mg, and less than half (40%) of subjects reached the more stringent LDL-C goal of 110 mg/dL (2.85 mmol/L) (18). Therefore, novel compounds that further reduce LDL cholesterol levels when added to statin therapy are of interest.

Limited data are available for the combination of ezetimibe and simvastatin (19) 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 (3.4 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% vs 53% and 63% vs 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 vs. achieving treatment goals.

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 such as muscle symptoms, Creatine Phosphokinase (CPK) increase, or elevations in Aspartate aminotransferase (AST)/ Alanine aminotransferase (ALT) were reported in some patients (20). 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 (11). 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.

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

Proprotein convertase subtilisin kexin type 9 (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 (21, 22). 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 LDL-C removal and, therefore higher LDL-C circulating levels. Experiments with mice have shown that increasing PCSK9 protein levels decreases levels of LDL-R protein in the liver while PCSK9 knockout mice have increased levels of LDL-R in the liver (23, 24).
In humans, PCSK9 mutations have been identified: the gain-of-function mutations are rare and cause an autosomal dominant form of severe hypercholesterolemia and premature CHD, whereas loss of-function mutations are more common and are associated with reduced plasma levels of LDL-C and protection from CHD (25, 26).

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 (21).

Summary of adult clinical studies with alirocumab selected for relevant information:

All relevant information concerning the compound is available in the Clinical Investigator's Brochure (CIB).

In the Phase 3 program, 2 dosing regimens have been evaluated, every 2 weeks (Q2W) and every 4 weeks (Q4W). The doses of alirocumab include 75 mg Q2W, 150 mg Q2W, 150 mg Q4W, and 300 mg Q4W. Dose adjustment schemes (initiation of alirocumab with 75mg Q2W, 150 mg Q4W or 300 mg Q4W, with a potential subsequent adjustment to 150mg Q2W) have been evaluated in Phase 3 studies. These studies evaluated heFH patients, non-FH patients, mostly at high/very high CV risk, including patients with mixed dyslipidemia and patients with diabetes, and patients not taking statins including patients who are intolerant to statins due to skeletal muscle-related adverse effects.

Phase 3 studies that evaluated the Q2W regimen:

These studies demonstrated reductions in LDL-C from baseline to Week 24 ranging from -42.7% to -50.6% in patients administered alirocumab 75 mg with possible up titration to150 mg Q2W, and from -45.7% to -61.0% in patients administered alirocumab 150 mg Q2W. Superiority in LDL-C reduction was demonstrated in all placebo-controlled studies with alirocumab administered as add-on to a maximally tolerated dose of statin. Superiority in LDL-C reduction was also demonstrated in all ezetimibe-controlled studies, with alirocumab being administered as add-on to statin, or to LMTs other than statin, or in monotherapy, including patients with a history of statin intolerance.

In all studies, the LDL-C reduction was observed at the first LDL-C measurement following the first alirocumab dose (Week 4), and the LDL-C reduction observed at Week 24 was maintained through the treatment period (24, 52, 78 or 104 weeks, depending on the study).

While reductions in LDL-C represent the primary goal of treatment in guidelines and the primary efficacy parameter in these studies, other lipid parameters are also associated with CV risk, for which alirocumab demonstrated a beneficial or at least neutral effect. Changes in Non-HDL-C, Apo B, and Total-C at Week 24 tend to correlate to some degree with LDL-C since LDL-C is the major component of non-HDL-C and Total-C. A consistent decrease in Lp(a) (ranging from -16.7% to -30.3%) was observed with alirocumab. Treatment with alirocumab was associated with modest but consistent changes in fasting TGs (decrease from baseline ranging from -6.0% to -15.6% overall, and from -14.4% to -32.0% in patients with mixed dyslipidemia) and HDL-C (increase from baseline from +3.5% to +8.8%). In statin-treated patients, the effect of alirocumab on TGs was significantly greater than placebo in most studies, but not significantly different from ezetimibe.

<u>Phase 3 studies that evaluated Q4W regimen</u>:

Two studies EFC13786-DBTP and R727-CL-1308, have evaluated 150 mg Q4W and 300 mg Q4W, respectively, as initiation dose regimen with a possible dose adjustment to 150 mg Q2W.

For both studies, LDL-C reduction was observed at Week 4, and was maintained over the whole duration of the study up to Week 24 for EFC13786-DBTP, and up to Week 48 for R727-CL-1308. As with Q2W dosing, changes in Non-HDL-C, Apo B, and Total-C tended to correlate with LDL-C.

The R727-CL-1308 study included patients with and without concomitant statin in two separate strata. In both of these populations, there were statistically significant effects in favor of alirocumab 300 mg Q4W with possible dose adjustment to 150 mg Q2W versus placebo for both co-primary efficacy endpoints (percent change in LDL-C from baseline to Week 24 and to averaged Weeks 21 – 24) and for all key secondary efficacy endpoints (except Apo A-1 for the concomitant statin population). For LDL-C reduction, the LS mean treatment difference for alirocumab versus placebo at Week 24 was -52.4% and -58.7% for the no concomitant statin population and concomitant statin population, respectively. The results obtained at Week 12 were consistent with those at Week 24 for both populations, whereby the Week 12 effect assessed the sole contribution of the 300 mg Q4W dose regimen.

The EFC13786-DBTP study included only patients not receiving statin therapy (many on background ezetimibe), with a vast majority of statin intolerant patients. At Week 24, the LS mean treatment difference for alirocumab (150 mg Q4W with possible up-titration to 150 mg Q2W) versus placebo of -56.4% was statistically significant for LDL-C reduction. The results obtained at Week 12 showed a statistically significant LS mean treatment difference of -44.9%, whereby the Week 12 effect assessed the sole contribution of the 150 mg Q4W dose regimen. The key secondary endpoint was statistically significant up to Lp(a) reduction at Week 24. Favorable trends were reported in HDL-C, TG and Apo A-1.

Safety from Phase 2 and Phase 3 studies:

Alirocumab administration to date in clinical trials, has been associated with a favorable safety and tolerability profile in the completed clinical trials. The pooled safety analysis was performed in 5234 patients with hypercholesterolemia from the double-blind phase 2/3 studies receiving 75 mg Q2W or 150 mg Q2W dosing. Of these, 3340 patients were treated with alirocumab at a dose of 75 or 150 mg Q2W. Two pools were analyzed based on the comparator arm in the study (placebo-controlled or ezetimibe-controlled).

In the placebo-controlled and ezetimibe-controlled pooled studies, no dose relationship was noted for any adverse events (AEs) and there was no evidence of a pattern in the type of AEs observed. The percentages of patients who experienced at least 1 TEAE, at least 1 treatment-emergent SAE and any TEAEs leading to permanent treatment discontinuation were similar between the alirocumab and control groups.

Local injection site reactions, allergic reactions, neurologic events and neurocognitive disorders, alanine aminotransferase (ALT) increase, hepatic disorders, adjudicated CV events, and ophthalmologic disorders were evaluated as adverse events of special interest (AESI); diabetes mellitus, and skeletal-muscle related disorders were evaluated as other events of interest. There was no clinical concern with neurologic events and neurocognitive disorders, ALT increase and hepatic disorders, adjudicated CV events, diabetes mellitus, skeletal-muscle related disorders, and ophthalmologic disorders. However, neurocognitive events are considered a potential risk for alirocumab and continue to be monitored.

No particular safety concerns were observed in the group of patients with 2 consecutive LDL-C values <25 mg/dL (<0.65 mmol/L). However, in a post-randomization comparison analysis (global pool of phase 3 studies) cataract was reported at a higher frequency (2.6%) in alirocumab-treated patients who achieved 2 consecutive LDL-C values <25 mg/dL (<0.65 mmol/L) compared

to alirocumab-treated patients who did not achieve 2 consecutive LDL-C values <25 mg/dL (<0.65 mmol/L) (0.8%). In the pool of placebo-controlled studies, the PT cataract was reported with a similar frequency in both the alirocumab and the placebo groups. There is no mechanistic explanation to this finding. This analysis was exploratory in nature, and because of baseline differences in the post-randomization subgroups, it should be interpreted with caution. The sponsor will continue to monitor the events of cataracts associated to low LDL-C to further evaluate this potential risk.

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 were 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. The most common adverse reaction in patients treated with alirocumab was local injection site reactions (6.3% patients in the alirocumab group versus 4.3% in control groups in the global pool).

The analysis of pooled data from Q2W dosing as well as data from individual Phase 2 and Phase 3 studies demonstrated a favorable safety profile for alirocumab. Overall, the safety profile of the alirocumab Q4W dosing regimen was similar to alirocumab Q2W regimen, except for the frequency and onset of injection site reactions. Compared to those observed in the 75 Q2W with possible up titration to 150 Q2W regimen, local injection site reactions were more frequent, started earlier, and lasted longer with the Q4W dosing regimen, but were also transient, non-serious and not severe.

Rationale for protocol design:

This study is designed to evaluate the efficacy, safety and pharmacokinetics (PK) of alirocumab in the pediatric population in order to support appropriate dose selection of alirocumab for the Phase 3 pediatric study. The study population will consist of children and adolescents aged of 8 to 17 years with heFH on stable LMT and LDL-C ≥130 mg/dL (3.37 mmol/L). The stable LMT will consist of an optimal stable daily dose of statin therapy ± other LMT(s) for at least 4 weeks prior to screening period. Optimal doses of statin are based on pediatric guidelines followed by the site (27 or equivalent reference).

Based on the final adult population PK model including Phase 3 data, simulations were performed to define the pediatric doses. The model included body weight (BW) as a covariate (on clearance) and allowed to perform simulations with different BW. The targeted lower dose to be tested in pediatric patients was simulated to achieve drug exposure that corresponds to the lowest dose evaluated in adult patients, ie, 50 mg Q2W. This 50 mg Q2W dose in adult Phase 2 resulted in approximately 40% LDL-C reduction. The higher dose was simulated to correspond to the lower adult therapeutic dose of 75 mg Q2W. Simulations were also conducted to achieve an approximately 45-50% LDL-C reduction when alirocumab is administered monthly. Following these simulations, a fixed dosage was defined according to BW categories, with staggered doses of 30 mg Q2W and 40 mg Q2W or 75mg Q4W for children with a BW below 50 kg, and doses of 50 mg Q2W and 75 mg Q2W or 150 mg Q4W for children with a BW ≥50 kg.

This study will consist of an 8-week open-label dose-finding treatment period with a post-treatment follow-up period of 6 weeks (Cohort 3) or 8 weeks (Cohorts 1 & 2) identified as main phase; followed by an open-label extension period identified as extension phase.

In Cohort 1, Cohort 2, and Cohort 3, where each cohort will enroll 10 patients, a minimum number of at least 4 patients will be required in one of the two BW categories. This will allow the evaluation of the pharmacokinetics/pharmacodynamics (PK/PD) profile in each BW category and to compare with PK/PD profile observed in adult patients.

[redacted] At the end of the 8-week study treatment period followed by the 6 or 8-week post-treatment follow-up period, patients enrolled in Cohort 1 will be offered entry into an open-label extension study where the dose received during the study treatment period will be continued (ie, 30 mg for BW <50 kg and 50 mg for BW ≥50 kg, Q2W). Similar approach will be implemented for Cohort 2 (40 mg for BW <50 kg and 75 mg for BW ≥50 kg, Q2W) and Cohort 3 (75 mg for BW <50 kg and 150 mg for BW ≥50 kg, Q4W). However, once the final doses for the Phase 3 study are selected, then these final doses from the Q2W or Q4W regimens will be administered to the patients, based on their body weight (BW) at the time of the dose change, if needed and if the device is available. This alirocumab administration during the open-label extension will continue until approximately 10 weeks before the initiation of the pediatric Phase 3 study or December 2018 at the latest. The patients, after a wash-out period of at least 10 weeks after the last injection of alirocumab, will have the opportunity to participate in the Phase 3 study.

Cohort 4:

The DFI14223 study has completed the 8-week dose finding treatment period in 31 pediatric patients enrolled in the 3 cohorts. This study started with a fixed dosage according to body weight (BW) categories, with sequential doses of 30 mg Q2W (Cohort 1), 40 mg Q2W (Cohort 2) or 75 mg (Q4W) (Cohort 3) for patients with a BW <50 kg (ie, lower BW category, LBWC), and doses of 50 mg Q2W (Cohort 1), 75 mg Q2W (Cohort 2) or 150 mg Q4W (Cohort 3) for patients with a BW ≥50 kg (ie, higher BW category, HBWC). Sequential approach was employed as a conservative safety approach in the first evaluation of alirocumab administration in the pediatric population, starting with Cohort 1 using lower doses considered suboptimal with regard to the efficacy before escalating to the doses that should provide expected efficacy. Regarding the Q2W dosing regimen, as expected, the effect on LDL-C and safety were analyzed. The primary efficacy endpoint as measured by the percent change in LDL-C from baseline to Week 8 demonstrated a greatest reduction, overall, in Cohort 2 (LS mean change from baseline in LDL-C of -46.1%). Patients in Cohort 1, overall, had a LS mean change from baseline in LDL-C of -21.2%. However, for the Cohort 3 using the Q4W dosing regimen, overall, the LS mean change from baseline in LDL-C was -7.7%, with inconsistency between the 2 doses as per BW category (mean reduction of LDL-C of -17.5 % with 75 mg Q4W in the LBWC and an mean increase in LDL-C of + 4.0% with 150 mg Q4W in the HBWC). For all 6 dose groups, 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 also no adverse events of special interest (AESI) including, neurological events, neurocognitive events, increase in ALT, allergic drug reactions, or local injection site reactions or new and clinically significant adverse events for all of the 6 dose groups to date. Alirocumab was well tolerated in this pediatric population with no observed, particular safety concern.

Cohort 3 that evaluated Q4W regimen had overall minimal reductions in LDL-C that were not as expected. Using the Q4W dosing regimen, the primary endpoint measurement of LDL-C at Week 8 was obtained 4 weeks after the last injection. The individual patient results showed that there was a varied range of effect on LDL-C for both BW categories, with some patients having mild to moderate reductions, while other patients having near neutral changes, and the remaining patients having a marked increase. One likely explanation is that the doses for both BW categories were not high enough to achieve larger and sustained reductions in the LDL-C over the entire dosing interval. This variability over the dosing interval, which was already identified in adults with this dosing interval, has also been reported by the other approved PCSK9 inhibitor, evolocumab (28), and is thought to be due to the subset of patients with higher rates of PCSK9 mediated clearance of alirocumab.

Given these inconclusive results for the Q4W dosing regimen evaluated in Cohort 3, the protocol is amended to include an additional cohort (Cohort 4) that will evaluate the Q4W regimen at higher doses of 150 mg for BW <50 kg and 300 mg for BW ≥50 kg to evaluate if an effect on LDL-C closer to the therapeutic target of 50% can be approached. The dose of 300 mg Q4W is currently approved for use in adults in the US and EU. It is anticipated that alirocumab exposures in Cohort 4 with the higher doses for both BW categories should be similar to alirocumab exposures in adults who have received 300 mg Q4W. The pediatric Steering Committee and the pediatric Data Monitoring Committee have specifically endorsed this more extensive effort to evaluate these higher doses with a Q4W administration of alirocumab, given the monthly convenience for children and adolescents and the favorable safety data to date. Cohort 4 will include a total of approximately 10 patients with 4 to 6 patients per body weight category and has an overall similar design to Cohort 3 except for a longer main phase (12 weeks) including 2 additional visits (visit 7 at Week 10 and Visit 8 at Week 12), but without a post – treatment follow up period prior to entry into OLE.

The addition to the higher doses in the Q4W cohort with extended 12 week study duration (including 2 new visits at Week 10 and Week 12) for the open label dose-finding period will more appropriately ensure that steady state has been reached after 3 alirocumab injections (2 interdose intervals) in terms of PK and LDL-C and related parameter reduction efficacy. An intermediate visit between the dosing interval (Week 10) is specifically introduced to better document the PK and LDL-C data from the Q4W dosing regimen that is known to show some peak-trough variability over the 4-week dosing interval, ie, a peak in the decrease at the mid dosing interval time point and trough reduction in LDL-C at the end of dosing interval time period. Thus, extending the duration of a higher Q4W dosing regimen to 12 weeks (an additional 4 weeks) will secure more comprehensively data on the LDL-C related profile reduction potential of a Q4W dosing regimen for alirocumab.

Given the 12 week duration, only LDL-C and key related parameters (TC, non-HDL-C, and TG) will be measured at Week 10 and Week 12 to minimize blood collection. The post-treatment follow-up period is no longer needed based on the data collected from the previous 3 cohorts.

All patients in Cohort 4 will receive alirocumab at 150 mg Q4W for BW <50 mg/300 mg Q4W for BW ≥50 kg using prefilled syringes.

Cohort 4, similar to the other cohorts, will include alirocumab administration during the open-label extension that will continue until approximately 10 weeks before the initiation of the pediatric phase 3 study or December 2018 at the latest. The patients, after a wash-out period of at least 10 weeks after the last injection of alirocumab, will have the opportunity to participate in the phase 3 study. Though Cohorts 1 to 3 will be switched to the optimal regimen selected for the phase 3 study, Cohort 4 will remain on their initial regimen given the planned study end date of December 2018.

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

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

Immunogenicity and systemic hypersensitivity are considered as identified risks.

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.

There was no safety signal observed with neurologic events, alanine aminotransferase (ALT) increase and hepatic disorders, adjudicated CV 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 compared to 0.8% of alirocumab-treated patients who did not achieve such low levels. Although limitation has to be consider 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 in this study.

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

This specific study is undertaken to demonstrate the safety and the reduction of LDL-C with alirocumab in the heFH pediatric population and to support appropriate dose selection for the Phase 3 study. Because of the rapid clinical progression of atherosclerotic disease in children and

adults with familial hypercholesterolemia pediatric guidelines 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. Different doses according to BW categories (<50 kg and ≥50 kg) will be evaluated through, in the first step, through 3 sequential independent cohorts with treatment duration of 8 weeks, followed by 6 or 8-week post-treatment follow-up period. An additional cohort, Cohort 4, will evaluate further the Q4W dosing regimen over a treatment of 12 weeks.

5 STUDY OBJECTIVES

5.1 PRIMARY

The primary objective of the study is to evaluate the effect of alirocumab administered Q2W or Q4W on low-density lipoprotein cholesterol (LDL-C) levels after 8 weeks of treatment in heterozygous familial hypercholesterolemia (heFH) patients aged of 8 to 17 years, with LDL-C ≥130 mg/dL (3.37 mmol/L) 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, for at least 4 weeks prior to the screening period.

5.2 SECONDARY

- To evaluate the safety and tolerability of alirocumab.
- To evaluate the pharmacokinetics profile of alirocumab.
- To evaluate the effects of alirocumab on other lipid parameters (eg, Apolipoprotein B (Apo B), non-high density lipoprotein cholesterol (non-HDL-C), Total-Cholesterol (Total-C), high-density lipoprotein cholesterol (HDL-C), Lipoprotein (a) (Lp[a]), Triglycerides (TGs), Apolipoprotein A-1 (Apo A-1) levels after 8 weeks of treatment.
- To evaluate the development of anti- alirocumab antibodies.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE PROTOCOL

This study is an open-label, dose-finding, sequential group, multi-national, multi-center study with repeated dose of subcutaneous (SC) alirocumab injections administered every 2 weeks (Q2W) or every 4 weeks (Q4W) in children and adolescents aged of 8 to 17 years with heFH having LDL-C ≥130 mg/dL (3.37 mmol/L). A sequential enrollment into the 4 separate and independent Cohorts 1 to 4, is applied. Patients should be treated with an optimal dose of statin with or without other LMT(s), or non-statin LMT(s) if statin intolerant, at stable daily dose(s) for at least 4 weeks. 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 maximally tolerated dose of statin, statin intensification should be carefully considered prior to inclusion in this study in order to ensure that the addition of a non-statin LDL-C lowering therapy (ie, alirocumab) would be the next appropriate step in the management of the patient's hypercholesterolemia. The highest dose of statin should not exceed the maximum labeled dose of statin for pediatric patients as per the local prescribing information. Each independent cohort below will include 10 patients with no less than 4 patients in each BW category:

- Cohort 1 will receive 30 mg Q2W for body weight (BW) <50 kg and 50 mg Q2W for BW ≥50 kg.
- Cohort 2 will receive 40 mg Q2W for BW <50 kg and 75 mg Q2W for BW ≥50 kg.
- Cohort 3 will receive 75 mg Q4W for BW <50 kg and 150 mg Q4W for BW ≥50 kg.
- Cohort 4 will receive 150 mg Q4W for BW <50 kg and 300 mg Q4W for BW ≥50 kg.

For each cohort, the study consists of a main phase and an optional extension phase. The main phase is comprised of 3 periods; screening (including run-in, if applicable), open-label dose finding treatment, and follow-up only for Cohorts 1, 2, and 3, and 2 periods: screening (including run-in, if applicable) and open-label dose finding treatment for Cohort 4.These periods of the main phase are described as below.

MAIN PHASE:

Screening Period:

- The screening period will last up to 6 (+1) weeks, with patients to be enrolled as soon as all inclusion and no exclusion criteria are met.
  - 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 4 weeks, and be enrolled when eligibility is confirmed, including eligible LDL-C value obtained after stable LMT dosing has been maintained for at least 4 weeks. Stable LMT refers to patients receiving either stable optimal daily dose of statin ±other LMT(s) or stable dose of non-statin LMT(s) if statin intolerance for at least 4 weeks prior to screening.

It is not authorized to select patients treated with statin *de novo,* to avoid unstable lipid modifying treatment (LMT) during the screening period.

- Patients suspected of having heFH but without confirmation (prior genetic testing results obtained or diagnosed clinically by Simon Broome criteria) will undergo genetic testing, once separate consent for heFH genotyping is signed, and can be enrolled when eligibility is confirmed. This genotyping will be mandatory for patients without either clinical diagnosis or without previous documented genotyping who consent to participate in the study.

  This genotyping testing is offered optionally to others whose heFH diagnosis has already been confirmed (prior genetic testing results obtained or diagnosed clinically by Simon Broome criteria). If patients agree to perform this centralized genotyping and/or they agree to use a previous documented genotyping, they will be required to sign a separate genetic testing informed consent form (ICF) prior to collection of the DNA sample and/or request for previous genotyping results.

  If the diagnosis of heFH to establish eligibility is based on clinical criteria or a documented previous genotyping, the results of this elective centralized genotyping will not impact their eligibility inclusion.

- The report of the heFH genotyping done as part of this study will provide an interpretation of the results. However, all patients should have their results reviewed with a genetics counselor or equivalent. Genetic testing performed will be limited to testing for heFH-associated genes only. All samples will be destroyed once testing is completed. No additional genetic testing and no long-term storage will be done for these samples.

- Special procedures, including procedures for collection, handling, storage and shipment of DNA specimens for genetic testing for heFH, are summarized in the genetic testing manual provided by the central lab performing heFH testing.

All patients who successfully screen for Cohort 1 and are not included in Cohort 1, due to the appropriate Cohort 1 weight group being fully enrolled, may participate to Cohort 2 but only after eligibility, including safety assessments, is reconfirmed. Patients who are successfully screened for Cohort 2 but are not enrolled, due to the appropriate Cohort 2 weight group being fully enrolled, may participate in Cohort 3 without the need to repeat the run-in/screening period if there is no more than 3 months between eligibility confirmation and inclusion. In such a circumstance, the run-in/screening period from Cohort 2 will substitute for the run-in/screening period for Cohort 3. If there is more than 3 months between initial screening and planned enrollment in Cohort 3, patient eligibility, including safety assessments, must be reconfirmed.

Safety and eligibility assessments noted above include all lab tests listed as exclusionary, based on specified results.

Patients should be instructed to follow a diet in accordance with the American Academy of Pediatrics (AAP) guidelines (1) or equivalent throughout the entire study (ie, both phases). The dietician or site staff with appropriate training will review the patient's diet at the screening visit and periodically throughout the study.

Main Open-Label Dose Finding Treatment Period:

- An open-label dose finding treatment period of 8 weeks with alirocumab for Cohorts 1 to 3, and 12 weeks for Cohort 4. Four independent cohorts (Cohorts 1 to 4) will be administered SC alirocumab injections Q2W or Q4W in a sequential enrollment.
- The DMC will review data on a regular basis during the dose finding treatment period.
- After Cohort 1 completes the open-label dose finding treatment period, the DMC will continue to review the safety data and make a recommendation on dose escalation to Cohorts 2 and 3. Cohort 2 will initially begin enrollment. Once enrollment is completed for Cohort 2, then this will immediately be followed by enrollment into Cohort 3 (ie, sequential enrollment). Cohort 4 is an independent cohort with a separate enrollment.
- Cohorts 1 and 2 (Q2W): Alirocumab injections will be prepared from vials by the pharmacist (or equivalent). Detailed instructions on preparation of injections from vials will be provided in a separate document. Alirocumab injections will be administered at Weeks 0, 2, 4, and 6. The Weeks 0 and 4 alirocumab injections will be administered at the clinical site by the site staff. The Weeks 2 and 6 alirocumab injections will be administered at the clinical site by the site staff or at the patient's home by a health care professional, depending upon local arrangements and preferences of the investigator/patient.
- Cohort 3 (Q4W): Alirocumab injections will be prepared from vials by the pharmacist (or equivalent). Detailed instructions on preparation of injections from vials will be provided in a separate document. Alirocumab injections will be administered at Weeks 0 and 4 at the clinical site by the site staff.
- Cohort 4 (Q4W): Alirocumab injections will be administered with prefilled syringes. Alirocumab injections will be administered Week 0, Week 4, and Week 8 at the clinical site by site staff.
- The lipid results from specimens obtained during the open-label dose finding treatment period will be masked for the clinical site/Investigator and patients. No attempts should be made by the investigator or patient to routinely have the patient's lipid values independently evaluated after entry into the open-label dose finding treatment period and until the final follow-up visit for Cohort 1, Cohort 2, and Cohort 3, and entry into the OLE period for Cohort 4. The sponsor and the DMC will closely monitor the lipid results during the 8-week open-label dose finding treatment period. If any safety concerns are noted during this period, including very low LDL-C levels (ie, LDL-C <50 mg/dL [1.30 mmol/L] on one or more occasion), then appropriate action will be taken by the Sponsor in consultation with the DMC.

Follow-Up Period, only for Cohorts 1 to 3:

- A follow-up period (off treatment) of 6 (Cohort 3) or 8 weeks (Cohorts 1 and 2) after the end of open-label dose finding treatment period visit. For these 3 cohorts, the final follow-up visit corresponds to 10 weeks after the last alirocumab injection administered during the open-label dose finding treatment period, since the last injection for Cohorts 1 & 2 is Week 6 and for Cohort 3 it is Week 4.

The daily optimal dose of statin or of other LMT (if applicable) should be stable from screening through the end of the follow-up visit unless there is a safety concern, as per the Investigator's judgment.

Cohorts 1 to 3 will have a follow-up period before entry in the extension period.

Open-label extension treatment period:

At the end of the follow-up period of the main phase for Cohorts 1 to 3 and end of the 12 week open label dose-finding for Cohort 4, patients enrolled in all cohorts who successfully complete (provided they have not experienced AEs leading to permanent discontinuation during the main treatment period, or had significant protocol deviations, in the investigator's judgment) the main phase will be offered entry into an optional extension phase. The extension phase includes an open-label extension (OLE) period as follows:

- All doses/dose regimen administered during the open-label dose finding treatment period of the main phase are expected to be efficacious. Thus, the initial dose of alirocumab that will be administered Q2W or Q4W during the OLE period, will be a continuation of the same doses/dose regimen administered during the open-label dose finding treatment period of the main phase. However, once the final optimal doses for the phase 3 study are selected, then these final optimal doses from the Q2W or Q4W regimen will be administered to all patients during the OLE period, based on the patient's body weight at the time of the dose change. For Cohort 4, patients will remain on their initial regimen given the planned study end date of December 2018.
- For Cohorts 1 to 3, alirocumab injections may be prepared from vials by the pharmacist (or equivalent) or supplied as prefilled syringes (PFS) depending on availability and additional considerations:
  - If the PFS is available in the extension phase, then patients may either switch from alirocumab injections prepared from vials to PFS or directly initiate PFS (depending on patient's date of entry into the extension phase). After appropriate training, the parent/guardian or patient (if appropriate) will administer the PFS at home or another preferred location. In certain cases, alternative arrangements may be made for the administration of the PFS,
  - If the PFS is not available in the extension phase, then alirocumab injections prepared from vials will be administered at the clinical site (by the site staff) or at the patient's home or another preferred location contingent upon alternative arrangements being made for such an administration.
- All patients from all cohorts that participate in the DFI14223 study will have the opportunity to enroll in the pediatric phase 3 study provided that they meet the eligibility criteria. The alirocumab administrations during the OLE period will continue until at least 10 weeks (corresponding to the wash out period) before the initiation of the pediatric phase 3 study in the site where the patient is potentially participating or December 2018 at the latest.
- The lipid levels will be communicated to the investigator during the OLE period. The Investigator will be responsible, based on his/her own judgment related to the patients' LDL-C levels and the safety profile, to continue or discontinue alirocumab throughout the study. The 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 based on the Investigator's judgment throughout the study. Further recommendations for the management and monitoring of patients who achieve very low LDL-C levels (ie, LDL-C <50 mg/dL [1.30 mmol/L] on one or more occasion) are provided in Section 10.6.3.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

Main open-label treatment phase:

For Cohorts 1 to 3, a study duration of approximately 16-23 weeks (screening/run in period: up to 6 [+1] weeks, main open-label treatment period: 8 weeks, follow-up period: 6-8 weeks)

For Cohort 4, a study duration of approximately 14-19 weeks (screening period: up to 6 [+1] weeks, open-label dose-finding treatment period: 12 weeks).

Open-label extension phase:

Patients who enroll in the open-label extension treatment period will continue alirocumab administration until at least 10 weeks before the initiation of the pediatric Phase 3 study in the site where the patient is potentially participating. Therefore, patients who consent to participate in the pediatric phase 3 study could have their last alirocumab injection in the OLE period up to December 2018, depending on timing of site initiation for the phase 3 study planned to be done no later than December 2018. All other patients, enrolled in the OLE period, who decline the participation in the phase 3 study, will have their last alirocumab injection on December 2018. This corresponds to a maximum of approximately 24 months for the first patients enrolled in Cohorts 1 to 3. For Cohort 4, this corresponds to a maximum of approximately 7 months for the first patients enrolled.

For both phases, patients who experience an ongoing Serious Adverse Event (SAE) or an Adverse Event of Special Interest (AESI), at the pre-specified study end-date, should be followed until resolution, stabilization, or death and related data will be collected.

End of study per patient:

If patient does not participate to the open label extension period, then the end of the study is the last on site visit as scheduled by protocol (ie, visit Week 14 or Week 12 (Cohorts 3 & 4, respectively) or Week 16 (Cohorts 1 & 2) or the resolution/stabilization of all SAEs, and AESI, whatever comes last.

If patient participates in the open label extension period, then the end of the study is the last on site visit as scheduled by protocol (ie, visits will continue until visit end of OLE at least 2 or 4 weeks after last alirocumab injection (with a follow-up phone call at least 10 weeks after the last alirocumab administration) before the initiation of the pediatric Phase 3 study in the site where the

patient is potentially participating or December 2018, at the latest, or the resolution/stabilization of all SAEs, and AESI, whatever comes last.

A follow-up phone contact will take place at least 10 weeks after the last IMP of each cohort, including Cohort 4.

6.2.2 Determination of end of clinical trial (all patients)

The end of the clinical trial is defined as being the last visit/contact of the patients at the study level.

6.3 INTERIM ANALYSIS

No formal interim analysis is planned. However, analyses will be conducted at the end of the main phase to select the dose that will be used in the Phase 3 study.

6.4 STUDY COMMITTEES

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.

Among its responsibilities, the Steering Committee will review data during the conduct of the study. The Steering Committee will also review the recommendations from the Data Monitoring Committee throughout the study. The Steering Committee members and Sponsor will participate in regular meetings. Detailed activities and responsibilities of the Steering Committee are described in the Steering Committee charter.

Data Monitoring Committee (DMC):

The DMC is composed of external, independent expert physicians with experience in pediatric lipids field and/or pediatric cardiology. The independent DMC will monitor periodically patient safety by conducting reviews of accumulated safety data, including Cohort 4. 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 review data on a regular basis during the dose finding treatment period. The DMC is tasked to provide recommendations periodically and on dose escalation decision from Cohort 1 to Cohorts 2, 3.

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

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

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

I 01. Children and adolescent male and female patients aged 8**** to l7 years at the time of signed informed consent.

For Russia only:
Male and female patients aged ≥12 and ≤17 years at the time of signed informed consent

I 02. Patients with diagnosis of heterozygous familial hypercholesterolemia (heFH) through genotyping or clinical critiera.*

I 03. Patients treated with optimal dose of statin** ± other LMT(s) or non-statin LMT(s) if statin intolerant*** at stable dose for at least 4 weeks.

I 04. Patients with calculated LDL-C greater than or equal to 130 mg/dL (≥3.37 mmol/L) 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.

I 05. Patients with body weight greater than or equal to 25 kg.

I 06. Patients aged of 8 to 9 years to be at Tanner stage 1 and patients aged of 10 to 17 years to be at least at Tanner stage 2 in their development.

I 07. A signed informed consent indicating parental permission with or without patient assent, depending on capacity for understanding based on developmental maturity. In cases involving emancipated or mature minors with adequate decision-making capacity, or when otherwise permitted by law, a signed informed consent directly from patients.

* Diagnosis of heFH must be made either by previous genotyping, current 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 consenting to undergo mandatory genotyping during the screening period with results supporting a diagnosis of heFH. The clinical diagnosis should be based on the Simon Broome criteria for possible or definite FH. (see Appendix F). Once eligibility is confirmed based on prior genetic testing or Simon Broome criteria, results of elective genetic testing will not impact patient's eligibility.

** 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 inclusion in this study in order to ensure that the addition of a non-statin LDL-C lowering therapy (ie, alirocumab) would be the next appropriate step in the management of the patient's hypercholesterolemia. The highest dose of statin should not exceed the maximum labeled dose of statin for pediatric patients as per the local prescribing information.

*** 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.

**** Patients age of 8 to less than 10 years have had other available interventions to lower calculated LDL-C but these have been insufficient.

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 subsection.

7.2.1 Exclusion criteria related to study methodology

E 01. Age of less than 8 or greater than 17 years at the time of signed informed consent.
E 02. Calculated LDL-C <130 mg/dL (3.37 mmol/L) during the screening period, after patient has been on stable LMT for at least 4 weeks.
E 03. Patient without a diagnosis of heFH by genotyping or clinical criteria.
E 04. Patients aged of 8 to <10 years in whom other available interventions to lower LDL-C have been sufficient.
E 05. Patients not on a stable dose of LMT (including statin, as applicable) for at least 4 weeks prior to the screening visit and from screening visit to Day 1.
E 06. Daily dose of statin that is above the maximum recommended dose for pediatric patients as per the local prescribing label.
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. Body weight <25 kg.
E 10. Patients aged of 8 to 9 years not being at Tanner Stage 1 and patients aged of 10 to 17 years not being at least at Tanner Stage 2 in their development.
E 11. Patients with secondary hyperlipidemia.
E 12. Patients with diagnosis of homozygous familial hypercholesterolemia.
E 13. Patient who has received lipid apheresis treatment within 2 months prior to the screening period, or has plans to receive it during the study.
E 14. Known history of type 1 or type 2 diabetes mellitus.
E 15. Known history of thyroid disease.
E 16. Known history of hypertension.
E 17. Fasting triglycerides >350 mg/dL (3.95 mmol/L) at the screening visit.
E 18. Severe renal impairment (ie, eGFR <30 mL/min/1.73 m^2 at the screening visit).
E 19. ALT or AST >2 xULN (1 repeat lab is allowed).
E 20. CPK >3 xULN (1 repeat lab is allowed).

E 21. Patient/parents who withdraws consent during the screening period (patient who is not willing to continue or fails to return).

E 22. 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 23. Treatment with any investigational medicinal product (IMP) within 8 weeks or 5 half-lives prior to the screening period, whichever is longer.

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

7.2.2 Exclusion criteria related to mandatory background therapies

E 24. All contraindications to the background statins or other LMTs (as applicable) 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 25. Hypersensitivity to alirocumab or to any of the ingredients of alirocumab injections.

E 26. Females who have experienced menarche or females of childbearing potential who are sexually active who are unwilling or unable to be tested for pregnancy.

E 27. Positive pregnancy test in females who have experienced menarche or females of childbearing potential who are sexually active.

E 28. Females who are breast-feeding.

E 29. Females of childbearing potential who are sexually active and not protected by highly effective contraceptive method(s) of birth control (as defined in the informed consent form and/or in a local protocol addendum) and/or who are unwilling or unable to be tested for pregnancy.

Note: Females of childbearing potential who are sexually active or females who have experienced menarche must have a confirmed negative pregnancy test at screening and other study visits. Females of childbearing potential who are sexually active must use an effective contraceptive method throughout the entire duration of the study treatment and for at least 10 weeks after the last injection. The applied methods of contraception have to meet the criteria for a highly effective method of birth control according to the "International Conference on Harmonisation of

Technical Requirements for Registration of Pharmaceuticals for Human Use. M3(R2): Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals. ICH. 2009 Jun: 1-25." (24). See Appendix G.

7.2.4 Additional exclusion criteria during or at the end of screening or run-in phase before inclusion

E 30. Patient who has withdrawn consent before inclusion (starting from signed informed consent).

E 31. Despite screening of the patient, inclusion is stopped at the study level.

7.3 EXCLUSION CRITERIA FOR THE OPEN-LABEL EXTENSION TREATMENT PERIOD

7.3.1 Exclusion criteria related to study methodology

E 32. Significant protocol deviation in the main phase based on the Investigator judgment, such as non-compliance by the patient.

E 33. Patient who experienced an adverse event leading to permanent discontinuation from the main open label dose finding treatment period.

E 34. Patients having any new condition or worsening of existing condition which in the opinion of the Investigator would make the patient unsuitable for entry into the extension phase, or could interfere with the patient participating in or completing the study.

7.3.2 Exclusion criteria related to the current knowledge of alirocumab

E 35. Hypersensitivity to alirocumab or to any of the ingredients of alirocumab injections.

E 36. Positive pregnancy test at last visit of the main treatment period (Week 14 [Cohort 3]/ Week16 [Cohorts 1 & 2], Visit 8).

E 37. Females who have experienced menarche or females of childbearing potential not willing to continue highly-effective method(s) of birth control (as defined in the informed consent form and/or in a local protocol addendum) and/or who are unwilling or unable to be tested for pregnancy.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

For Cohorts 1 to 3, sterile alirocumab drug product will be supplied at a concentration of 150 mg/mL as 1.2 mL minimum extractable volume in a 3 mL vial filled with 1.9 mL solution for the main treatment period and in 3 mL vials (or in prefilled syringes if available) for patient included in the extension period.

A detailed manual for alirocumab solution preparation will be provided to the pharmacist (or equivalent) for individual dose preparation.

For Cohort 4, sterile alirocumab drug product will be supplied at a concentration of 150 mg/mL as 1 mL volume in a prefilled syringe (PFS).

Main treatment period (Open-Label, Repeated Dose-Finding, Sequential Group):

The different doses prepared according to the cohort and the body weight will be:

- For Cohort 1: 30 mg Q2W for BW <50 kg and 50 mg Q2W for BW ≥50 kg.
- For Cohort 2: 40 mg Q2W for BW <50 kg and 75 mg Q2W for BW ≥50 kg.
- For Cohort 3: 75 mg Q4W for BW <50 kg and 150 mg Q4W for BW ≥50 kg.
- For Cohort 4: 150 mg Q4W for BW <50 kg and 300 mg Q4W for BW ≥50 kg.

The body weight assessed at inclusion visit will be the reference for alirocumab solution preparation.

For Cohorts 1 & 2: The study treatment is a single SC injection of 0.5 mL for 30, 40, 50 or 75 mg dose of alirocumab (according to the cohort and the body weight) extracted from vials, administered every 2 weeks in the abdomen, thigh, or outer area of the upper arm.

For Cohort 3: The study treatment is a single SC injection of 1 mL for 75 or 150 mg dose of alirocumab (according to the body weight) extracted from vials, administered every 4 weeks in the abdomen, thigh, or outer area of the upper arm.

For Cohort 4, sterile alirocumab drug product will be supplied at a concentration of 150 mg/mL as 1 mL volume in a prefilled syringe (PFS).

For Cohort 4: The study treatment is a single SC injection of 1 mL for 150 mg dose of alirocumab and 2 injections of 1 mL containing 150 mg each to provide a total 300 mg (2 mL) of alirocumab through PFS administered every 4 weeks in the abdomen, thigh, or outer area of the arm.

Dosing for the main dose finding treatment period should ideally be administered Q2W SC or Q4W SC at approximately the same time of the day; however, it is acceptable to have a treatment window of ±3 days. The time of day is based on the patient's preference.

Open-label extension (OLE) treatment period:

For Cohorts 1 to 3, alirocumab injections may be prepared from vials by the pharmacist (or equivalent) or supplied as prefilled syringes (PFS) depending on availability and additional considerations.

If the PFS is available in the extension phase, then patients may either switch from alirocumab injections prepared from vials to PFS or directly initiate PFS (depending on patient's date of entry into the extension phase). After appropriate training, the parent/guardian or patient (if appropriate) will administer the PFS at home or another preferred location. In certain cases, alternative arrangements may be made for the administration of alirocumab with PFS.

If the PFS is not available in the extension phase for Cohorts 1 to 3, then alirocumab injections prepared from vials will be administered at the clinical site (by the site staff) or at the patient's home or another preferred location contingent upon alternative arrangements being made for such an administration.

The alirocumab dose/dose regimen received during the open-label dose finding treatment period of the main phase will be continued every 2 weeks or every 4 weeks during the OLE period, since [redacted].

However, once the final optimal doses for the Phase 3 study are selected, and if device is available, then these final optimal doses from the Q2W or Q4W regimen will be administered to all patients in Cohorts 1 to 3 during the OLE period, based on their body weight at the time of the dose change.

For Cohorts 1 & 2: The study treatment is a single SC injection of 0.5 mL for 30, 40, 50 or 75 mg dose of alirocumab (according to the last dose in each cohort and DMC recommendations) provided in a prefilled syringe or in a syringe (extracted from vial), administered every 2 weeks in the abdomen, thigh, or outer area of the upper arm. Study drug will be administered by SC injection Q2W, starting at Week 16 and continuing up to the last injection, 2 weeks before the end of the open-label extension period.

For Cohort 3: The study treatment is a single SC injection of 1 mL for 75 or 150 mg dose of alirocumab (according to the body weight, the last dose and DMC recommendations) provided in a prefilled syringe or in a syringe (extracted from vial), administered every 4 weeks in the abdomen, thigh, or outer area of the upper arm. Study drug will be administered by SC injection Q4W, starting at Week 14 and continuing up to the last injection, 4 weeks before the end of the open-label extension period.

For Cohort 4, sterile alirocumab drug product will be supplied at a concentration of 150 mg/mL as 1 mL volume in a prefilled syringe (PFS).

For Cohort 4: The study treatment is a single SC injection of 1 mL for 150 mg dose of alirocumab and 2 injections of 1 mL containing 150 mg each to provide a total 300 mg dose (2 mL) of alirocumab through PFS, administered every 4 weeks in the abdomen, thigh, or outer area of the upper arm. Study drug will be administered by SC injection Q4W, starting at Week 12 and continuing up to the last injection, 4 weeks before the end of the open-label extension period.

Dosing for the open-label extension treatment period should ideally be administered Q2W SC or Q4W SC at approximately the same time of the day; however, it is acceptable to have a treatment window of ±3 days. The time of day is based on the patient's preference.

Alirocumab administration will continue until at least 10 weeks before the initiation of the pediatric Phase 3 study in the site where the patient is potentially participating or December 2018, whichever comes first.

In the event an injection is delayed by more than 7 days or is completely missed, the patient should return to the original schedule of study drug dosing without administering additional injections. If the delay is less than or equal to 7 days from the missed date, the patient should administer the delayed injection and then resume the original dosing schedule.

Detailed instructions for transport, storage, preparation, and administration of IMP will be provided by the site to the patient/caregiver.

8.1.1 Route and method of administration

A manual for alirocumab administration (injection instruction manual) will be provided to investigators (or parents/patients according to the phase of the study) containing detailed instructions on use.

During the main treatment dose finding study period for Cohorts 1 and 2, the injections will be administered by the staff at the clinical site or by a trained health care professional at home for visits Week 2 and Week 6, the injections at Week 0 and 4 will be administered at the clinical site by the study staff. For Cohort 3 the injections at Week 0, and at Week 4 will be administered at the clinical site by the study staff. For Cohort 4, the injections at Week 0, Week 4, and Week 8 will be administered at the clinical site by the study staff. During the open-label extension, alirocumab could be administered at clinical site or by study nurse at home or by self-injection or by another designated person (such as a parent, etc…) depending on availability or not of the prefilled syringes. The used syringe will be discarded in a sharps container which will be provided to staff site/nurse/patients. It is recommended that alirocumab injections be rotated within an anatomical area (eg, right thigh then left thigh or right abdomen then left abdomen). Staff site/Nurse/Patients also have the option to inject in a different anatomical area (eg, thigh then abdomen) during the study. If another concomitant drug or vaccine is being injected at the same site planned for alirocumab injection, then the staff site/nurse/patient should be advised to use an alternate location for administration of alirocumab.

IMP must be stored between +2°C and +8°C, and administered at room temperature. Specific information regarding dose preparation and administration is given in the relevant manuals.

Instructions as outlined in the relevant manuals should be provided to the investigator/nurse (or another designated person who will administer the injections) at training and as needed during the course of the study. Close supervision and feedback should be given at the training visit if applicable and other visits as needed. Anyone that plans to administer IMP must be trained by the study staff.

8.1.2 Timing of administration

During the main dose finding treatment period the first alirocumab injection for each cohort will start at Week 0 (after each respective screening period and DMC agreement for Cohorts 2 and 3) as soon as possible after the call for inclusion using the treatment kit number provided by the IRT according to cohort number and body weight. The first injection after call for inclusion will be done at the site by the investigator staff. Patients will be monitored at the investigational site for at least 30 minutes after this first injection.

The investigator staff will administer subsequent injections on site at the clinic, according to the dosing schedule at approximately the same time of the day. On days where the clinic study visit coincides with dosing, the dose of study drug will be administered after all study assessments have been performed and all laboratory samples (including PK) collected. For visits where home injection is allowed, the health care professional will administer the injection at the patient's home, as described in the relevant manuals.

During the main dose finding treatment period, alirocumab will be administered subcutaneously every 2 weeks or every 4 weeks at approximately the same time of the day; however it is acceptable to have a window period of ±3 days.

Follow-up period during the main phase without treatment

No alirocumab administration between W8 and W16 for Cohort 1.

No alirocumab administration between W8 and W16 for Cohort 2.

No alirocumab administration between W8 and W14 for Cohort 3.

There is no follow up period for Cohort 4.

During the open-label extension period for Cohorts 1 & 2 the first injection administration will start at Week 16 after the last injection administration at Week 6 (ie, 10 weeks after the last administration of alirocumab. The treatment kit(s) number(s) will be provided by IRT according to the last dose administered in Cohort1/Cohort 2. The first injection of the extension period will be done at the site by the investigator staff. If the self-injections by patient or another designated person (such as parent, nurse, etc.) are decided during the extension period a training injection should be planned 2 weeks before the first self-injection, under direct site staff supervision.

During the open-label extension period for Cohort 3, the first injection administration will start at Week14 after the last injection administration at Week 4 (ie, 10 weeks after the last administration of alirocumab). The treatment kit number will be provided by IRT according to the last dose administered in Cohort 3. The first injection of the extension period will be done at the site by the investigator staff. If the self-injections by patient or another designated person (such as parent, nurse, etc.) are decided during the extension period a training injection should be planned 4 weeks before the first self-injection, under direct site staff supervision.

During the open-label extension period for Cohort 4, the first injection administration will start at Week 12 at the end of the 12-week open-label dose finding. The treatment kit number will be provided by IRT according to the last dose administered in Cohort 4. The first injection of the extension period will be done at the site by the investigator staff. If the self-injections by patient or another designated person (such as parent, nurse, etc.) are decided during the extension period a

training injection should be planned 4 weeks before the first self-injection, under direct site staff supervision.

During the extension treatment period, IMP should ideally be administered every 2 weeks SC or every 4 weeks 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 visit's time or patient's preference in case of self-injections.

If by mistake or due to other circumstances an injection is delayed by more than 7 days or completely missed (for Cohorts 1 and 2) or by more than 14 days or completely missed (for Cohort 3 and Cohort 4), 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 (for Cohorts 1 and 2) from the missed date or if the delay is less than or equal to 14 days for (Cohort 3 and Cohort 4) from the missed date, then the patient should administer the delayed injection and then resume the original schedule of study treatment administration.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCT(S)

The following classes of drugs are identified as non-IMP because the medication is 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).

8.3 BLINDING PROCEDURES

8.3.1 IMP

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

8.3.2 Lipid parameters

Lipid parameter values from blood samples obtained after the inclusion visit and during the main 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 during the main treatment period for all cohorts and up to the end of the follow-up period for Cohorts 1-3.

During the open-label extension period, 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 continue or discontinue alirocumab throughout the study. The reasons of any adjustment should be documented and recorded in the e-CRF.

8.3.3 Anti-alirocumab antibodies

Patients' anti-alirocumab antibody results will not be communicated to the sites, during the main phase, so that the patient's ADA levels do not influence the Investigator's safety evaluation during the main dose finding treatment period for all cohorts and up to the end of the follow-up period for Cohorts 1-3.

Patients who do not enter the extension phase or who prematurely discontinue the main phase and have a titer at or above 240 for anti-alirocumab antibody at the follow-up visit (for Cohorts 1-3) or at the end of the dose finding treatment period (for Cohort 4) 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 extension phase will be monitored for anti-alirocumab antibodies as per the study flowchart (Section 1.4).

8.3.4 Committee

The DMC will receive unblinded lipid parameter results and confidential reports (Section 6.4).

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

The list of treatment kit number will be generated centrally by Sanofi. The IMP (Cohorts 1 & 2 (Q2W) or Cohort 3 (Q4W), body weight less than 50 kg or greater or equal to 50 kg) will be packaged in accordance with this list. The below table represents the allocation according to the doses/ dose regimen:

Table 1 - Allocation according to the doses/dose regimen for dose-finding treatment period and extension period until PFS will be available

	30 mg Q2W	40 mg Q2W	50 mg Q2W	75 mg Q2W	75 mg Q4W	150 mg Q4W
Solvent for alirocumab vial	1	2	1	0	1	0
150 mg vial	1	1	1	1	1	1

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.

Patients will be allocated to receive repeated dose of SC alirocumab injections administered every 2 weeks (Q2W) or every 4 weeks (Q4W) in 4 independent cohorts of children and adolescents aged 8 to 17 years. Each independent cohort below will include up to 10 patients with no less than 4 patients in each BW category:

- Cohort 1 will receive 30 mg Q2W for body weight (BW) <50 kg and 50 mg Q2W for BW ≥50 kg.
- Cohort 2 will receive 40 mg Q2W for BW <50 kg and 75 mg Q2W for BW ≥50 kg.
- Cohort 3 will receive 75 mg Q4W for BW <50 kg and 150 mg Q4W for BW ≥50 kg.

- Cohort 4 will receive 150 mg Q4W for BW <50 kg and 300 mg Q4W for BW ≥50 kg.

For Cohorts 1 & 2: The treatment kit numbers will be allocated using the centralized treatment allocation system on visit 2 (Day 1, Week 0 to Week 6 according to the cohort and the body weight: main treatment period), and then at Week 16 according to the cohort (open label dose finding treatment period) and every 3 months (open label extension treatment period) when PFS are available or every 2 weeks if PFS are not available as resupply visits, and at unscheduled visits, if needed.

For Cohort 3: The treatment kit numbers will be allocated using the centralized treatment allocation system on visit 2 (Day 1, Week 0 and second injection, Week 4 according to the body weight: main treatment period), and then at Week 14 (open label dose finding treatment period) and every 3 months (open label extension treatment period) when PFS are available or every 4 weeks if PFS are not available as resupply visits, and at unscheduled visits, if needed.

For Cohort 4: The treatment kit numbers will be allocated using the centralized treatment allocation system on visit 2 (Day 1, Week 0 and second injection, Week 4 according to the body weight: main treatment period, with third injection, Week 8), and then at Week 12 (open label dose finding treatment period) and every 3 months (open label extension treatment period).

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

An included 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 included 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 included 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 PACKAGING AND LABELING

Open Label dose finding treatment period:

For Cohorts 1, 2 and 3: Each kit will contain one vial: either a vial of alirocumab 150 mg/mL or a vial solvent for alirocumab. The number of kits and types of kits (active or solvent) to be dispensed depend on the treatment doses / dose regimen (see Table 1).

For Cohort 4, patients will receive 1 or 2 kit(s) for the 12 week alirocumab treatment period depending on the dose group (1 kit for 150mg Q4W & 2 kits for 300mg Q4W). Each kit will contain 4 PFS of alirocumab 150 mg/mL

Open Label Extension period:

If PFS are available:

Cohorts 1 & 2: patients will receive 2 kits for 12-weeks alirocumab treatment period. Each kit will contain 4 PFS.

Cohort 3: patients will receive 1 kit for 12-weeks alirocumab treatment period. Each kit will contain 4 PFS.

Cohort 4: patients will receive 1 or 2 kit(s) of PFS for up to a 12 week alirocumab treatment period, depending on dose group.

If PFS are not available for Cohorts 1 to 3:

The packaging will be the same as for Open Label Dose finding:

Each kit will contain one vial: either a vial of alirocumab 150 mg/mL or a vial solvent for alirocumab. The number of kits and types of kits (active or solvent) to be dispensed depend on the treatment doses / dose regimen (see Table 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.

The IMP that will be stored at the investigational site should be kept in an appropriate locked room, under the responsibility of the investigator or designee or other authorized person in accordance with 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 should be managed according to the rules provided by the Sponsor.

During the extension period 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.

8.7 RESPONSIBILITIES

The Investigator, the hospital pharmacist, the nurse or other personnel allowed to store, prepare 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 IMPs will be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of IMP issued and returned is maintained.

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

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

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

8.7.1 Treatment accountability and compliance

IMP administration data will be recorded by the investigator on eCRF for the main treatment period and when alirocumab is prepared from vials during the extension phase and by patients/parents on a patient's diary in case of self-injection with prefilled syringes during the extension period.

Measures taken to ensure and document IMP compliance and accountability (vials and PFS if available) are described below:

- The investigator or designee will obtain via IVRS/IWRS the treatment kit number(s) and he/she will dispense the treatment kit(s) to the patient.
- The accountability at site is to be performed at IMP kit re-supply visits only (see Section 10.1). During the extension period in case of self-injections, 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) (until follow-up visit).

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 the first 8 weeks of the main treatment period and follow-up period if applicable. During the extension 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.

Main treatment phase:

From the inclusion visit (Day 1) until Week 14 or 16 end of the follow-up period for Cohorts 1-3 or until Week 12 end of the open label dose finding treatment period for Cohort 4, 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 main treatment phase, lipid profile values from samples obtained after inclusion will be blinded.

Extension treatment phase:

During the optional extension phase the lipid levels will be communicated to the investigators.

The Investigator will be responsible, based on his/her own judgment related to the patients' LDL-C levels and the safety profile, to continue or discontinue alirocumab throughout the study.

The 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 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 who are sexually active must use an effective contraceptive method throughout the entire duration of the study treatment (including main treatment period and extension phase, as applicable) and for at least 10 weeks after the last IMP injection (see Appendix G).

8.8.3 Prohibited concomitant medications

- Prohibited concomitant medications from the initial screening visit until the follow-up visit for Cohorts 1-4 / end of open label dose finding treatment period visit include the following:
  - Oral and injectable corticosteroids,
  - Fibrates (except fenofibrates),
  - Immunosuppressants.
- Prohibited concomitant medications from the start of the open-label extension 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

The primary efficacy endpoint will be the percent change in calculated LDL-C from baseline to Week 8, which is defined as: 100x (calculated LDL-C value at Week 8 minus calculated LDL-C value at baseline)/calculated LDL-C value at baseline.

The baseline calculated LDL-C value will be the last LDL-C level obtained before the first injection IMP. For patients included and not treated, the baseline value is defined as the last available value obtained up to inclusion.

The calculated LDL-C at Week 8 will be the LDL-C level obtained within the Week 8 analysis window.

All calculated LDL-C values (scheduled or unscheduled, fasting or not fasting) may be used in the analyses if appropriate according to above definition and analysis windows used to allocate a time point to a measurement. Analysis windows will be defined in the Statistical Analysis Plan (SAP).

9.2 SECONDARY ENDPOINTS

9.2.1 Secondary efficacy endpoint(s)

- The absolute change in calculated LDL-C from baseline to Week 8.
- The proportion of patients achieving a calculated LDL-C <130 mg/dL (3.37 mmol/L) at Week 8.
- The proportion of patients achieving a calculated LDL-C level <110 mg/dL (2.84 mmol/L) at Week 8.
- The percent change in LDL-C from baseline to Week 12 only for Cohort 4.
- The percent change in Apo B from baseline to Week 8. Same definition and rules as for the primary endpoint.
- The percent change in non-HDL-C from baseline to Week 8. Same definition and rules as for the primary endpoint.
- The percent change in Total-C from baseline to Week 8. Same definition and rules as for the primary endpoint.
- The percent change in Lp(a) from baseline to Week 8. Same definition and rules as for the primary endpoint.
- The percent change in TG from baseline to Week 8. Same definition and rules as for the primary endpoint.
- The percent change in HDL-C from baseline to Week 8. Same definition and rules as for the primary endpoint.

- The percent change in Apo A-1 from baseline to Week 8. Same definition and rules as for the primary endpoint.
- The absolute change in Apo B from baseline to Week 8.
- The absolute change in non HDL-C from baseline to Week 8.
- The absolute change in Total-C from baseline to Week 8.
- The absolute change in Lp(a) from baseline to Week 8.
- The absolute change in HDL-C from baseline to Week 8.
- The absolute change in TG from baseline to Week 8.
- The absolute change in Apo A-1 from baseline to Week 8.
- The absolute change in ratio Apo B/Apo A-1 from baseline to Week 8.

9.2.2 Efficacy assessment method

9.2.2.1 Lipid parameters

Total-C, HDL-C, TG, Apo B, Apo A-1, and Lp(a) will be directly measured by the Central Laboratory as per the schedule in Section 1.3 and Section 1.4. LDL-C will be calculated using the Friedewald formula by the Central Laboratory as per the schedule in Section 1.3 and Section 1.4. 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.

9.2.3 Safety endpoints

The safety endpoints will be adverse events, serious adverse events, adverse events of special interest, laboratory data, vital signs, Tanner stage assessment, body weight, and height assessed throughout the study.

9.2.3.1 Observation period

The observation of safety data will be as follows:

- Pretreatment period: The Pretreatment observation period is defined from the signed informed consent up to the first dose of IMP.
- Treatment emergent adverse event (TEAE) period: The TEAE observation period is defined as the time from the first dose of IMP to the last dose of IMP injection +70 days

(10 weeks) as residual effect of alirocumab is possible until 10 weeks after the stop of treatment IMP injection.

- Post-treatment period: The post-treatment observation period is defined as the time starting the day after the end of the TEAE period up to the end of the study (see definition in Section 6.2.2).

9.2.3.2 Adverse event

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 deemed to be allergic (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 for patients in the Q2 week regimen and <14 calendar days for patients in the Q4 week regimen, or twice the planned dose at one injection due to IMP preparation error), to be reported using the corresponding screens in the eCRF using the term "symptomatic overdose (accidental or intentional)". The patient should be monitored and appropriate symptomatic treatment instituted,
- 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).

9.2.3.3 Safety laboratory

- The clinical laboratory data consist of blood analysis, hematology (RBC count, hemoglobin, hematocrit, platelets, WBC count with differential blood count), standard chemistry (glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, uric acid, total protein, lactate dehydrogenase (LDH), albumin, γ Glutamyl Transferase [γGT]), liver panel (ALT, AST, ALP, and total bilirubin), CPK, cortisol (with reflexive ACTH levels if cortisol <lower limit of normal range [LLN]) and dehydroepiandrosterone sulfate (DHEAS), luteinizing hormone (LH) and follicle-stimulating hormone (FSH), testosterone (male) and estradiol (females),vitamins A (retinol), D (25 hydroxy vitamin D), E (alpha-tocopherol), and K (phylloquinone).

Some additional safety laboratory parameters may be reflexively measured, based on actual data (please refer to Section 10.4.6).

Clinical laboratory values will be analyzed after conversion into standard international units.

Standard international units will be used in all listings and tables.

9.2.4 Vital signs measurement

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

9.2.5 Tanner stages measurement

The Tanner stages will be measured (see Appendix E) throughout the study according to the schedule in Section 1.3 and Section 1.4. 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 ANTI-ALIROCUMAB ANTIBODY ASSESSMENTS

Anti-alirocumab antibodies include the antibody status (positive/negative) and antibody titers.

9.3.1.1 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 and Section 1.4. All scheduled samples will be obtained before IMP injection (predose). Patients who prematurely discontinue the main phase or do not enter the optional extension phase, prematurely discontinue the extension phase or decide not to proceed to the Phase 3 study and who have a titer at or above 240 for anti- alirocumab antibody at follow-up visit (for Cohorts 1-3) / end of dose finding treatment period (Cohort 4) / end of extension phase 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. The sponsor will notify the sites.

9.3.1.2 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.

9.3.1.3 Bioanalytical method

All anti- alirocumab antibody (ADA; anti-drug antibody) 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 (Bioanalytical Validation Report [redacted]

9.4 OTHER ENDPOINTS

9.4.1 Pharmacokinetics

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

9.4.1.1 Sampling time

Serum samples for total alirocumab concentration will be collected before IMP (pre-dose) at Week 0 (inclusion visit) and then at several visits until the end of the follow-up period (for Cohorts 1-3) / end of dose finding treatment period (Cohort 4), as per the study flowchart (see Section 1.3).

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

9.4.1.2 Pharmacokinetics handling 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 PK sample.

Table 2 - 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 (-80°C preferred)

9.4.1.3 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). [redacted]

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

9.4.2 Pharmacogenetic assessment

No pharmacogenetic testing will be done in this study.

9.4.3 Pharmacodynamic variables

The PD effect of alirocumab corresponding to the effect on LDL-C is described in the efficacy section (see Section 9.2.2).

9.4.4 Efficacy and safety during the extension phase

The long-term efficacy and safety of alirocumab will be evaluated during the extension phase.

9.5 FUTURE USE OF SAMPLES

Not applicable.

9.6 APPROPRIATENESS OF MEASUREMENTS

See Section 4.

10 STUDY PROCEDURES

For all visits after Day 1/Week 0 (inclusion visit), a timeframe of a certain number of days will be allowed. The window period for all visits until Week 8 is ±3 days and for the follow-up period and Visits 9 and 10 it is ±7 days. During the open label extension period, the visit window is ±14 days for Visits 11 onward, and ±7 days for the end of treatment visit and the end of OLE visit.

For all visits after Day 1/inclusion visit, if one visit date is changed, then the next visit should take place according to the original schedule as outlined in Section 1.3 and Section 1.4.

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.

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).

Laboratory tests:

The laboratory data are collected in accordance with the study schedule in Section 1.3 and Section 1.4, 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.
- 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, ALP (alkaline phosphatase) 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).
- Adrenal gland hormones: cortisol (with reflexive 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).
- Serum pregnancy test. Pregnancy test should be done on females of childbearing potential who are sexually active 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.

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 D.

CPK-MB and Troponin I should be performed by local laboratory and data collected in case of serious cardiac event.

Pharmacokinetic samples:

Serum samples for assessment of alirocumab concentration will be obtained periodically throughout the study as per schedule note in study flowchart of Section 1.3.

For all cohorts, blood samples will be collected before IMP injection for visits 2 (Week 0), 4 (Week 4), 6 (Week 8), then for Cohorts 1 to 3 at visit 8 (Week 14/16 [for patients entering the extension phase]) and, for Cohort 4, at visit 4 (Week 4), visit 6 (Week 8), visit 7 (Week 10), and visit 8 (Week 12).

Blood samples should be collected before IMP injection.

Physical examination:

A general physical examination should be performed at the time points indicated in the study schedule flowchart Section 1.3 and Section 1.4. If a new clinically significant abnormality or worsening from baseline is detected after inclusion, then an AE should be reported and the patient should be considered for further clinical investigations and/or specialist consultation as per the Investigator's medical judgment.

Blood pressure (BP)/heart rate:

BP should be measured in sitting position under standardized conditions, approximately at the same time of the day, on the same arm, with the same apparatus (after the patient has rested comfortably in sitting position for at least 5 minutes). 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 at the time of the measurement of BP.

Tanner stages:

The Tanner stages (29, 30) 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 E. 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.

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.

10.1 VISITS SCHEDULE

10.1.1 Screening period

Only patients who meet/are likely to meet the inclusion criteria as noted in Section 7.1 should be screened. The screening period (including run in) will take place up to 6 (+1) weeks or 42 (+7) days (and as short as possible, upon receipt of laboratory eligibility criteria) prior to inclusion/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. The screening visit can take place from 42 (+7) days before the inclusion visit (for patients without a stable background LMT [optimal statin dose ± other LMTs or non-statin LMTs if statin intolerant] for at least 4 weeks prior to the screening visit and/or patients suspected of being heFH but without a confirmed diagnosis and consenting to undergo the centralized genotyping) up to 14 (-7) days before the inclusion 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.

During the screening period the following procedures should be followed:

Visit 1 (Week -6 (+1) to Week -2 (-1)) at clinical site:

- Complete informed consent - the patient and their parents will receive complete information about the study both verbally and in writing. Written informed consent for the study must be obtained prior to any study related investigations.

- Complete informed consent for genetic testing for patient electing to undergo genotyping for heFH and/or for use of previous documented genotyping. Written informed consent for the study must be obtained prior to genotyping consent and sampling.
- Contact IVRS/IWRS for notification of screening. Patient number will be allocated by the IVRS/IWRS. This 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 (the 5-digit patient chronological number is 00001 for the first patient screened in a center, 00002 for the second patient screened in the same center).
- Assess inclusion/exclusion criteria.
- Obtain patient demography – age, gender, race, and ethnicity.
- Obtain medical history, surgical history, alcohol habits and smoking habits for adolescents.
- Obtain family medical history (including risk factors relating to premature CHD, see Appendix F: Simon Broome Register Diagnostic Criteria for heFH), allergy.
- Document prior medication history within the previous 12 weeks, especially for lipid modifying therapy (including statin) and nutraceutical products that may affect lipids (eg, omega-3 fatty acids, plant stanols such as found in Benecol, flax seed oil, psyllium).
- Record concomitant medications.
- Check stability of background LMT.
- Get body weight and height measurements.
- Get Tanner stage measurement by the same investigator/designee at each visit if possible.
- Perform physical examination. Take vital signs including HR and BP.
- Genotyping if patient consents to undergo centralized genotyping for heFH (Note: Buccal swab, saliva, or blood sample needed; if blood sample is drawn for genotyping only, the patient does not need to be fasting).
- Collect AEs from this point onward:
  - All AEs and SAEs will be collected from the time of informed consent signature and throughout the study until the post study treatment follow-up visit.
- Obtain fasting blood sample for:
  - Lipid panel 1: total-C, 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),
  - Hematology: red blood cell count including hematocrit, hemoglobin, WBC count with differential count and platelets,
  - Chemistry: glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, uric acid, total protein, LDH, albumin, and γGT,
  - Liver panel (ALT, AST, ALP, and total bilirubin),
  - CPK,
  - Pregnancy test (blood test) for females who have experienced menarche.

- An appointment will be given for the next visit.
- Give instruction on diet: Patients will be instructed to follow a diet in accordance with the American Academy of Pediatrics guidelines (1) or equivalent throughout the entire study (ie, both phases).
- Give instruction on stable background LMT: Patients will be instructed to be treated with stable optimal dose of statin ± other LMT for at least 4 weeks, if not already on stable optimal dosing for at least 4 weeks, or to continue the LMTs at the same dose.

  Note: All patients will be qualified for inclusion based on the confirmation of heFH diagnosis by genotyping or clinical criteria, stable dose of LMT (including statin at optimal dose, unless intolerant) for at least 4 weeks prior to the screening visit, and by the LDL-C value obtained during the screening period, on stable dose of statins ± other LMTs after at least 4 weeks.

  All patients who successfully screen for Cohort 1 and are not included in Cohort 1, due to the appropriate Cohort 1 weight group being fully enrolled, may participate to Cohort 2 but only after eligibility, including safety assessments, is reconfirmed. Patients who are successfully screened for Cohort 2 but are not enrolled, due to the appropriate Cohort 2 weight group being fully enrolled, may participate in Cohort 3 without the need to repeat the run-in/screening period if there is no more than 3 months between eligibility confirmation and inclusion. In such a circumstance, the run-in/screening period from Cohort 2 will substitute for the run-in/screening period for Cohort 3. If there is more than 3 months between initial screening and planned enrollment in Cohort 3, patient eligibility, including safety assessments, must be reconfirmed.

  Safety and eligibility assessments noted above include all lab tests listed as exclusionary, based on specified results.

  Patients should be instructed to follow a diet in accordance with the American Academy of Pediatrics (AAP) guidelines (1) or equivalent throughout the entire study (ie, both phases). The dietician or site staff with appropriate training will review the patient's diet at the screening visit and periodically throughout the study.

10.1.2 Dose finding Treatment Period

The timelines of the visits should be the same for each Cohort, but patients from Cohort 2 will be included after patients from Cohort 1 complete the open label dose finding treatment period and after DMC recommendation on dose escalation. Patients from Cohort 3 will be included after patients from Cohort 2 complete enrollment.

- **Cohorts 1 & 2**: screening visits from W-6 to W-2 (±1), inclusion visit W0, study visits W2, W4, W6, end of main treatment period visit W8, first follow-up visit W12, second follow-up visit W16.
- **Cohort 3**: screening visits from W-6 to W-2 (±1), inclusion visit W0, study visits W2, W4, W6, end of main treatment period visit W8, first follow-up visit W10, second follow-up visit W14.

- **Cohort 4**: screening visits from W-6 to W-2 (±1), inclusion visit W0, study visits W2, W4, W6, W8, W10 and end of main treatment period visit W12.

10.1.2.1 Inclusion visit (Visit 2/Week 0/Day 1) at clinical site

- Assess Inclusion/Exclusion Criteria in particular confirmation of heFH diagnosis by genotyping or clinical criteria.
- Collect AEs.
- Record concomitant medication.
- Check stability of background LMT.
- Review patient's diet. Patient should be on a diet in accordance with the American Academy of Pediatrics guidelines (1) or equivalent.
- Perform physical examination.
- Get body weight measurement.
- Take vital signs including HR and BP.
- Urine pregnancy test (females who have experienced menarche only).
- Obtain fasting blood sample for:
  - Lipids: total-C, calculated LDL-C, HDL-C, TG, non-HDL-C, Apo B, Apo A-1, ratio Apo B/Apo A-1, and Lp(a),
  - Adrenal gland hormones: cortisol (with reflexive ACTH levels if cortisol <LLN), dehydroepiandrosterone sulfate (DHEAS),
  - Gonadal and pituitary hormones: testosterone (male) and estradiol (female), luteinizing hormone (LH), follicle-stimulating hormone (FSH),
  - Fat soluble vitamins: retinol (vitamin A), 25hydroxy-vitamin D (vitamin D), alpha-tocopherol (vitamin E), phylloquinone (vitamin K).
- Anti-alirocumab antibodies.
- Serum alirocumab concentration (PK).
- PCSK9 levels (free and total).
- If the patient is confirmed eligible (and in fasting conditions), the Investigator will start the next study procedures:
  - Contact IVRS/IWRS for notification of inclusion. Investigators should never allocate a treatment kit number to a patient without contacting IVRS/IWRS. IVRS/IWRS contact for allocation of a batch number for inclusion kit,
  - Record batch number allocated in e-CRF,
  - Main treatment period IMP kits dispensation as per treatment kit numbers provided by IVRS along with schedule reminder for visits. The investigator/patient injection instruction manual and treatment administration package should be provided to the investigator staff.

- The first alirocumab injection will take place at the study site, but only after the collection of the fasting blood samples and after the assessment of all evaluations planned at that visit. The patient should be observed for at least 30 minutes after the first injection.

- Reminder:
  - An appointment will be given for the next study site visit or visit at patient's home.

10.1.2.2 Visit 3/Week 2, (Day 14 ±3) at clinical site or nurse visit at patient's home. For Cohort 3 and Cohort 4, a phone call may be done instead.

- Collect AEs.
- Record concomitant medication.
- IVRS/IWRS contact.
- Check of stability of background LMT.
- For Cohorts 1 & 2: The second alirocumab injection will take place at the study site or patient's home, but only after the assessment of all evaluations planned at that visit (no injection for Cohort 3 or Cohort 4 at this visit).
- Reminders:
  - An appointment will be given for the next study site visit,
  - Remind patient to be in fasting conditions (ie, overnight, at least 8-hour fast and refrain from smoking) for next study site visit. Also, alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the next study site visit are discouraged.

10.1.2.3 Visit 4/Week 4 (Day 28 ±3) at clinical site

- Collect AEs.
- Record concomitant medication.
- Get body weight measurement.
- IVRS/IWRS contact.
- Review patient's diet. Patient should be on a diet in accordance with the American Academy of Pediatrics guidelines (1) or equivalent.
- Take vital signs including HR and BP.
- Check of stability of background LMT.
- Obtain fasting blood sample for:
  - Liver panel (ALT, AST, ALP, and total bilirubin),
  - Hematology: red blood cell count including hematocrit, hemoglobin, WBC count with differential count and platelets,
  - Chemistry: glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, uric acid, total protein, LDH, albumin, and γGT,

- Lipids: total-C, calculated LDL-C, HDL-C, TG, non-HDL-C,
- CPK,
- Serum alirocumab concentration (PK),
- PCSK9 levels (free and total).

- For Cohorts 1 & 2: The third alirocumab injection will take place at the study site, but only after the assessment of all evaluations planned at that visit. For Cohort 3: the second and last alirocumab injection of this period will take place at the study site, but only after the assessment of all evaluations planned at that visit.
- For Cohort 4, the second injection out of 3 of this period will take place at the study site.
- Reminder:
  - An appointment will be given for the next study site visit or visit at patient's home.

10.1.2.4 Visit 5/Week 6 (Day 42 ±3) at clinical site or nurse visit at patient's home. For Cohorts 3 and 4, a phone call may be done instead.

- Collect AEs.
- Record concomitant medication.
- IVRS/IWRS contact.
- Check of stability of background LMT.
- For Cohorts 1 & 2: The fourth and the last alirocumab injection for this period will take place at the study site or the patient's home, but only after the assessment of all evaluations planned at that visit (no injection for Cohort 3 or 4 at this visit).
- Reminders:
  - An appointment will be given for the next study site visit,
  - Remind patient to be in fasting conditions (ie, overnight, at least 8-hour fast and refrain from smoking) for next study site visit. Also, alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the next study site visit are discouraged.

10.1.2.5 Visit 6/Week 8 (Day 56 ±3)/ at clinical site (end of the OL dose finding treatment period)

- Collect AEs.
- Record concomitant medication.
- Review patient's diet. Patient should be on a diet in accordance with the American Academy of Pediatrics guidelines (1) or equivalent.
- Perform physical examination.
- Get body weight measurement.
- Take vital signs including HR and BP.

- Urine pregnancy test (female who have experienced menarche only).
- Obtain fasting blood sample for:
  - Lipids: total-C, calculated LDL-C, HDL-C, TG, non-HDL-C, Apo B, Apo A-1, ratio Apo B/Apo A-1, and Lp(a),
  - Hematology: red blood cell count including hematocrit, hemoglobin, WBC count with differential count and platelets,
  - Chemistry: glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, uric acid, total protein, LDH, albumin, and γGT,
  - Liver panel (ALT, AST, ALP, and total bilirubin),
  - CPK,
  - Adrenal gland hormones: cortisol (with reflexive ACTH levels if cortisol <LLN), dehydroepiandrosterone sulfate (DHEAS),
  - Gonadal and pituitary hormones: testosterone (male) and estradiol (female), luteinizing hormone (LH), follicle-stimulating hormone (FSH),
  - Fat soluble vitamins: retinol (vitamin A), 25hydroxy-vitamin D (vitamin D), alpha-tocopherol (vitamin E), phylloquinone (vitamin K).
- Anti-alirocumab antibodies.
- Serum alirocumab concentration (PK).
- PCSK9 levels (free and total).
- Check of stability of background LMT.
- Reminder:
  - An appointment will be given for the next study site visit or phone call visit (first follow-up study visit).
- For Cohort 4, the final third injection of this period will take place at the study site

10.1.2.6 Visit 7/Week 10 (Day 70 ±7) at clinical site (Cohort 4 Only):

- Collect AEs.
- Record concomitant medication.
- Obtain fasting blood sample for:
  - Lipids: total-C, calculated LDL-C, HDL-C, TG, non-HDL-C.
  - PCSK9 levels (free and total) / Serum alirocumab concentration (PK).

10.1.2.7 Visit 8/Week 12 (end of the OL dose finding treatment period) (Cohort 4 only)

- Collect AEs.
- Record concomitant medication.
- Get body weight and height measurements.

- Assess Tanner stage.
- Take vital signs including HR and BP.
- IVRS/IWRS contact.
- Check of stability of background LMT.
- Urine pregnancy test (female who have experienced menarche only).
- Obtain fasting blood samples for:
  - Lipids: total-C, calculated LDL-C, HDL-C, TG, non-HDL-C.
  - PCSK9 levels (free and total) / Serum alirocumab concentration (PK).

10.1.3 Follow-Up Period

The follow-up period is mandatory for cohorts 1-3 but not for Cohort 4.

10.1.3.1 First Follow-Up Visit (Visit 7 / Week 10/Day 70 ±7 [Cohort 3] / Week 12/Day 84 ±7 [Cohorts 1 & 2]) at clinical site or phone call if no safety concerns by the investigator at the previous visit or between the 2 visits "visit 6" and "visit 7"

- Collect AEs.
- Record concomitant medication.
- Perform physical examination (only in case of clinically relevant abnormality at the end of treatment visit) if visit at clinical site.

10.1.3.2 Second Follow-Up Visit (Visit 8 / Week 14 for Cohort 3/Day 98 ±7/ Week 16 for Cohorts 1 & 2 / Day 112 ±7) at clinical site (end of the main study period).

- Collect AEs.
- Record concomitant medication.
- Get body weight and height measurements.
- Take vital signs including HR and BP.
- Perform physical examination (only in case of clinically relevant abnormality at the Week 8/end of treatment visit).
- Get Tanner stages measurement by the same investigator/designee at each visit if possible.
- IVRS/IWRS contact to document the end of the main phase period and the start of the optional open-label extension period if patient agrees for participation in this extension.
- Urine pregnancy test (females who have experienced menarche only).
- Obtain fasting blood sample for:
- Anti-alirocumab antibodies,
- Serum alirocumab concentration (PK),
- PCSK9 levels (free and total).

- Only in case of clinically relevant abnormal values for these parameters at the end of treatment visit will the following be obtained at this visit:
  - Hematology: red blood cell count including hematocrit, hemoglobin, WBC count with differential count and platelets,
  - Chemistry: glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, uric acid, total protein, LDH, albumin, and γGT,
  - Liver panel (ALT, AST, ALP and total bilirubin),
  - CPK.

10.1.4 Open label extension treatment period (OLETP, optional)

Patients who successfully complete the main treatment period and follow-up period will be eligible (provided they have not experienced AEs leading to permanent discontinuation during the main treatment period, or had significant protocol deviations, in the Investigator's judgment) to enter an optional open-label treatment period. Treatment for these patients will start after the follow-up period and the last dose/dose regimen of the main treatment period should be administered again during this extension period (start Week 16 for Cohorts 1 and 2, and Week 14 for Cohort 3). Cohort 4 will start the extension phase on Week 12 or have the option of direct entry into the phase 3 study.
This dose/dose regimen may be modified after the final doses for the Phase 3 study have been selected and based on the body weight at the time of possible dose change for Cohorts 1-3 and will not be modified for Cohort 4 as these patients will remain on their initial regimen given the planned study end date of December 2018. Alirocumab administration will be continued until at least 10 weeks before the initiation of the pediatric phase 3 study in the site where the patient is potentially participating or December 2018, whichever comes first.

- During the OLETP:
- A window of ±7 days or ±14 days according the visit is authorized for each visit planned every 12 weeks from Week 16 or Week 14 to Week 130 for all cohorts (see Section 1.4),
  - An IVRS/IWRS contact for open-label extension treatment allocation should be done every 2 weeks by the investigator to prepare for using vials in Cohorts 1 & 2 until availability of PFS.

10.1.4.1 Visit 8/Week 16 for Cohorts 1 & 2 or Visit 8/Week 14 for Cohort 3 /Week 12 for Cohort 4 (same visit as the last visit of the main treatment period)

At this visit, patients will undergo end of follow-up period assessments and baseline open-label extension treatment period assessments, as appropriate, concurrently. Study site personnel should review treatment requirements of the open-label extension treatment period with patients and remind patients that dosing in the open-label extension treatment period begins at this visit. The following information will be collected:

- Assess Exclusion Criteria for open-label extension treatment period (see Section 7.3).

- All evaluations performed for the end of the follow-up period are the same for the first visit of the open-label extension treatment period (see previous Section) except blood sample for lipids evaluation.
- Review patient's diet. Patient should be on a diet in accordance with the American Academy of Pediatrics guidelines (1) or equivalent.
- Check of stability of LMT dosing.
- Urine pregnancy test (females who have experienced menarche only).
- If the patient is confirmed eligible (and in fasting conditions), the Investigator will start the next study procedures:
  - IVRS/IWRS contact for open-label extension treatment allocation of one 7-digit treatment kit number according to the treatment number list for the alirocumab injections. Investigators should never allocate a treatment kit number to a patient without contacting IVRS/IWRS.
- If the prefilled syringe becomes available: open-label extension treatment IMP kits dispensation as per treatment kit numbers provided by IVRS along with schedule reminder. Injection training to be provided. The patient injection instruction manual and treatment administration package should be provided. The patient's diary should be given and instructions on its completion should be reviewed for Cohorts 1 to 3.
- The first open-label extension alirocumab injection will take place at the study site, but only after the collection of the fasting blood samples and after the assessment of all evaluations planned at this visit. Close supervision, feedback and training (if prefilled syringes) to be provided for IMP administration in case of self-injection or injection administered by parent/legal custodian.
- Obtain fasting blood sample for:
  - Lipids: total-C, calculated LDL-C, HDL-C, TG, non-HDL-C, Apo B, Apo A-1, ratio Apo B/Apo A-1, and Lp(a) for Cohorts 1 to 3,
  - Lipids: total-C, calculated LDL-C, HDL-C, TG, non-HDL-C for Cohort 4.
- Reminders:
  - An appointment will be given for the next study site visit,
  - Patient to bring the diary, and used and unused kits, at the next study site visit (if applicable ie, prefilled syringes).
- The alirocumab injections should be done every 2 weeks for Cohorts 1 and 2 or every 4 weeks for Cohort 3 and Cohort 4 at clinical site, by a health care professional at patients' home, or by patient or representative (parent…) at home according to the type of supplied syringe (prefilled or not) during all the extension period. This alirocumab administration during the open-label extension will continue until approximately 10 weeks before the initiation of the pediatric Phase 3 study or December 2018, at the latest.

10.1.4.2 Visit 9/Week 20 for Cohorts 1 & 2 /Week 18 for Cohort 3/Week 16 for Cohort 4 (Phone Call Option)

- Collect AEs.
- Record concomitant medication.
- Review patient's diet. Patient should be on a diet in accordance with the American Academy of Pediatrics guidelines (1) or equivalent.
- Review patient's diary and compliance check of IMP if applicable.
- Check of stability of LMT dosing.
- Reminders:
- An appointment will be given for the next study site visit,
- Patient to bring the diary, and used and unused kits, at the next study site visit (if applicable ie, prefilled syringes).

10.1.4.3 Visit 10/Week 24 for Cohorts 1 & 2 /Week 22 for Cohort 3/Week 20 for Cohort 4 (Phone Call Option)

- Collect AEs.
- Record concomitant medication.
- Review patient's diet. Patient should be on a diet in accordance with the American Academy of Pediatrics guidelines (1) or equivalent.
- Check of stability of LMT dosing.
- Reminders:
  - An appointment will be given for the next study site visit,
  - Remind patient to be in fasting conditions (ie, overnight, at least 8 hours fast and refrain from smoking) for next study site visit. Also, alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the next study site visit are discouraged,
  - Patient to bring the diary, and used and unused kits, at the next study site visit (if applicable ie, prefilled syringes).

10.1.4.4 Visits 11, 13, 15, 17, 19 (every 24 weeks)/ Visit 11 only for Cohort 4

- Collect AEs.
- Record concomitant medication.
- Urine pregnancy test (females who have experienced menarche only).
- Review patient's diet. Patient should be on a diet in accordance with the American Academy of Pediatrics guidelines (1) or equivalent.

- If the prefilled syringe becomes available: Data collection on alirocumab administration and alirocumab compliance check by review of diary and treatment kit accountability for Cohorts 1 to 3.
- Cohort 4 will receive second alirocumab allocation and administration for OLE phase.
- Check of stability of background LMT.
- IVRS/IWRS contact to get treatment kit number for 1 kit resupply.
- Obtain fasting blood sample for:
  - Lipids: total-C, calculated LDL-C, HDL-C, TG, non-HDL-C, Apo B, Apo A-1, ratio Apo B/Apo A-1, and Lp(a) for Cohorts 1 to 3.
  - Lipids: total-C, calculated LDL-C, HDL-C, TG, non-HDL-C for Cohort 4.
  - Liver panel (ALT, AST, ALP, and total bilirubin),
  - Hematology: red blood cell count including hematocrit, hemoglobin, WBC count with differential count and platelets,
  - Chemistry: glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, uric acid, total protein, LDH, albumin, and γGT,
  - CPK,
  - Anti-alirocumab antibodies,
  - Adrenal gland hormones: cortisol (with reflexive ACTH levels if cortisol <LLN), dehydroepiandrosterone sulfate (DHEAS),
  - Gonadal and pituitary hormones: testosterone (male) and estradiol (female), luteinizing hormone (LH), follicle-stimulating hormone (FSH),
  - Fat soluble vitamins: retinol (vitamin A), 25hydroxy-vitamin D (vitamin D), alpha-tocopherol (vitamin E), phylloquinone (vitamin K).
- Reminders:
  - An appointment will be given for the next study site visit,
  - Remind patient to be in fasting conditions (ie, overnight, at least 8 hours fast and refrain from smoking) for next study site visit. Also, alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the next study site visit are discouraged,
  - Patient to bring the diary, and used and unused kits at the next study site visit.

10.1.4.5 Visits 12, 14, 16, 18 (every 24 weeks)/ Visit 12 only for Cohort 4

- Collect AEs.
- Record concomitant medication.
- Perform physical examination.
- Get body weight and height measurements.
- Get Tanner stage measurement by the same investigator/designee at each visit if possible.

- Take vital signs including HR and BP.
- Urine pregnancy test (females who have experienced menarche only).
- Review patient's diet. Patient should be on a diet in accordance with the American Academy of Pediatrics guidelines (1) or equivalent.
- If the prefilled syringe becomes available: Data collection on alirocumab administration and alirocumab compliance check by review of diary and treatment kit accountability.
- Check of stability of background LMT.
- IVRS/IWRS contact to get treatment kit number for 1 kit resupply.
- Obtain fasting blood sample for:
  - Lipids: total-C, calculated LDL-C, HDL-C, TG, non-HDL-C, Apo B, Apo A-1, ratio Apo B/Apo A-1, and Lp(a), for Cohorts 1 to 3.
  - Lipids: total-C, calculated LDL-C, HDL-C, TG, non-HDL-C for Cohort 4.
- Reminders:
  - An appointment will be given for the next study site visit,
  - Remind patient to be in fasting conditions (ie, overnight, at least 8 hours fast and refrain from smoking) for next study site visit. Also, alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the next study site visit are discouraged,
  - Patient to bring the diary, and used and unused kits at the next study site visit.
- Cohort 4 will receive third and final alirocumab allocation and administration for OLE phase.

10.1.4.6 Visit 20, Week 130 for Cohorts 1 to 3/EOS, Week 48 for Cohort 4 [Visit 13 for Study Flow Chart, Main Phase or Visit 20 for eCRF (end of open-label extension period)]

- Collect AEs.
- Record concomitant medication.
- Perform physical examination.
- Get body weight and height measurement.
- Take vital signs including HR and BP.
- Get Tanner stage measurement by the same investigator/designee at each visit if possible.
- Review patient's diet. Patient should be on a diet in accordance with the American Academy of Pediatrics guidelines (1) or equivalent.
- IVRS/IWRS contact to document the end of OLETP treatment, no injection will be done at this visit.
- If prefilled syringe becomes available: Data collection on IMP administration and IMP compliance check by review of diary and treatment kit accountability.
- Check of stability of background LMT.

- Urine pregnancy test (females who have experienced menarches only).
- Obtain fasting blood sample for:
  - Lipids: total-C, calculated LDL-C, HDL-C, TG, non-HDL-C, Apo B, Apo A-1, ratio Apo B/Apo A-1, and Lp(a), for Cohorts 1 to 3,
  - Lipids: total-C, calculated LDL-C, HDL-C, TG, non-HDL-C for Cohort 4,
  - Hematology: red blood cell count including hematocrit, hemoglobin, WBC count with differential count and platelets,
  - Chemistry: glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, uric acid, total protein, albumin, and γGT,
  - Liver panel (ALT, AST, ALP, and total bilirubin),
  - Adrenal gland hormones: cortisol (with reflexive ACTH levels if cortisol <LLN), dehydroepiandrosterone sulfate (DHEAS),
  - Gonadal and pituitary hormones: testosterone (male) and estradiol (female), luteinizing hormone (LH), follicle-stimulating hormone (FSH),
  - Fat soluble vitamins: retinol (vitamin A), 25hydroxy-vitamin D (vitamin D), alpha-tocopherol (vitamin E), phylloquinone (vitamin K),
  - CPK,
  - Anti-alirocumab antibodies.

10.1.4.7 Follow-up Phone contact at least 10 weeks after the last IMP injection for all cohorts

- Collect AEs if any.
- Record concomitant medication.
- In case of clinically relevant abnormality not recovered at the end of OLE visit, plan an unscheduled visit & perform physical examination/ laboratory examinations if needed.

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 child-bearing 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 subinvestigator).
- IVRS/IWRS confirmation fax (screening, screen failure, inclusion, treatment reallocation, discontinuation, end of open-label dose finding treatment period, end of follow-up period, start of extension period, end of study).
- Adverse events and follow-up:
  - In case of SAE, the site should file in the source document at least copies of the hospitalization reports and any relevant examination reports documenting the follow-up of the SAE.
- Date of premature study discontinuation (if any) and reason.

Source documentation may be found in the following:

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

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

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

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

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

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 should be recorded by the Investigator in the appropriate eCRF screens when considered as confirmed.

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

10.3.2 Permanent treatment discontinuation with investigational medicinal product(s)

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

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

10.3.3 List of criteria for permanent treatment discontinuation

The patients may withdraw from treatment 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 child-bearing 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 inclusion.

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

10.3.4 Handling of patients after permanent treatment discontinuation

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

- At the time of treatment discontinuation, the patient should have, as soon as possible, an unscheduled visit with assessments normally planned at end of open-label dose finding treatment period visit except lipids, PK and ADA (this should take place within 5 days of treatment discontinuation, if possible), except if the timing of this visit corresponds to Week 8 visit. Lipids, PK and ADA should be assessed in an additional unscheduled visit:
  - Cohorts 1 and 2 (Q2W): This visit should take place 14 to 21 days after last alirocumab injection.
  - Cohort 3 & Cohort 4 (Q4W): this visit should take place 28 to 35 days after last alirocumab injection.
- Week 8 visit, as described in Section 1.3, regardless of its timing in relation to the last alirocumab injection.

All efforts should be done to perform these assessments.

Patients who prematurely discontinue study treatment (regardless of the reason) during the open-label extension period should undergo an unscheduled visit with assessments normally planned at end of open-label extension period visit except lipids and ADA (this should take place within 5 days of treatment discontinuation, if possible). Lipids and ADA should be assessed in an additional unscheduled visit:

- Cohorts 1 & 2 (Q2W): This visit should take place 14 to 21 days after last alirocumab injection.
- Cohort 3 & Cohort 4 (Q4W): this visit should take place 28 to 35 days after last alirocumab injection.

Whatever the period of premature treatment discontinuation, the patient, at a minimum, should then be followed up for at least 10 weeks from last study treatment administration or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last. A final end of study visit can take place with assessments as specified in the end of study visit at 10 weeks after the premature treatment discontinuation.

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

For patients included and not treated, all efforts should be made to perform the Week 8 visit in order to collect the laboratory data and at the least, the lipid parameters.

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. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-patient contact follow-up, eg, medical records checks. Patients requesting withdrawal should be informed that withdrawal of consent for follow-up may jeopardize the public health value of the study. If possible, the patients should be assessed using the procedure defined above.

If possible, the patients are assessed using the procedure normally planned for the end-of-study visit including a pharmacokinetics sample, if appropriate.

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

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

For patients who fail to return to the site, the Investigator should make the best effort to recontact the patient (eg, contacting patient's family or private physician, review available registries or health care database), 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).

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

Patients who have withdrawn from the study cannot be re-included (treated) in the study. Their inclusion and treatment number must not be reused.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

Please refer to Appendix B for AE reporting requirements.

10.4.1.1 Adverse event

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

10.4.1.2 Serious adverse event

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

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

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

  - Intensive treatment in an emergency room or at home for:
    - Allergic bronchospasm,
    - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc),
    - Convulsions (seizures, epilepsy, epileptic fit, absence seizures, etc).
- Development of drug dependence or drug abuse,
- ALT >3 xULN + total bilirubin >2 xULN or asymptomatic ALT increase >10 xULN,
- Suicide attempt or any event suggestive of suicidality,
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling),
- Bullous cutaneous eruptions,
- Cancers diagnosed during the study or aggravated during the study,
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study,
- 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 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 prespecified manner described in the protocol. Please see Appendix B 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 (Please refer to related flowchart in Appendix B).
- Allergic events:
  - Any general allergic events regardless of the cause' and/or local injection site reactions deemed to be allergic (or have an allergic component) 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, and/or all injection site reactions having an allergic component or deemed to be allergic, 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 prespecified 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 for Q2W regimen or 2 or more injections from the treatment kit are administered in <14 calendar days for Q4W regimen) to be reported using the corresponding screens in the eCRF using the term "symptomatic overdose (accidental [or intentional])". The patient should be monitored and appropriate symptomatic treatment instituted if needed,

- The circumstances of the overdose should be clearly specified in the verbatim,

- 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 considered by the Investigator as non-allergic events and 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 C. Special eCRF screens will need to be completed. If such an AE were to occur, then do not report the individual components of the reaction but rather the term “local injection site reaction”, the individual components being described in the specific eCRF screen.

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

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

Not applicable.

10.4.3 General guidelines for reporting adverse events

All AEs regardless of seriousness or relationship to IMP, spanning from the signature of the informed consent form, until the end of the study (post study treatment follow-up visit), are to be recorded on the corresponding screen(s) included in the eCRF.

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

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.

See Appendix B for a summary of AE reporting guidelines.

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. 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.

10.4.4 Instructions for reporting serious adverse events

In the case of occurrence of a 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.
- SEND (within 24 hours) (preferably by fax or e-mail) the photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the Monitoring Team whose name, fax number and email address appear on the Clinical Trial Protocol. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the Clinical Trial are properly mentioned on any copy of source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the e-CRF as appropriate, and further documentation as well as additional information (for Lab data, concomitant Medication, patient status) should be sent (by fax or e-mail) to the Monitoring Team within 24 hours of knowledge. 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 Appendix B, 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 Section 10.4.

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 D.

The following laboratory abnormalities with prespecified monitoring should be monitored, documented, and managed by the investigators according to the related flowchart in protocol in Appendix B and Appendix D:

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

Use of local labs for follow-up testing should be considered. In case the amount of blood needed to perform all follow-up testing noted in the algorithms exceeds what can be safely drawn or exceeds local requirements, clinical judgment should be used to prioritize tests obtained. In the algorithms, except when specified to be permanent, treatment discontinuation should be temporary, at least until a cause for the abnormality is found. Clinical judgment should be used to determine if and when study treatment should be resumed.

10.5 OBLIGATIONS OF THE SPONSOR

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

- All SAEs, that are both unexpected and at least reasonably related to the IMP (Suspected Unexpected Serious Adverse Reaction [SUSAR]), to the regulatory authorities, IECs/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,
  - Allergic events,
  - Pregnancy,
  - Symptomatic Overdose with IMP alirocumab,
  - Neurologic Events,
  - 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.

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

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. See Section 10.4.1.4 and Appendix C for further information.

10.6.2 Allergic adverse events

Specific eCRF 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 considered to be reported on the General Allergic adverse event and/or Local Injection Site Reaction Complementary Form.

Local injection site reactions deemed to be allergic 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 General Allergic adverse event 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 inclusion visit. Patients should be treated symptomatically if any AEs are observed. Patients are to remain at the site until any acute injection reaction is assessed as stable, per the Investigator's discretion. General Allergic Reaction and/or Local Injection Site Reaction Complementary Form will have to be completed.

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

If a patient achieves a very low LDL-C level (ie, LDL-C<50mg/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 continuation. Regardless of the action taken regarding alirocumab 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.

10.7 ADVERSE EVENTS MONITORING

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

11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

No power sample size calculations were performed for the main phase. A sample size of 10 patients per cohort is empirical and based on the sample size of the Phase 1 studies (R727-CL-904 and R727-CL-1001) conducted in adults. No less than 4 patients with BW <50 kg and no less than 4 patients with BW ≥50 kg will be enrolled in 4 independent cohorts (Cohort 1, Cohort 2, Cohort 3, and Cohort 4), which will allow the evaluation of the pharmacokinetics/pharmacodynamics (PK/PD) profile and safety of different alirocumab doses/dose regimen in each BW category and to compare with PK/PD profile and safety observed in adult patients.

11.2 DISPOSITION OF PATIENTS

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

Included patients consist of all screened patients, with open-label treatment kit numbers allocated and recorded in the IVRS/IWRS database, regardless of whether the treatment kits were used or not. Patients treated without being included or treated with an open-label treatment kit before the inclusion will not be considered as included and will not be included in any analysis population. The safety experience of patients treated and not included will be reported separately.

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

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

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy populations

The primary efficacy analysis population will be the modified intent-to-treat (mITT) population as defined below.

11.3.1.1 Modified intent-to-treat population

Modified ITT (mITT) population is defined as all included patients who took at least one dose or part of a dose of IMP during the open-label dose-finding period and had an evaluable primary endpoint. The primary endpoint is considered as evaluable when both of the following conditions are met:

- Availability of at least 1 calculated LDL-C value before first open-label IMP (see Section 9.1.1).

- Availability of at least 1 calculated LDL-C value during the main efficacy period and in one analysis window up to Week 8 analysis window.

Patients in the mITT population will be analyzed according to the alirocumab dose allocated by IVRS.

11.3.2 Safety population

The Safety population considered for safety analyses will be the included population who did actually receive at least one dose or part of a dose of the open-label IMP. Patients will be analyzed according to the dose of alirocumab actually received.

In addition:

- Included patients for whom it is unclear whether they took the study medication will be included in the safety population as assigned by the IVRS.
- For patients receiving IMP from more than 1 alirocumab dose during the open-label dose-finding treatment period, the alirocumab dose 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 PK analysis will be performed on all treated patients (safety population) with at least one evaluable blood sample for PK post first open-label IMP injection.

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 open-label IMP injection.

11.4 STATISTICAL METHODS

The following sections detail the analyses of the open-label dose finding treatment period. Analyses of open-label extension period will be done separately and will be detailed in the 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 alirocumab dose received within the safety population.

11.4.1.1 Extent of investigational medicinal product exposure

The duration of IMP injection exposure in weeks will be defined as: (last dose of open-label IMP injection date - first dose of open-label IMP injection date +14)/7 (for Cohorts 1 & 2) or (last dose of open-label IMP injection date - first dose of open-label IMP injection date +28)/7 (for Cohorts 3 & 4), regardless of unplanned intermittent discontinuations.

11.4.1.2 Compliance

Compliance will be assessed using the injection frequency defined for each patient as the average number of days between 2 injections, that is: (last injection date – first injection date)/(number of injections -1) and will be summarized descriptively (N, Mean, SD, Median, Min and Max).

11.4.2 Analyses of efficacy endpoints

There will be no formal statistical test for the efficacy endpoints. All efficacy analyses will be descriptive.

11.4.2.1 Analysis of primary efficacy endpoint(s)

The primary analysis will be based on an on-treatment approach, and will use LDL-C values collected during the efficacy treatment period. The efficacy treatment period is defined as the period from first alirocumab injection to last alirocumab injection +21 days (for Cohorts 1 & 2) or + 35 days (for Cohort 3 & Cohort 4) during the open-label dose finding treatment period.

The percent change from baseline in calculated LDL-C at Week 8 as defined in Section 9.1.1 will be analyzed in the mITT population using a mixed-effect model with repeated measures (MMRM) approach to handle missing data. All post-baseline data available during the open-label dose-finding treatment period and within analysis windows will be used and the missing data will not be imputed. The model will include the fixed categorical effects of alirocumab doses/dose regimen (30 mg Q2W [<50 kg], 40 mg Q2W [<50 kg], 50 mg Q2W [≥50 kg], and 75 mg Q2W [≥50 kg]) and Q4W (75 mg Q4W [<50 kg] , 150 mg Q4W [≥50 kg], 150 mg Q4W [<50 kg] and 300 mg Q4W ([≥50 kg]), time point (Week 4, Week 8), dose-by-time point interaction, as well as, the continuous fixed covariates of baseline LDL-C value and baseline value-by-time point interaction.

This model will be run using SAS Mixed procedure with an unstructured correlation matrix to model the within-patient errors. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Denominator degrees of freedom will be estimated using Satterthwaite's approximation. This model will provide baseline adjusted least-squares means estimates at Week 8 for each alirocumab dose, with their corresponding SEs and 95% CIs. In addition, LS mean with 95% confidence intervals will be provided for each cohort using appropriate contrasts.

Additionally, for Cohort 4 only, the percent change from baseline in calculated LDL-C at Week 12 will be analyzed using the same model as for the primary endpoint: All post-baseline data available during the open-label dose-finding treatment period and within analysis windows for Cohort 4 will be used and the missing data will not be imputed. The model will include the fixed categorical effects of alirocumab doses/dose regimen (150 mg Q4W [<50 kg] and 300 mg Q4W ([≥50 kg]), time point (Week 4, Week 8, Week10, Week 12), dose-by-time point interaction, as well as, the continuous fixed covariates of baseline LDL-C value and baseline value-by-time point. This model will provide baseline adjusted least-squares means estimates at Week 12 for each alirocumab dose of Cohort 4, with their corresponding SEs and 95% CIs. In addition, LS mean with 95% confidence intervals will be provided for cohort 4 overall using appropriate contrasts.

11.4.2.2 Analyses of secondary efficacy endpoints

Continuous secondary variables defined in Section 9.2 will be analyzed in the mITT population using the same MMRM model as for the primary endpoint with the corresponding baseline value as covariate. For TG and Lp(a) known to have non Gaussian distribution, the methodology that will be used will be described in the SAP.

For binary secondary efficacy variables defined in Section 9.2, the methodology that will be used will be described in the SAP.

Percent change, and when appropriate absolute change from baseline in calculated LDL-C, total C, HDL-C, TG, and non-HDL-C will be summarized at each time point in the mITT population (including Week 10 and W12 time points for Cohort 4). All measurements, scheduled or unscheduled, collected from screening up to 21 days (for Cohorts 1 & 2) or + 35 days (for Cohorts 3 & 4) after the last open-label IMP injection, will be assigned to analysis windows defined in the SAP in order to provide an assessment for these time points. Laboratory assessments other than the ones provided by the central laboratory will be excluded. For TG, measurements on not fasting patients will be excluded. Same kind of tables (with either percent change from baseline or absolute change from baseline) and plots will be provided for other efficacy parameters: Apo B, Apo A-1, ratio Apo B/Apo A-1, Lp(a).

11.4.2.3 Multiplicity considerations

Since there will be no formal statistical test for the efficacy endpoints, no adjustment for multiplicity will be made.

11.4.3 Analyses of safety data

The summary of safety results will be presented by alirocumab dose. 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 open-label IMP.

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 as the time from first dose of open-label IMP to the last dose of open-label IMP injection +21 days (for Cohorts 1 & 2) or + 35 days (for Cohorts 3 & 4).

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, ALP and total bilirubin, are used to assess possible drug induced liver toxicity. The proportion of patients with PCSA values at any post-baseline visit by baseline status will be displayed 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 will be presented on a logarithmic scale. The graph will be divided into 4 quadrants with a vertical line corresponding to 3 xULN for ALT and a horizontal line corresponding to 2 xULN for total bilirubin.

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

11.4.3.1 Adverse events

Adverse event incidence tables will present by system organ class (SOC) (sorted by internationally agreed order), high-level group term (HLGT), high level term (HLT) and preferred term (PT) sorted in alphabetical order 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 (defined with a PT or a prespecified grouping), all treatment emergent SAEs and all TEAEs leading to permanent treatment discontinuation. If any clinically significant signal is detected and need further characterization or for AE of clinical interest, exploration of time to onset will be performed for these selected TEAEs.

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 and 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.

11.4.4 Analyses of other endpoints

Serum total alirocumab concentrations, total and free PCSK9 concentrations will be summarized by alirocumab dose and visit using descriptive statistics. Serum concentration time profiles will be provided by alirocumab dose. Additional plots will be prepared, as deemed necessary.

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

Further details will be provided in SAP.

The ADA status (positive/negative) and ADA titers will be summarized by visit using descriptive statistics. If appropriate, correlations between ADA titers, safety, and/or efficacy endpoints will be provided by graphical methods. Further details will be provided in SAP.

11.4.5 Analyses of Patient Reported Outcomes (Health-related Quality of Life/health economics variables

Not applicable.

11.5 INTERIM ANALYSIS

There will be no interim analysis. However, analyses will be conducted at the end of the main phase to select the dose that will be used in the Phase 3 study.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

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

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

12.2 INFORMED CONSENT

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

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

In addition, participants will assent as detailed below or will follow the 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.

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

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

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

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

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

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

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

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

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

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

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

13.2 RESPONSIBILITIES OF THE SPONSOR

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

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

13.3 SOURCE DOCUMENT REQUIREMENTS

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

secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

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

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

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

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

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

13.5 USE OF COMPUTERIZED SYSTEMS

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

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

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

14.2 RECORD RETENTION IN STUDY SITES

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

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

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

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

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

14.3 CONFIDENTIALITY

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

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

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

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

14.4 PROPERTY RIGHTS

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

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

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

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

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

14.5 DATA PROTECTION

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

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

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

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

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

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

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

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

14.8.1 By the Sponsor

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

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

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

14.8.2 By the Investigator

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

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

14.9 CLINICAL TRIAL RESULTS

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

14.10 PUBLICATIONS AND COMMUNICATIONS

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

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

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

The Sponsor has the right at any time to publish the results of the study and is free to publish, and to communicate the recommendations made by the DMC, using all existing or future means of communication with an agreement between both parties.

The Steering Committee involved in the clinical trial will be responsible for the first international publication on the study.

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

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

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

Any amendment to the clinical trial protocol requires written approval/favorable opinion by the IRB/IEC prior to its implementation, unless there are overriding safety reasons. In case of substantial amendment to the clinical trial protocol, approval from the health authorities (competent regulatory authority) will be sought before implementation.

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

16 BIBLIOGRAPHIC REFERENCES

1. American Academy of Pediatrics, Committee on Nutrition. Cholesterol in childhood. Pediatrics.1998;101:141-7.

2. Goldstein JL, Hobbs HH, Brown MS. Familial hypercholesterolemia. In: Scriver CR, Beaudet AL, Valle D, Sly WS, editors. The Metabolic and Molecular Bases of Inherited Disease. 8 ed. New York, NY: McGraw-Hill,2001:2863-913.

3. Kavey RE, Allada V, Daniels SR, Hayman LL, McCrindle BW, Newburger JW, et al. Cardiovascular risk reduction in high-risk pediatric patients: a scientific statement from the American Heart Association Expert Panel on Population and Prevention Science; the Councils on Cardiovascular disease in the Young, Epidemiology and Prevention, Nutrition, Physical Activity and Metabolism, High Blood Pressure Research, Cardiovascular Nursing, and the Kidney in Heart Disease; and the Interdisciplinary Working Group on Quality of Care and Outcome Research: endorsed by the American Academy of Pediatrics. Circulation. 2006;114:2710-38.

4. De Jongh S, Lilien MR, op't Roodt J, Stroes ES, Bakker HD, Kastelein JJ. Early statin therapy restores endothelial function in children with familial hypercholesterolemia. J Am Coll Cardiol. 2002;40:2117–21.

5. Wiegman A, de Groot E, Hutten BA, Rodenburg J, Gort J, Bakker HD, et al. Arterial intima-media thickness in children heterozygous for familial hypercholesterolaemia. Lancet. 2004;363:369-70.

6. Sankatsing RR, de Groot E, Jukema JW, de Feyter PJ, Pennell DJ, Schoenhagen P, et al. Surrogate markers for atherosclerotic disease. Curr Opin Lipidol. 2005;16:434–41.

7. Newman WP 3rd, Freedman DS, Voors AW, Gard PD, Srinivasan SR, Cresanta JL, et al. Relation of serum lipoprotein levels and systolic blood pressure to early atherosclerosis. The Bogalusa Heart Study. N Engl J Med. 1986;314:138-44.

8. McGill HC Jr, McMahan CA, Zieske AW, Sloop GD, Walcott JV, Troxclair DA, et al. Associations of coronary heart disease risk factors with the intermediate lesion of atherosclerosis in youth. The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. Arterioscler Thromb Vasc Biol. 2000;20:1998-2004.

9. McGill HC, McMahan CA, Gidding SS. Preventing heart disease in the 21st century: implications of the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study. Circulation. 2008;117:1216-27.

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

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

12. National Cholesterol Education Program (NCEP): highlights of the report of the expert panel on blood cholesterol levels in children and adolescents. Pediatrics. 1992;89:495-501.

13. Daniels SR, Gidding SS, de Ferranti SD, National Lipid Association Expert Panel on Familial Hypercholesterolemia. Pediatric Aspects of Familial Hypercholesterolemias: recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol 2011;5(3 Suppl):S30-7.

14. Wiegman A, Hutten BA, de Groot E, Rodenburg J, Bakker HD, Büller HR, et al. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: a randomized controlled trial. JAMA. 2004;292:331–7.

15. Stein EA, Illingworth DR, Kwiterovich PO Jr, Liacouras CA, Siimes MA, Jacobson MS, et al. Efficacy and safety of lovastatin in adolescent males with heterozygous familial hypercholesterolemia: a randomized controlled trial. JAMA. 1999;281:137–44.

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

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

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

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

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

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

22. McKenney JM, Koren MJ, Kereiakes DJ, Hanotin C, Ferrand AC, Stein EA. Safety and Efficacy of a Monoclonal Antibody to Proprotein Convertase Subtilisin/Kexin Type 9 Serine Protease, SAR236553/REGN727, in Patients With Primary Hypercholesterolemia Receiving Ongoing Stable Atorvastatin Therapy. J Am Coll Cardiol. 2012;9:2344–53.

23. Stein EA, Gipe D, Bergeron J, Gaudet D, Weiss R, Dufour R, et al. Effect of a monoclonal antibody to PCSK9, REGN727/ SAR236553, to reduce low-density lipoprotein cholesterol

in patients with heterozygous familial hypercholesterolaemia on stable statin dose with or without ezetimibe therapy: a phase 2 randomised controlled trial. Lancet. 2012;380:29-36.

24. Note for guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals (CPMP/ICH/286/95). Available at http://www.ema.europa.eu/pdfs/human/ich/028695en.pdf.

25. Cohen JC, Boerwinkle E, Mosley TH Jr, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N Engl J Med. 2006;354:1464-72.

26. Steinberg D, Witztum JL. Inhibition of PCSK9: a powerful weapon for achieving ideal LDL cholesterol levels. Proc Natl Acad Sci U S A. 2009; 106:9546-7.

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

28. Giugliano RP, Desai NR, Kohli P, Rogers WJ, Somaratne R, Huang F etl al. LAPLACE-TIMI 57 Investigators. Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 in combination with statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57): a randomized, placebo-controlled, dose-ranging, phase 2 study. Lancet 2012; 380 (9858): 2007-17.

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

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