STATISTICAL ANALYSIS PLAN

An 8-Week Open-Label, Sequential, Repeated Dose-Finding Study to Evaluate the Efficacy and Safety of Alirocumab (SAR236553/REGN727) in Children and Adolescents with Heterozygous Familial Hypercholesterolemia Followed by an Extension Phase

SAR236553/REGN727-DFI14223

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE:	adverse event
Apo:	apolipoprotein
AST:	aspartate aminotransferase
ATC:	anatomic therapeutic chemical
BW:	body weight
CPK:	creatine phosphokinase
CV:	cardiovascular
DMC:	Data Monitoring Committee
DNA:	deoyribonucleic acid
eDISH:	evaluation of drug-induced serious hepatotoxicity
eGFR:	estimated glomerular filtration rate
HDL-C:	high density lipoprotein cholesterol
heFH:	heterozygous familial hypercholesterolemia
ie:	id est = that is
IMP:	investigational medicinal product
LDH:	lactate dehydrogenase
LDL-C:	low-density lipoprotein cholesterol
LLOQ:	lower limit of quantification
LMT:	lipid modifying therapy
Lp (a):	lipoprotein a
LS:	least square
MI:	myocardial infarction
OLDFI:	open-label dose finding
OLE:	open-label extension
P:	percentile
PD:	pharmacodynamics
PK:	pharmacokinetics
TG:	triglycerides
Total-C:	total cholesterol
ULN:	upper limit of normal range
ULOQ:	upper limit of quantification
γGT:	gamma glutamyl transferase

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

This 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).

The study consists of a main phase (Open-Label Dose Finding (OLDFI) Treatment Period of 8 weeks for the first 3 cohorts, and 12 weeks for Cohort 4) and an optional extension phase (Open-Label extension (OLE) treatment period), offered to patients who successfully completed the main phase (provided they have not experienced any permanent treatment discontinuation AEs, or had significant protocol deviations, in the investigator opinion). For Cohort 4, patients can be offered direct entry into the Phase 3 study instead of the optional OLE, depending on the time of site initiation.

After a screening period of up to 6 (+1) weeks, patients will be enrolled sequentially in the main phase into 4 separate and independent cohorts of children and adolescents with heterozygous familial hypercholesterolemia (heFH) aged of 8 to 17 years, having LDL-C≥130 mg/dL (3.37 mmol/L) on optimal stable daily dose of statin therapy with or without other lipid modifying therapies (LMTs), or on a stable dose of non-statin LMTs in case of intolerance to statins, for at least 4 weeks. Each independent cohort below will include 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.

Patients who have not been on stable LMTs for at least 4 weeks when initially seen can participate in a run-in period until LMTs dose(s) have been stable for 4 weeks and be enrolled when eligibility is confirmed. Patients suspected of having heFH without documented heFH diagnosis through genotyping or clinical criteria at screening undergo a genetic testing and can be enrolled when eligibility is confirmed.

After Cohort 1 completes the main phase, the Data Monitoring Committee (DMC) reviews the safety data and makes a recommendation on dose escalation to Cohorts 2 and 3. Cohort 4 is an independent cohort with a later start date.

For Cohorts 1- 3, the initial dose of alirocumab that will be administered during the extension phase, will be the continuation of same doses/regimens administered during the main phase up to the time when the final optimal doses for the Phase 3 study are selected and prefilled syringes

available. Then these final optimal doses will be administered to all patients during the extension phase, based on their body weight at the time of dose change.

For Cohort 4, if patients enter the OLE phase, patients will continue on their doses from the main phase.

At the end of each study phase, patients are to be followed 10 weeks after last alirocumab injection on site (for main phase, only for Cohorts 1-3 as this follow up period doesn't apply for Cohort 4) or by phone (for extension phase, for all cohorts). Patients with any adverse event (AE) should be followed until resolution, stabilization, or death, as specified in the protocol.

Approximately 40 patients (10 patients per cohort) were to be enrolled from approximately 28 sites.

1.2 OBJECTIVES

1.2.1 Primary objectives

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.

1.2.2 Secondary objectives

The secondary objectives of the study are:

- 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.

1.3 DETERMINATION OF SAMPLE SIZE

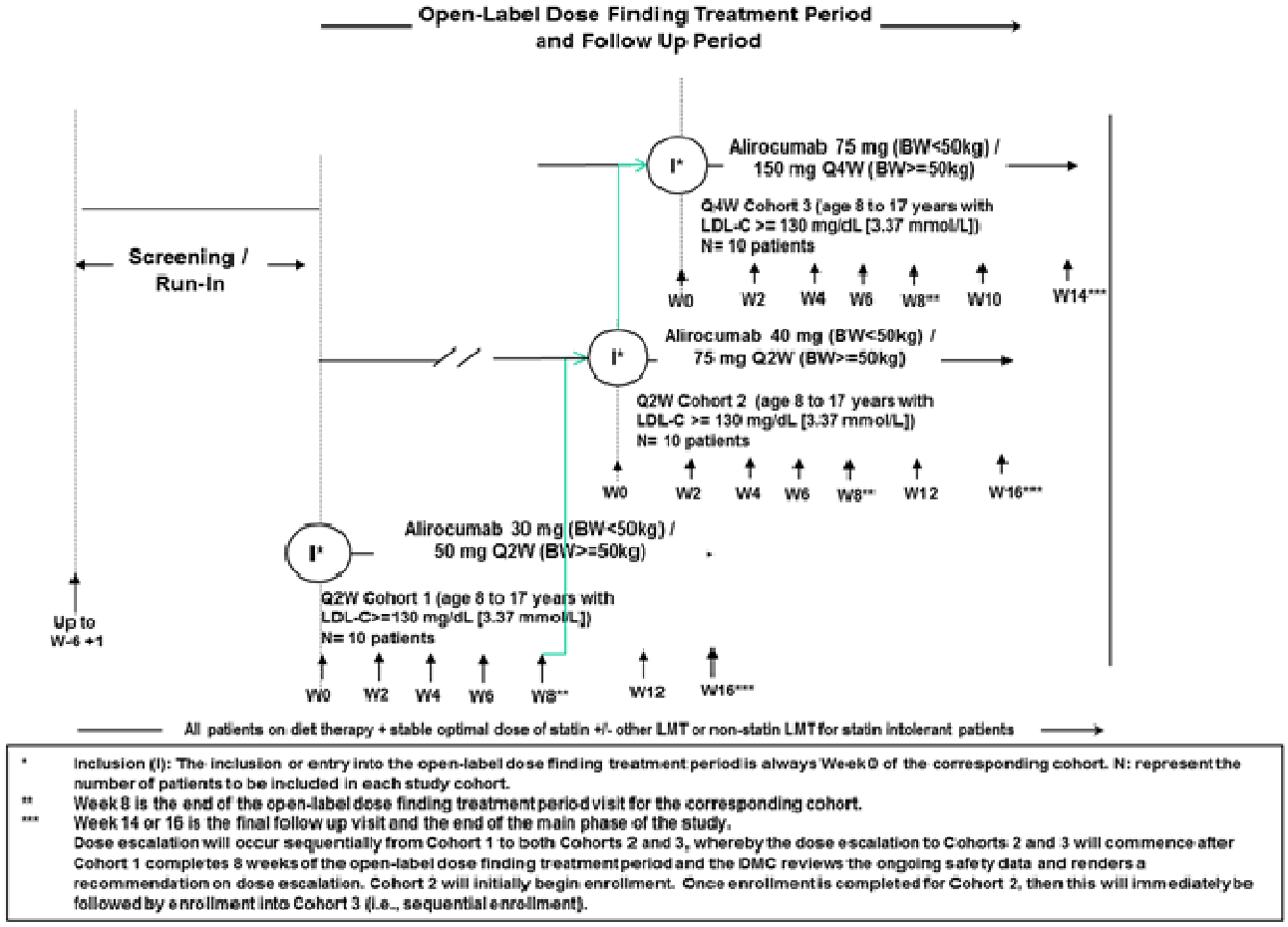
No power sample size calculations were performed for the main phase. A sample size of 10 patients per cohort is empirical and based on the sample size of the Phase 1 studies (R727-CL-904 and R727-CL-1001) conducted in adults. No less than 4 patients with BW <50 kg and no less than 4 patients with BW ≥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.

1.4 STUDY PLAN

The following figures present the graphical study design:

Figure 1 - Graphical study design (main phase, Cohorts 1 to 3)



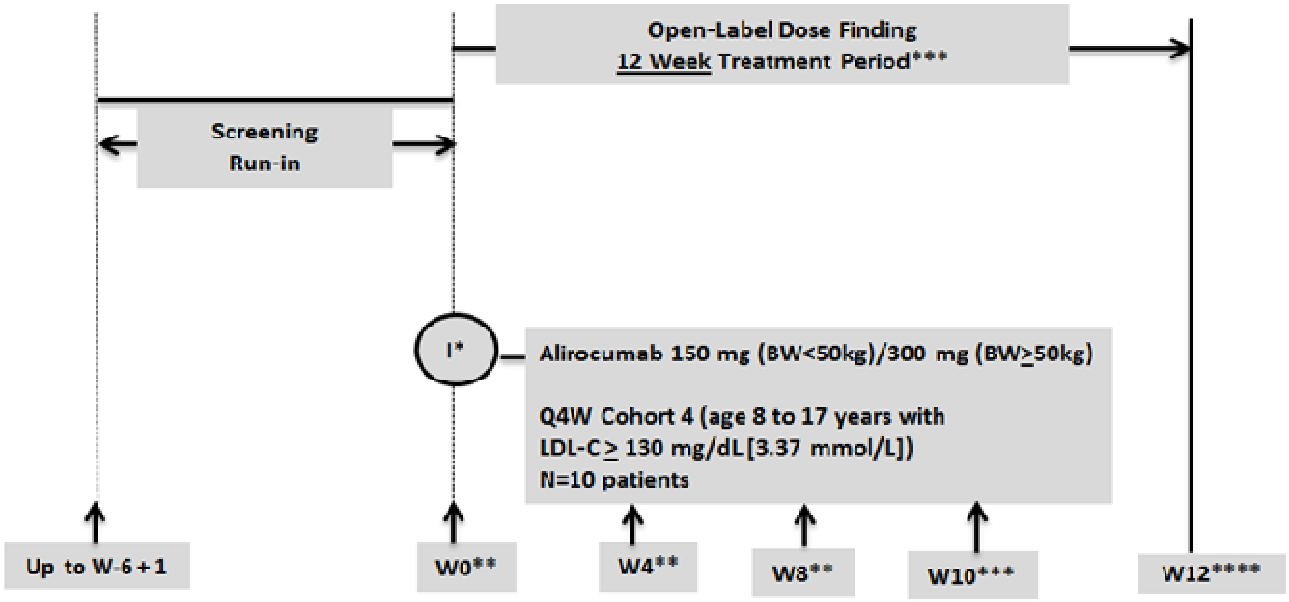
* Inclusion (I): The inclusion or entry into the open-label dose finding treatment period is always Week 0 of the corresponding cohort. N: represent the number of patients to be included in each study cohort.

** 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.

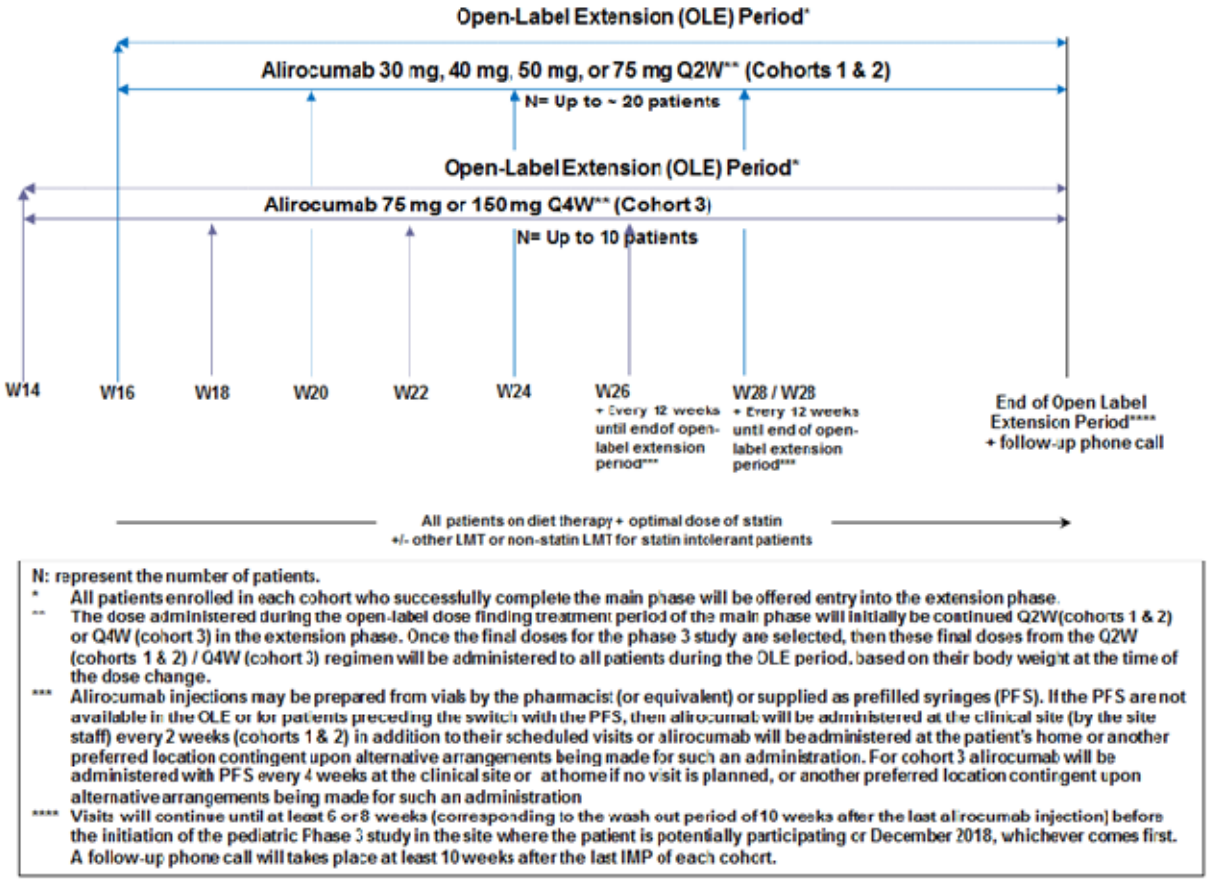
Dose escalation will occur sequentially from Cohort 1 to both Cohorts 2 and 3, whereby the dose escalation to Cohorts 2 and 3 will commence after Cohort 1 completes 8 weeks of the open-label dose finding treatment period and the DMC reviews the ongoing safety data and renders a recommendation on dose 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).

Figure 2 - Graphical study design (main phase, 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.

Figure 3 - Graphical study design (optional extension phase, Cohorts 1 to 3)



N: represent the number of patients.

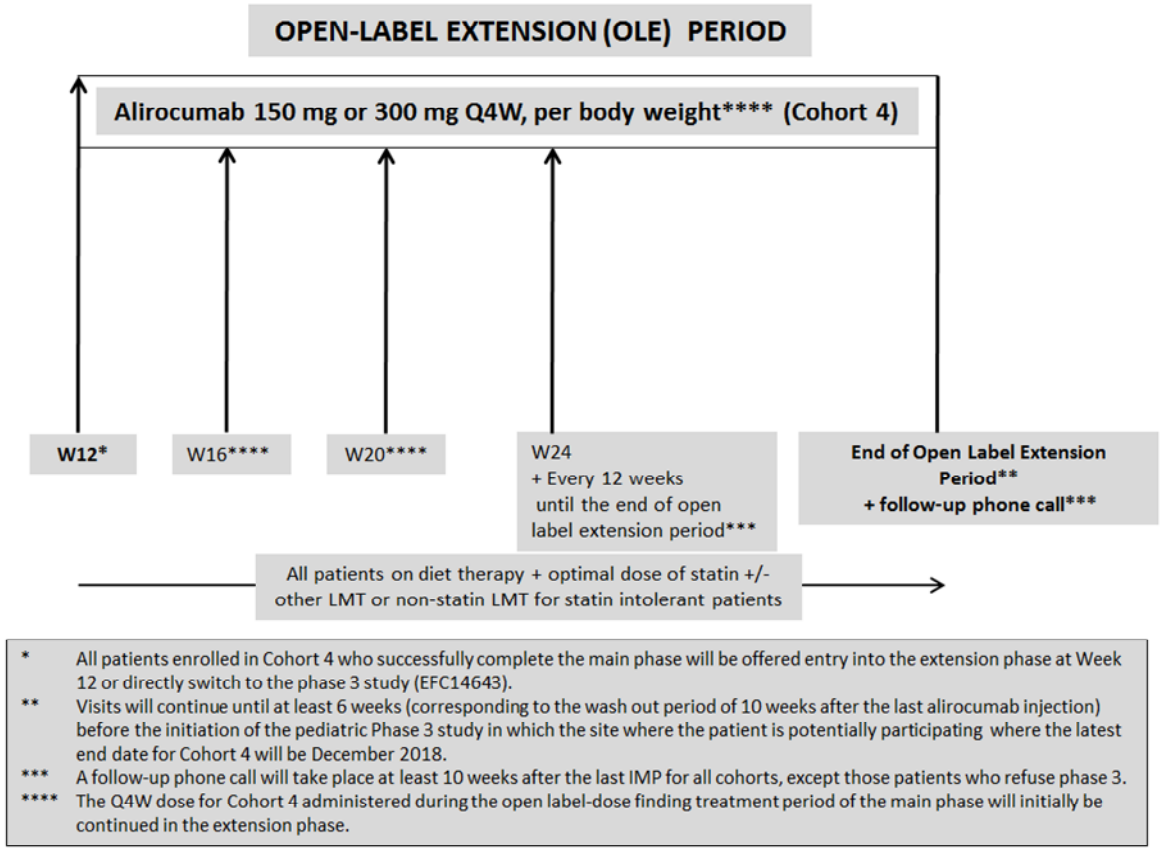
* All patients enrolled in each cohort who successfully complete the main phase will be offered entry into the extension phase.

** 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.

Figure 4 - Graphical study design (optional extension phase, 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.

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

This section summarizes major changes to the protocol statistical section.

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

The first patient was enrolled on 29-Sep-2016 and the first patient enrolled for Cohort 4 is planned on 01-May-2018.

Table 1 - Protocol amendment statistical changes

Amendment Number	Date Approved	Rationale	Description of statistical changes
1	11-Aug-2016	First step analysis was added to select the dose that will be used in the Phase 3 study	Addition of first step analysis
2	11-Dec-2017	Addition of a cohort (Cohort 4) to further evaluate the every 4 weeks (Q4W) dosing regimen at higher doses (150 mg for body weight <50 kg / 300 mg for body weight ≥50 kg)	Addition of efficacy and safety analyses for Cohort 4 data including efficacy analyses specific to Cohort 4

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

This section summarizes major changes in statistical analysis features made in approved SAP versions, with emphasis on changes after study start (after the first patient was enrolled). The statistical section of the protocol is considered as the first approved SAP.

The statistical analysis plan history table below gives the timing, rationale, and key details for major changes to the statistical analysis features in the statistical analysis plan.

Table 2 - Statistical analysis plan statistical changes

SAP version number	Date approved	Rationale	Description of statistical changes
1	15-Dec-2016	Harmonization of as-treated group definition with previous studies of the project	The alirocumab dose to be used for the as-treated analyses was changed from the dose the patient was treated with the longest duration to the dose the patient was treated with the highest number of injections (see Section 2.3.2).

SAP version number	Date approved	Rationale	Description of statistical changes
2	This version	To assess the efficacy and safety of 150 mgQ4W for body weight <50 kg / 300 mg Q4W for body weight ≥50 kg	Addition of efficacy and safety analyses for Cohort 4 data including efficacy analyses specific to Cohort 4.
	This version	To better assess the effect of the doses.	Addition of details on the handling of patients who switch to the selected doses for Phase 3.

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline value is defined as the last available value obtained up to the date and time of the first investigational medicinal product (IMP) administration in the main phase. For patients included and not treated, the baseline value is defined as the last available value obtained up to the date and time of inclusion.

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

Demographic characteristics

Demographic variables are gender (Male, Female), race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Island, Other), age in years (quantitative and qualitative variable: <10, ≥10 to <12, and ≥12 years, ethnicity (Hispanic or Latino, Not-Hispanic or Latino).

Medical or surgical history

This information will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

Medical or surgical history at the time of entry into the main phase will be presented.

Medical or surgical history includes medical history of specific interest such as cardiovascular (CV) history and cardiovascular risk factors other than hypercholesterolemia, subject medical allergic history and family medical allergic history, and relevant medical or surgical history other than CV, CV Risk and allergies. Medical history will be described using all pre-printed terms collected in the dedicated medical history e-CRF pages:

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

- Family history of Myocardial Infarction (MI) (below 50 years of age in 2nd degree relative or below 60 years of age in 1st degree relative)
- Family history of raised cholesterols (>7.5 mmol/L (290 mg/dL) in adult 1st or 2nd degree relative or >6.7 mmol/L (260 mg/dL) in child or sibling under 16 years of age)
- Tendon xanthoma in family (in 1st or 2nd degree relative)
- Familial defective apo B-100

- DNA-based evidence of an LDL receptor mutation (of the subject)
- Tendon xanthoma (of the subject)
- Subject history of raised Total-C (Total-C >6.7 mmol/l (260 mg/dL) in a child under 16 years of age OR >7.5 mmol/l (290 mg/dL) above 16; Levels either pre-treatment or highest on treatment)
- Subject history of raised LDL cholesterol (LDL cholesterol >4.0 mmol/l (155 mg/dL) in a child under 16 years OR >4.9 mmol/l (190 mg/dL) above 16; Levels either pre-treatment or highest on treatment)
- Hypertension (of the subject)
- Type 1 Diabetes (of the subject)
- Type 2 Diabetes (of the subject)

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

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

Disease characteristics at baseline

Specific disease characteristics include:

- Time from diagnosis of heFH (years);
- Confirmation of diagnosis at any time prior to or during the study (genotyping [Yes, No], Simon Broome Criteria [Definite/possible]):
  - If Yes is ticked for genotyping, time of diagnosis will be described (prior to screening, at baseline with centralized genotyping , post-baseline with centralized genotyping;
- Statin intolerant status, as per protocol definition [Yes, No]:
  - If Yes, reason the subject is statin intolerant: [Subject is not receiving a daily regimen of statin/Not tolerating daily dose, Subject unable to tolerate statins, having tried at least 2 statins: one statin at the lowest daily starting dose, AND another statin at any dose, due to skeletal muscle-related symptoms];
  - If Not statin intolerant: [Subject treated with maximal dose of statin he can tolerate due to AE at higher dose [Yes, No]:
    - If Yes, AE(s) encountered at higher doses: [Skeletal muscle related events, Liver function test abnormalities, Co-morbid conditions such as impaired glucose tolerance/impaired fasting glucose, Other].

- Type of lipid-modifying therapy ever taken by subjects age 8 to <10 years (HMG COA reductases inhibitors [statin], fibrates, bile acid sequestrant, cholesterol absorption inhibitor, nicotinic acid and derivates, omega 3 fatty acids ≥1000 mg/day, other);
- Background lipid modifying therapy at enrollment, as reported in the dedicated prior & concomitant medications e-CRF pages:
  - Atorvastatin daily dose in mg (<10, 10, 20, >20, Other);
  - Rosuvastatin daily dose in mg (<5, 5, 10, 20, >20, Other);
  - Simvastatin daily dose in mg (<10, 10, 20, 40, >40, Other) ;
  - Pravastatin daily dose in mg (<10, 10, 20, 40, >40, Other);
  - Lovastatin daily dose in mg (<10, 10, 20, 40, >40, Other);
  - Fluvastatin daily dose in mg (<20, 20, 40, 80, >80, Other);
  - Pitavastatin (at any dose);
- Any LMT other than statins
  - Any LMT other than nutraceuticals (by chemical class and drug name) including fenofibrate and ezetimibe or other non-Statin LMT;
  - Nutraceuticals (Omega 3 fatty acids (<1000mg/day), Phytosterols, Psyllium/plantago, Policosanol, Other nutraceuticals);

Other baseline characteristics

Other baseline characteristics include body mass index (BMI) in kg/m² (quantitative and qualitative variable using BMI percentiles defined according to age for boys and girls: <P5: Underweight, ≥P5 to <P85: Healthy weight, ≥P85 to <P95: Overweight and ≥P95: Obesity using the World Health Organization (WHO) growth reference 5-19 years **(**1, 2, 3), smoking status and alcohol habits.

Efficacy lipid parameters (quantitative variables for all efficacy parameters and the following qualitative variables) will be also summarized at baseline (see definition in Section 2.1.1):

- Calculated LDL-C: <130, ≥130 to <160, ≥160 to <190, ≥190mg/dL, ie, <3.37, ≥3.37 to <4.14, ≥4.14 to <4.91, ≥4.91 mmol/L;
- HDL-C: <40 , ≥40 mg/dL, ie <1.04 , ≥1.04 mmol/L;
- Non-HDL-C: <160, ≥160 to <190, ≥190 to <220, ≥220 mg/dL (ie, <4.14, ≥4.14 to <4.91, ≥4.91 to 5.69, ≥5.69 mmol/L);
- Fasting TGs: <150, ≥150 to <200, ≥200 mg/dL, category ≥150 mg/dL (mixed dyslipidaemia) will be also displayed, ie, <1.7 , ≥1.7 to <2.3, ≥2.3 mmol/L;
- Lp(a): <30, ≥30 to <50, ≥50 mg/dL, category ≥30 mg/dL will be also displayed, ie, <0.3, ≥0.3 to <0.5, ≥0.5 g/L;
- Apo B: <75, ≥75 to <90, ≥90 mg/dL (ie, <0.75, ≥0.75 to <0.9, ≥0.9 g/L).

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

2.1.2 Prior or concomitant medications

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

- Previous and concomitant statin drugs;
- Previous and concomitant lipid modifying therapies excluding statin;
- Previous and concomitant medications (other than statin, lipid modifying therapies and anesthetic used for any reasons including IMP injection, blood sampling or surgery);
- Topical anesthetic for IMP injection only.

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

- Prior medications are those the patient used within 12 weeks prior to screening visit and prior to first OLDFI IMP administration. Prior medications can be discontinued before first administration or can be ongoing during treatment phase.
- OLDFI concomitant medications are any treatments received by the patient concomitantly with the IMP, from first OLDFI IMP to the last OLDFI IMP injection +70 days. For patients entering in the OLE, concomitant medications will be truncated at the day before first OLE IMP injection. A given medication can be classified both as a prior medication and as a concomitant medication.
- Post-treatment OLDFI medications are those the patient took in the period starting from 71 days after the last OLDFI IMP injection. . For patients entering in the OLE, post-treatment OLDFI medications will be truncated at the day before first OLE IMP injection.
- In addition concomitant medications for the entire study combining main phase and extension phase (OLDFI/OLE combined period) will be summarized and are defined as any treatments received by the patient from the first OLDFI IMP injection to the last OLE IMP injection (or to last OLDFI IMP injection for patients not entering into the extension phase) +70 days.
- Post-treatment medications for the OLDFI/OLE combined period are those the patient took in the period starting from 71 days after the last OLE IMP injection (or after last OLDFI IMP injection for patients not entering into the extension phase).

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

2.1.3 Efficacy endpoints

Efficacy parameters include lipid parameters (ie, Total-C, calculated LDL-C, measured LDL-C, HDL-C, TGs, non-HDL-C, Apo B , Apo A-1, ratio Apo B/Apo A-1, Lp (a)). All these parameters are measured or calculated by a Central Laboratory, for both scheduled and unscheduled time points. Calculated LDL-C is obtained using the Friedewald formula. Non-HDL-C is calculated by subtracting HDL-C from the Total-C. If TG values exceed 400 mg/dL (4.52 mmol/L), the LDL-C should be measured by the Central Laboratory (via beta quantification method) rather than calculated. All measured LDL-C values provided by the Central Laboratory will not be used for the analysis of calculated LDL-C endpoints.

Unless otherwise specified, all lipid values (scheduled or unscheduled, fasting or not fasting) may be used to provide a value for the efficacy endpoints. All measurements, scheduled or unscheduled, fasting or not fasting, will be assigned to analysis windows defined in Section 2.5.4 Table 3 and Table 4 in order to provide an assessment for time points when the lipid values were to be collected as per protocol. For TGs, only fasting measurements will be used. Measurements with missing fasting status will be excluded from the analyses.

For all time points post baseline, the value used for the analyses at a given time point is the value obtained within the corresponding analysis window.

The baseline value is defined as the last available value obtained up to the date and time of the first OLDFI IMP administration. For patients included and not treated, the baseline value is defined as the last available value obtained up to the date and time of inclusion.

2.1.3.1 Primary efficacy endpoint(s)

The primary efficacy endpoint is the percent change in calculated LDL-C from baseline to Week 8 in the mITT population, using all calculated LDL-C values during the OLDFI efficacy treatment period defined in Section 2.3.1 (on-treatment estimand). Primary endpoint is defined as: 100x (calculated LDL-C value at Week 8 - calculated LDL-C value at baseline) / calculated LDL-C value at baseline.

2.1.3.2 Secondary efficacy endpoint(s)

The secondary efficacy endpoints are:

- The absolute change in calculated LDL-C from baseline to Week 8 (on-treatment estimand);
- The percent change in LDL-C from baseline to Week 12 only for Cohort 4 (on-treatment estimand);
- The percent change in Apo B, non-HDL-C, Total-C, Lp(a), HDL-C, TG, and Apo A-1 from baseline to Week 8 (on-treatment estimand);
- The proportion of patients reaching calculated LDL-C <130 mg/dL (3.37 mmol/L) at Week 8 (on-treatment estimand);

- The proportion of patients achieving calculated LDL-C level <110 mg/dL (2.84 mmol/L) at Week 8 (on-treatment estimand);
- The absolute change in Apo B, non-HDL-C, Total-C, Lp(a), HDL-C, TG, Apo A-1, and ratio Apo B/Apo A-1 from baseline to Week 8 (on-treatment estimand).

2.1.4 Safety endpoints

The safety analyses will be based on the reported adverse events (AEs) and other safety information, such as clinical laboratory data, vital signs, and tanner stage assessment.

Observation period

The period of safety observation starts from the time when the patient gives informed consent and is divided into the following periods:

- The PRE-TREATMENT period: defined as the time from the signed informed consent up to the first dose of IMP injection in the study;
- The OLDFI treatment-emergent adverse event (TEAE) period: defined as the time from the first OLDFI IMP injection up to the day of last OLDFI IMP injection + 70 days (10 weeks) as residual effect of alirocumab is expected until 10 weeks after discontinuation. For patients entering in the OLE, the OLDFI TEAE period will be truncated at the day before the first OLE IMP injection in the extension period;

  The OLDFI TEAE period will include:

  - The OLDFI TREATMENT period: defined as the time from the first OLDFI IMP injection up to the day of last OLDFI IMP injection + 21 days (for Cohorts 1 & 2) or + 35 days (for Cohort 3 & 4) . For patients entering in the OLE, the OLDFI treatment period will truncated at the day before the first OLE IMP injection in the extension period
- The OLDFI POST-TREATMENT period defined as the time starting the day after the end of OLDFI TEAE period. For patients entering in the OLE, the OLDFI POST-TREATMENT period will be truncated at the day before the first OLE IMP injection in the extension period;
- The OLDFI/OLE combined TEAE period: defined as the time from the first OLDFI IMP injection up to the day of last OLE IMP injection (or to last OLDFI IMP injection for patients not entering into the extension phase) + 70 days ;

  The OLDFI/OLE combined TEAE period will include:

  - The OLDFI/OLE combined TREATMENT period defined as the time from the first OLDFI IMP injection up to the day of last OLE IMP injection (or to last OLDFI IMP injection for patients not entering into the extension phase) + 21 days (for Cohorts 1 to 2) or + 35 days (for Cohorts 3 & 4). For patients from Cohort 3 who switched to selected Phase 3 doses, the OLDFI/OLE combined TREATMENT period is defined as

the time from the first OLDFI IMP injection up to the day of last OLE IMP injection + 21 days.

- The OLDFI/OLE combined POST-TREATMENT period defined as the time starting the day after the end of the OLDFI/OLE combined TEAE period.

The OLDFI on-study observation period is defined as the time from the day of first OLDFI IMP injection until the last protocol planned OLDFI visit of the patient. The last protocol planned OLDFI visit is defined as the final follow-up visit if done, else 10 weeks after last OLDFI IMP injection.

The OLDFI/OLE combined on-study observation period is defined as the time from the first OLDFI IMP injection until the last protocol planned visit of the patient. The last protocol planned visit is the final follow-up visit in OLDFI period for patients not proceeding into OLE period or in OLE period for patients proceeding into OLE period.

2.1.4.1 Adverse events variables

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

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

Adverse event observation period

- Pre-treatment AEs are AEs that developed or worsened or became serious during the pre-treatment period.
- OLDFI treatment-emergent adverse events are AEs that developed or worsened or became serious during the OLDFI TEAE period.
- OLDFI post-treatment AEs are AEs that developed or worsened or became serious during the OLDFI post-treatment period.
- OLDFI/OLE combined treatment-emergent adverse events are AEs developed or worsened or became serious during the OLDFI/OLE combined TEAE period.
- OLDFI/OLE combined post-treatment AEs are AEs that developed or worsened or became serious during the OLDFI/OLE combined post-treatment period.

Groupings of Adverse events

Grouping of Adverse events include the following:

- Local injection site reactions (AESIs or not), selected using e-CRF specific tick box on the adverse event page

- Allergic events
  - General allergic events (AESIs or not), selected using SMQ “hypersensitivity” (broad and narrow) excluding the following preferred terms linked to local injection site reactions (“infusion site dermatitis”, “infusion site hypersensitivity”, “infusion site rash”, “infusion site urticaria”, “injection site dermatitis”, “injection site hypersensitivity”, “injection site rash”, “injection site urticaria”, and “injection site vasculitis”)
  - General allergic events (AESIs or not) and local allergic reactions at IMP injection site will be described. This selection will be based on the above selection for general allergic event and on the following selection of PT from the symptoms complementary form for local injection site reaction ("Injection site dermatitis", "Injection site hypersensitivity", "Injection site oedema", "Injection site rash", "Injection site urticaria", "Injection site eczema", "Injection site vasculitis", "Injection site swelling", "Infusion site dermatitis", "Infusion site hypersensitivity", "Infusion site oedema", "Infusion site rash", "Infusion site urticaria", "Infusion site swelling")
- ALT >3 ULN, selected using laboratory data
- Neurologic events (AESIs or not), selected using a CMQ based on SMQs “demyelination” (broad and narrow), “peripheral neuropathy” (broad and narrow), and “Guillain-Barre syndrome” (broad and narrow) excluding the following preferred terms “acute respiratory distress syndrome”, “asthenia”, “respiratory arrest” and “respiratory failure” and including selected PTs from SMQ "optic nerve disorders" (see Table 6 for the list of terms)
- Neurocognitive events:
  - Selected using a CMQ, based on the following 5 HLGTs: “deliria (including confusion)”, “cognitive and attention disorders and disturbances”, “dementia and amnestic conditions”, “disturbances in thinking and perception”, and “mental impairment disorders”
  - A second grouping of terms for neurocognitive events was defined based on Regulatory Agency request (see Table 7 for the list of terms)
- Symptomatic overdose of IMP, selected using appropriate MedDRA codes and the tick boxes “Overdose of Alirocumab” and “Symptomatic Overdose” in the overdose adverse event form
- Pregnancy (including male patient’s partner) selected using appropriate MedDRA codes

Analyses of allergic and neurologic events will also be provided using the tick box on the e-CRF AE page as a second approach.

In addition the additional grouping of events will be provided:

- Hepatic disorder events using SMQ “Hepatic disorder”
- Diabetes mellitus or diabetic complications using HLGT “diabetes complications” (including PTs pertaining to the secondary SOC included in the HLGT), HLT “diabetes

mellitus", and HLT "carbohydrate tolerance analyses (incl diabetes)" excluding PTs "blood glucose decreased" and "Glycosylated haemoglobin decreased" and including the PTs "hyperglycaemia", "Hyperglycaemic unconsciousness" and "Hyperglycaemic seizure" from the HLT "Hyperglyceamic conditions NEC"

- Cataract using HLT "Cataract conditions"

2.1.4.2 Deaths

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

- Death on-study during OLDFI period: deaths occurring during the OLDFI on-study observation period,
- Death on-treatment during OLDFI period: deaths occurring during the OLDFI TEAE period,
- Death on-study during the OLDFI/OLE combined period: deaths occurring during the OLDFI/OLE combined observation period,
- Death on-treatment during the OLDFI/OLE combined treatment periods: deaths occurring during the OLDFI/OLE combined TEAE period,
- Death post-study: deaths occurring after the last planned protocol visit.

2.1.4.3 Laboratory safety variables

Clinical laboratory data consist of blood analysis, including hematology and clinical chemistry, fat soluble vitamins, gonadal hormones, pituitary hormones, and adrenal gland hormones . Clinical laboratory values will be analyzed into international units. Clinical laboratory values converted into conventional (US) units will be also available in the database. Analyses can be provided upon request. Unless otherwise specified below, blood samples for clinical laboratories were to be collected during:

- Screening at Visit 1 (up to Week -6),
- The OLDFI period at Visit 2 (Week 0), Visit 4 (Week 4), Visit 6 (Week 8)) or early termination , and during the follow-up visit [Visit 8 (Week 14 for Cohort 3 or Week 16 for Cohorts 1& 2)] (for pregnancy test or in case of abnormality at the visit 6 in hematology and chemistry parameters),
- The OLE period at Visit 8 (Week 16 for Cohorts 1& 2 or Week 14 for Cohort 3)], Visit 11 (Week 28 for Cohorts 1& 2 or Week 26 for Cohort 3 or Week 24 for Cohort 4), Visit 13 (Week 52 for Cohorts 1& 2 or Week 50 for Cohort 3 or Week 48/ end of OLE period for Cohort 4), Visits 15, 17, 19 (every 24 weeks for Cohorts 1 to 3) and Visit 20 (Week 130/ end of OLE period for Cohorts 1 to 3 or early termination during OLE period for all cohorts).

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

- Hematology
  - **Red blood cells and platelets**: hemoglobin, hematocrit, red blood cell count, platelet count;
  - **White blood cells**: white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils.
- Clinical chemistry
  - **Metabolism:** glucose, total protein, albumin, creatine phosphokinase (CPK);
  - **Electrolytes:** sodium, potassium, chloride, calcium, phosphorus, bicarbonate;
  - **Renal function:** creatinine, eGFR, blood urea nitrogen, uric acid;
  - **Liver function:** alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase (γGT), lactate hydrogenase (LDH), total bilirubin, and in case of total bilirubin values above the normal range, must include conjugated and non-conjugated bilirubin (used for describing individual cases only).
- **Adrenal gland hormones:** cortisol (with reflexive 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**: blood test at screening visit and local urine pregnancy test for all other tests.

Technical formulas are described in Section 2.5.1.

2.1.4.4 Vital signs variables

Vital Signs parameters include Weight, Heart Rate (HR), Systolic and Diastolic Blood Pressure (SBP and DBP) in sitting position and were to be measured during:

- Screening at Visit 1 (up to Week -6),
- The OLDFI period at Visit 2 (Week 0), Visit 4 (Week 4)), Visit 6 (Week 8) for Cohorts 1 to 4 or early termination (for Cohorts 1 to 3), and Visit 8 (follow-up visit for Cohorts 1 to 3, Week 14 for Cohort 3 or Week 16 for Cohorts 1& 2, and Week 12 or early termination for Cohort 4,

- The OLE period at Visit 8 (Week 16 for Cohorts 1& 2 or Week 14 for Cohort 3, or Week 12 for Cohort 4), Visit 12 (Week 40 for Cohorts 1& 2 or Week 38 for Cohort 3 or Week 36 for Cohort 4), Visit 13 (Week 48/ end of OLE period for Cohort 4), Visits 14, 16, 18 (every 24 weeks for Cohorts 1 to 3) and Visit 20 (Week 130/ end of OLE period for Cohorts 1 to 3 or early termination during OLE period for all cohorts).

2.1.4.5 Electrocardiogram variables

Not Applicable.

2.1.4.6 Tanner stages measurement

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

- Screening at Visit 1 (up to Week -6)
- The OLDFI period at Visit 8 (follow-up visit for Cohorts 1 to 3, Week 14 for Cohort 3 or Week 16 for Cohorts 1& 2) or Week 12 or early termination for Cohort 4,
- The OLE period at Visit 8 (Week 16 for Cohorts 1& 2 or Week 14 for Cohort 3 or Week 12 or early termination for Cohort 4), Visit 12 (Week 40 for Cohorts 1& 2 or Week 38 for Cohort 3 or Week 36 for Cohort 4), Visit 13 (Week 48/ end of OLE period for Cohort 4), Visits 14, 16, 18 (every 24 weeks) and Visit 20 (Week 130/ end of OLE period for Cohorts 1 to 3 or early termination during OLE period for all cohorts).

2.1.4.7 Other endpoints

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

- The proportion of patients with two consecutive results, spaced out by at least 21 days, of LDL-C <50 mg/dL (<1.30 mmol/L) and (calculated LDL-C <25 mg/dL ie, <0.65 mmol/L) respectively during OLDFI period or the OLDFI/OLE combined period
- The time to the first LDL-C <50 mg/dL (respectively, calculated LDL-C <25 mg/dL) for these patients within the relevant analysis period specified above.

2.1.4.8 Anti-alirocumab antibodies variables

Anti-alirocumab antibodies (ADA) are assessed:

- At baseline (see Section 2.1.1 for definition)
- During the OLDFI period at Week 8 or early termination and during follow-up (Week 16 for Cohorts 1& 2 or Week 14 for Cohort 3) and Week 12 for Cohort 4

- During the OLE period at Visit 8 (Week 16 for Cohorts 1& 2 or Week 14 for Cohort 3 or Week 12 for Cohort 4), Visit 11 (Week 28 for Cohorts 1& 2 or Week 26 for Cohort 3 or Week 24 for Cohort 4), Visit 13 (Week 52 for Cohorts 1& 2 or Week 50 for Cohort 3 or Week 48/ end of OLE period for Cohort 4), Visits 15, 17, 19 (every 24 weeks) and Visit 20 (Week 130/ end of OLE period for Cohorts 1 to 3 or early termination during OLE period for all cohorts).

ADA measurements will be assigned to the same analysis windows as defined for efficacy endpoints (Table 3 and Table 4).

The following variables will be described for both OLDFI period and the OLDFI/OLE combined period:

- ADA response (Positive or Negative).

  For ADA positive:

  - Titer levels
  - Neutralizing status (Positive or Negative)
- Pre-existing positive ADA defined as patients with positive ADA response at baseline with less than 4-fold increase in titer in the post-baseline period
- Treatment-emergent positive ADA response defined as
  - Patients with no ADA positive response at baseline but with any positive response in the post-baseline period (for OLDFI period: up to follow-up visit, for the OLDFI/OLE combined period: up to end of OLE period); OR
  - Patients with a positive ADA response at baseline and at least a 4-fold increase in titer in the post-baseline period (for OLDFI period: up to follow-up visit, for the OLDFI/OLE combined period: up to end of OLE period).
  - For treatment-emergent positive ADA, the following categories for ADA duration will be applied for the analysis performed on the OLDFI/OLE combined period:
  - A persistent positive response is a treatment-emergent ADA positive response detected in at least 2 consecutive post-baseline samples separated by at least a 12-week period
  - An indeterminate duration positive response is defined as ADA present only at the last sampling time point
  - A transient positive response is defined as any treatment-emergent positive ADA response that is neither considered persistent nor indeterminate

In addition, potential ADA samples to be collected in case of ADA titer >=240 at the last measurement for patients not entering to the OLE phase, or for patients proceeding into OLE phase but not entering into the Phase 3 study will be listed.

2.1.5 Pharmacokinetic variables

Concentrations of total alirocumab, total and free PCSK9 in serum are assessed before IMP (pre-dose) at baseline (Week 0), Week 4, Week 8, Week 10 (for Cohort 4), Week 12 (for Cohort 4) and end of the follow-up period of OLDFI period (Week 16 for Cohorts 1& 2 or Week 14 for Cohort 3).

Pharmacokinetic variable is the total alirocumab concentration at each time point. Depending on the timing of the sample versus the previous injection, Ctrough, Cmax and CFollow-Up will be defined as follows (see also Table 3):

- Cmax for Q2W and Q4W regimens: alirocumab concentration sample taken 5 days ±2 days after previous injection of alirocumab;
- Ctrough for Q2W regimen: alirocumab concentration sample taken between 8 and 21 days after previous injection of alirocumab (may be just prior the next injection);
- Ctrough for Q4W regimen: alirocumab concentration sample taken between 22 and 35 days after previous injection of alirocumab (may be just prior the next injection);
- CFollow-up for Q2W regimen: alirocumab concentration sample taken more than 21 days after last injection of alirocumab and no more than 14 weeks after last injection of alirocumab.
- CFollow-up for Q4W regimen: alirocumab concentration sample taken more than 35 days after last injection of alirocumab and no more than 14 weeks after last injection of alirocumab.

Alirocumab concentration and total and free PCSK9 concentration will be described by time-point following time windows as defined in Table 3 and Table 5.

2.1.6 Pharmacogenetic endpoints

Not Applicable.

2.1.7 Quality-of-life endpoints

Not Applicable.

2.1.8 Health economic endpoints

Not Applicable.

2.2 DISPOSITION OF PATIENTS

This section describes patient disposition for both patient study status and the patient analysis populations, for OLDFI period and for OLDFI/OLE combined period.

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

Included patients consist of all screened patients enrolled in the OLDFI period (patients not screened failed).

For patient study status in the OLDFI period, the total number of patients in each of the following categories will be presented in the clinical study report:

- Screened patients
- Screen failure patients and reasons for screen failure
- Included patients
  - Included but not treated patients and reason for not being treated;
  - Included and treated patients
- Patients who completed the OLDFI treatment period as per protocol
- Patients who did not complete the OLDFI treatment period as per protocol
- Patients who discontinued the OLDFI treatment by main reason for permanent treatment discontinuation
- Status at last study contact for patients not entering in the OLE period
- Patients participating in the OLE period

For all categories of patients (except for the screened categories) percentages will be calculated using the number of included patients as denominator.

In addition, patient study status in the OLE period will be provided: the total number of patients in each of the following categories will be presented:

- Patients treated during the OLE period (all patients who received at least one OLE IMP injection during the OLE period)
- Patients who completed the OLE treatment period as per protocol
- Patients who did not complete the OLE treatment period as per protocol
- Patients who discontinued OLE treatment by main reason for permanent treatment discontinuation

Patient with insufficient post-treatment follow-up will be described for each analysis study treatment period.

A patient is considered with insufficient post-treatment follow-up or without post-treatment follow-up in the following cases:

- If the patient is not assessed at the post-treatment follow-up phone call (for OLE period)/ final follow-up visit (for OLDFI period), or any on-site post-treatment visit

- If the patient has no follow-up phone call (for OLE period) or on-site post-treatment visit more than 9 weeks after the last IMP injection of the corresponding period.

All major deviations potentially impacting efficacy analyses, inclusion and drug-dispensing irregularities, and other important deviations will be summarized in tables giving numbers and percentages of deviations. These deviations are listed in the centralized monitoring plan.

Additionally, the following populations will be summarized:

- Included population.
- Efficacy population: mITT population
- Safety population
- Pharmacokinetics population
- Anti-alirocumab antibody population

Definitions of the study populations are provided in Section 2.3.

2.2.1 Enrollment and drug dispensing irregularities

Enrollment and drug-dispensing irregularities occur whenever:

1. An enrollment is not in accordance with the protocol-defined enrollment method, such as, a) a patient is enrolled twice.

   OR

2. A patient is dispensed an IMP kit not allocated by the protocol-defined allocation, such as a) a patient at any time in the study is dispensed a different treatment kit than as allocated (which may or may not contain the correct-as-allocated IMP).

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

All enrollment and drug-dispensing irregularities will be documented in the clinical study report. among included patients.

Enrollment and drug-dispensing irregularities to be prospectively identified include but are not limited to:

Enrollment and drug allocation irregularities
Kit dispensation without IRT transaction
Erroneous kit dispensation
Kit not available
Enrolled by error
Patient enrolled twice

2.3 ANALYSIS POPULATIONS

Included population: includes all included patients as defined in Section 2.2.

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.

2.3.1 Efficacy populations

The primary efficacy analysis population for OLDFI period and for the OLDFI/OLE combined period will be the mITT population.

2.3.1.1 Modified intent-to-treat population

The modified ITT (mITT) population includes all included patients who received at least one dose or partial dose of IMP injection and had an evaluable primary endpoint during the OLDFI efficacy treatment period. The primary endpoint will be considered as evaluable when both following conditions are met:

- Availability of baseline calculated LDL-C value.
- Availability of at least one calculated LDL-C value during the OLDFI efficacy treatment period and within one of the analysis windows up to Week 8 analysis window.

The OLDFI efficacy treatment period is defined as the period from the first IMP injection to last OLDFI IMP injection + 21 days (for Cohorts 1 & 2) or +35 days (for Cohorts 3 & 4). For patients entering in the OLE, the OLDFI efficacy treatment period will be truncated at the day before the first OLE IMP injection in the extension period.

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

2.3.2 Safety population

The Safety population considered for safety analyses in the OLDFI period and in OLDFI/OLE combined period will be the included population who actually received at least one dose or part of a dose of the IMP injection. Patients will be analyzed according to the dose of alirocumab actually received (ie, as-treated dose group, alirocumab 30 mg Q2W, alirocumab 40 mg Q2W, alirocumab 50 mg Q2W, alirocumab 75 mg Q2W, alirocumab 75 mg Q4W, alirocumab 150 mg Q4W [BW <50 kg], alirocumab 150 mg Q4W [BW ≥50 kg] or alirocumab 300 mg Q4W).

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 IVRS.

- For patients receiving the 2 alirocumab doses planned for the cohort during the treatment period (cases reported as protocol deviation), the alirocumab dose used for as-treated analysis will be the one to which the patient was treated with the highest number of injections; in case of the same number of injections of each dose received the as-treated dose will be the as-randomized dose.

2.3.3 Anti-alirocumab antibody population

The anti-alirocumab antibody (ADA) analyses in the OLDFI period and in the OLDFI/OLE combined period will be performed on all included and treated patients (safety population) with a blood sample on Week 0 (baseline) and at least one evaluable blood sample for antibodies post first IMP injection and up to the end of OLDFI period for patients not entering into OLE period, or up to end of OLE for patients proceeding into OLE period.

2.3.4 Pharmacokinetics population

The PK analysis in the OLDFI period will be performed on all included and treated patients (safety population) with at least one evaluable PK sample post first OLDFI IMP injection and up to the end of OLDFI period or first OLE IMP injection for patients proceeding into OLE period.

2.4 STATISTICAL METHODS

Statistical results will be presented for OLDFI period and for the OLDFI/OLE combined period with the exception of PK only assessed during OLDFI period.

For the OLDFI period, results will be presented by cohort and alirocumab dose group within each cohort and overall for demographic and baseline characteristics.

For Cohorts 1 to 3, two separate analyses will be performed for the OLDFI/OLE combined period:

- The first analysis will be truncated at the time before the switch to Phase 3 dose (s). This analysis will be presented by cohort and alirocumab dose group within each cohort;
- The second analysis will include data from the switch of Phase 3 dose(s) up to the end of OLE period and will be presented using selected Phase 3 doses regardless of doses previously received.

For Cohort 4, a single analysis will be performed for the OLDFI/OLE combined period since the patients from Cohort 4 who will enter the OLE phase will continue on their doses from main phase.

All summary tables will be provided for OLDFI period and for the combined analysis truncated at the time of the switch to Phase 3 dose (s) for Cohorts 1 to 3. For the analyses of the data from the switch, listings may be preferred to summary tables depending on the duration of follow-up and the amount of data post-switch.

2.4.1 Demographics and baseline characteristics

Parameters described in Section 2.1.1 will be summarized in patients included and treated (ie, safety population) according to the alirocumab dose group allocated by IVRS.

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

All reported patient's medical and surgical history will be presented by primary SOC and HLT. The tables will be sorted by SOC internationally agreed order and decreasing frequency of HLT based on the incidence in the whole population (all cohorts combined). In addition all medical history of specific interest (see Section 2.1.1) will also be presented.

2.4.2 Prior or concomitant medications

The prior, concomitant and post-treatment medications will be presented for the safety population.

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

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

The tables for concomitant and post-treatment medications will be sorted by decreasing frequency of ATC followed by therapeutic class based on the overall incidence across alirocumab doses groups from the Cohort 4 (all doses combined). In case of equal frequency across anatomic or therapeutic categories, alphabetical order will be used.

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

LMT (statins and other LMTs) use after enrollment will be summarized over time during OLDFI period graphically by LMTs intensity at enrollment using the following categories:

- Statin
- Only LMT other than statin
- No LMT

The LMTs intensity at enrollment is defined as:

- Statin
- Only LMT other than statin

2.4.3 Extent of investigational medicinal product exposure and compliance

The extent of IMP exposure and compliance will be summarized for the safety population using as-treated alirocumab dose group.

2.4.3.1 Extent of investigational medicinal product exposure

The total exposure to IMP will be assessed using the following parameters:

- Duration of OLDFI IMP injection exposure in weeks defined as (date of last OLDFI IMP injection– date of first OLDFI IMP injection + 14 days)/7 (for Cohorts 1& 2) or (date of last OLDFI IMP injection – date of first OLDFI IMP injection + 28 days)/7 (for Cohorts 3 & 4), regardless of unplanned intermittent discontinuations.
- The total number of OLDFI IMP injections by patient.
- For Cohorts 1 to 3, and for the OLDFI/OLE combined period the following parameters will be derived up to, and post switch of dose:
  - Duration of OLDFI/OLE combined period IMP injection exposure up to the switch to Phase 3 doses in weeks, defined as (date of last IMP injection up to the switch – date of first IMP injection + 14 days)/7 (for Cohorts 1& 2) or (date of last IMP injection up to the switch – date of first IMP injection + 28 days)/7 (for Cohorts 3 & 4), regardless of unplanned intermittent discontinuations.
  - Duration of IMP injection exposure post switch in weeks, defined as: (date of last IMP injection +14 – date of first IMP injection post switch)/7, regardless of intermittent discontinuations.
  - Total number of OLDFI/OLE combined period IMP injections up to, and post switch of dose.
- For Cohort 4, and for the OLDFI/OLE combined period, the following parameters will be derived:
  - Duration of OLDFI/OLE combined period IMP injection exposure in weeks, defined as (date of last IMP injection – date of first IMP injection + 28 days)/7, regardless of unplanned intermittent discontinuations.
  - Total number of OLDFI/OLE combined period IMP injections.
- For duration of IMP injection exposure calculation, see Section 2.5.3 for calculation in case of missing or incomplete data. Non-integer values will be rounded to one decimal place.

Duration of OLDFI IMP exposure will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum) and categorically using the following categories: ≥1 day to <1 week, ≥1 to <3 weeks, ≥3 to <5 weeks, ≥5 to <7 weeks, ≥7 to <9 weeks, ≥9 to <11 weeks, ≥11 weeks.

Duration of OLDFI/OLE combined period IMP injection exposure will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum) and categorically using the following categories: ≥1 day to <1 week, ≥1 to <3 weeks, ≥3 to <5 weeks, ≥5 to <7 weeks, ≥7 to <24 weeks, ≥24 to <52 weeks, ≥52 to <78 weeks, ≥78 to <104 weeks, ≥104 to <130 weeks, ≥130 weeks. In addition, cumulative exposure in patient-years will be provided.

2.4.3.2 Compliance

Compliance for the open-label dose finding treatment period (OLDFI) will be assessed using the following parameters:

- The mean injection frequency of IMP OLDFI injections will be defined for each patient as the average number of days between 2 consecutive OLDFI injections, that is: (last OLDFI injection date – first OLDFI injection date)/(number of OLDFI injections -1) for patients receiving at least 2 OLDFI injections.
- The overall compliance for OLDFI injections will be defined for each patient as: 100-(%days with under-planned dosing + %days with above-planned dosing). Under-planned and above-planned dosing will be defined as follows, considering that injections should be performed every 2 weeks or every 4 weeks (±3 days as per protocol):
  - The % days with under-planned dosing will be defined for each patient from Cohorts 1 & 2 as the number of days with no injection administered within the previous 17 days divided by the duration of IMP injection exposure in days. For example if a patient takes a dose 18 days after his/her previous injection, then 1 day is counted as a day under-planned dosing.
  - The % days with under-planned dosing will be defined for each patient from Cohorts 3 & 4 as the number of days with no injection administered within the previous 31 days divided by the duration of IMP injection exposure in days. For example if a patient takes a dose 32 days after his/her previous injection, then 1 day is counted as a day under-planned dosing.
  - The % days with above-planned dosing will be defined for each patient from Cohorts 1 & 2 as the number of days with more than one injection administered within the 11 days before divided by the duration of IMP injection exposure in days. For example if a patient takes a dose 9 days after his/her previous injection, then 2 days are counted as days above-planned dosing.
  - The % days with above-planned dosing will be defined for each patient from Cohorts 3 & 4 as the number of days with more than one injection administered within the 25 days before divided by the duration of IMP injection exposure in days. For example

if a patient takes a dose 23 days after his/her previous injection, then 2 days are counted as days above-planned dosing.

For the OLDFI/OLE combined period, only mean injection frequency will be assessed:

- For Cohorts 1 to 3, the mean injection frequency will be defined for each patient up to, and post switch of dose :
  - Up to the switch of dose, the average number of days between 2 consecutive injections is defined as (last injection date up to the switch – first injection date)/(number of injections up to the switch -1) for patients receiving at least 2 injections;
  - Post switch of dose, the average number of days between 2 consecutive injections is defined as (last injection date– first injection date post switch)/(number of injections post switch -1) for patients receiving at least 2 injections;
- For Cohort 4, the mean injection frequency will be defined for each patient for the entire period (no switch is planned for these patients):
  - The average number of days between 2 consecutive injections, defined as: (last injection date– first injection date)/(number of injections -1) for patients receiving at least 2 injections;

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

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

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

2.4.4 Analyses of efficacy endpoints

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

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

2.4.4.1 Analysis of primary efficacy endpoint(s)

The analysis will be based on an on-treatment approach, and will use LDL-C values collected during the OLDFI efficacy treatment period. The OLDFI efficacy treatment period is defined as the period from first OLDFI IMP injection to last OLDFI IMP injection +21 days (for Cohorts 1 & 2) or + 35 days (for Cohorts 3 & 4) . For patients entering in the OLE, the OLDFI efficacy treatment period will be truncated at the day before the first OLE IMP injection in the extension period.

The percent change from baseline in calculated LDL-C at Week 8 as defined in Section 2.1.3.1 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 OLDFI efficacy treatment period (Week 4 and Week 8) 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], 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 as defined in Section 2.5.4), 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 standard errors (SEs) and 95% confidence intervals (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.

2.4.4.2 Analyses of secondary efficacy endpoints

2.4.4.2.1 Continuous endpoints anticipated to have a normal distribution

Continuous secondary variables defined in Section 2.1.3.2 anticipated to have a normal distribution (ie, lipids other than TG and Lp(a)) will be analyzed in the mITT population using the same MMRM model as for the primary endpoint with fixed categorical effects of alirocumab doses/dose regimen, planned post-baseline time point up to Week 8, dose-by-time point interaction, as well as, the continuous fixed covariates of corresponding baseline value and baseline value-by-time point interaction.

2.4.4.2.2 Continuous endpoints anticipated to have a non-normal distribution

Continuous secondary efficacy variables defined in Section 2.1.3.2 anticipated to have a non-normal distribution (ie, TG and Lp(a)) will be analyzed in the mITT population using multiple imputation approach for handling of missing values. The percent change from baseline at time point of interest will be derived from observed and imputed lipid values at this time point. Multiple imputation will be followed by robust regression model (4) with endpoint of interest as response variable using M-estimation (using SAS ROBUSTREG procedure) with alirocumab doses/dose regimen, and corresponding baseline value(s) as effects. Means and SEs by dose and by cohort will be retrieved from this model using appropriate contrasts. Combined means estimates for all alirocumab dose groups and for each cohort, with their corresponding SEs, 95% CIs will be provided through the SAS MIANALYZE procedure.

Multiple imputation model

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

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

The imputation model for step 1 will include the values of the analyzed parameter at baseline and time-points up to Week 8.

The imputation model for step 2 will include the same variables as in step 1 as well as the dose group.

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

2.4.4.2.3 Binary endpoints

Binary secondary efficacy endpoints defined in Section 2.1.3.2 will be analyzed using multiple imputation approach for handling of missing values as described for non-normally distributed endpoints but without log-transformation (see Section 2.4.4.2.2 for details about multiple imputation).

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

The binary endpoint at time point of interest will be derived from observed and imputed lipid values at this time point. Combined estimates for proportion of patients reaching the target for each alirocumab dose groups and for each cohort will be obtained through the SAS MIANALYZE procedure.

2.4.4.2.4 Summary of results per time point

For the open-label dose finding treatment period, central laboratory values (in conventional (US) and international units), percent change from baseline, and/or when appropriate absolute change from baseline (in conventional and international units), for calculated LDL-C, Total-C, HDL-C, fasting TG, and non HDL-C at each time point (including Week 10 and W12 time points for Cohort 4), for Lp(a), Apo-B, Apo-A1 and ratio Apo-B/Apo-A1 (absolute change from baseline) at Week 8 time points will be summarized in the mITT population using:

- For lipids other than TG and Lp(a): LS mean and SE for each alirocumab dose group, obtained from the same MMRM models as used for endpoints above and including planned time points (see Section 2.4.4.2.1) and with raw values, changes from baseline, or percent change from baseline as response variable in the model as appropriate.
- For TG and Lp(a): mean and SE for each alirocumab dose group obtained from multiple imputation approach followed by the robust regression models as used for endpoints above and including planned time points (see Section 2.4.4.2.2) and with raw values or percent changes from baseline as response variable in the model as appropriate.

In addition, quantitative descriptive summaries by time point (value at visit and % change from baseline) will be presented for all lipids using observed (ie, non-missing) data.

The time profile in %change from baseline of each parameter (except ratio ApoB/Apo A-1 where absolute change will be used) will be plotted according to alirocumab dose received by using LS mean and SE except for TGs and Lp(a). For these 2 parameters, the combined estimate for mean and SE will be used.

For OLDFI /OLE combined period, only quantitative descriptive summaries by time point during the OLDFI/OLE combined efficacy treatment period will be presented for all lipids using observed data in the mITT population. Lipid results pre- versus post-switch to the selected Phase 3 doses will be analyzed separately for Cohorts 1 to 3.

The OLDFI/OLE combined efficacy treatment period is defined as the period from the first IMP injection to last OLE IMP injection + 21 days (for Cohorts 1 & 2) or +35 days (for Cohorts 3 & 4).

2.4.4.3 Multiplicity issues

Not Applicable.

2.4.4.4 Additional efficacy analysis(es)

Not Applicable.

2.4.5 Analyses of safety data

No formal inferential testing will be performed. Summaries will be descriptive in nature.

General common rules

All safety analyses will be performed on the safety population as defined in Section 2.3.2 unless otherwise specified, using the following common rules:

- Safety analyses for the OLDFI/OLE combined periods of Cohorts 1 to 3 will be performed separately for the period pre- versus post-switch to selected Phase 3 doses.
- The baseline value for both OLDFI and OLDFI/OLE combined periods is defined as the last available value obtained up to the date and time of the first OLDFI IMP injection.
- 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, vital signs, and ECG (PCSA in children version dated May 2014 [Appendix A] and PCSA in adults version dated May 2014 [Appendix B], for patients who become adults during the study, ie, aged 18 years or greater during the study).
- PCSA criteria will determine which patients had at least 1 PCSA during the TEAE period, taking into account all evaluations performed during the TEAE period, including nonscheduled or repeated evaluations.
- The treatment-emergent PCSA denominator by group for a given parameter will be based on the number of patients assessed for that given parameter at least once during the TEAE period.
- All measurements, scheduled or unscheduled, fasting or not fasting, will be assigned to analysis windows defined in Section 2.5.4, Table 3 and Table 4 in order to provide an assessment for Week 4 to Week 130 time points.
- For quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results and change from baseline values by visit, using analysis windows. Summaries will also include the last on-treatment value and the worst on-treatment value. The last on-treatment value is defined as the last value

collected during the treatment period of each study period (see Section 2.1.4). The worst on-treatment value is defined as the nadir and /or the peak value during the treatment period of each study period according to the direction (minimum or maximum) of the abnormality as defined in the PCSA list.

- TEAE period stands for OLDFI TEAE period (for safety analysis of OLDFI period) or OLDFI/OLE combined TEAE period (for safety analysis of OLDFI and OLE periods combined) (see Section 2.1.4).

2.4.5.1 Analyses of adverse events

Generalities

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

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

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

Sorting within tables ensures the same presentation for the set of all AEs within the observation period (pre-treatment, TEAE, and post-treatment). For that purpose, the table of all TEAEs presented by SOC and PT sorted by the internationally agreed SOC order and decreasing frequency of PTs within SOCs (in the cohort 4, all doses combined) will define the presentation order for all other tables by SOC and PT, unless otherwise specified. The tables of AEs by SOC, HLGT, HLT and PT will be sorted by the SOC internationally agreed order and the other levels (HLGT, HLT, PT) will be presented in alphabetical order, unless otherwise specified.

Analysis of all treatment-emergent adverse events

The following TEAE summaries will be generated:

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

- All TEAEs by primary SOC, HLGT, HLT, and PT
- All TEAEs by primary SOC and PT, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC (in the Cohort 3, all doses combined). This sorting order will be applied to all other tables by SOC and PT of TEAEs, unless otherwise specified;
- All TEAEs regardless of relationship and related to alirocumab according to investigator's opinion by primary SOC, HLGT, HLT and PT;
- All TEAEs by maximal intensity (ie, mild, moderate or severe), presented by primary SOC and PT, sorted by the sorting order defined above;

Analysis of all treatment emergent serious adverse event(s)

- All serious TEAEs by primary SOC, HLGT, HLT, and PT and by SOC/PT;
- All serious TEAEs regardless of relationship and related to alirocumab according to investigator's opinion, by primary SOC, HLGT, HLT, and PT;

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

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

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

All grouping of TEAEs including adverse events of special interest as listed in Section 2.1.4.1 will be analyzed using selections defined in Section 2.1.4.1 and will be presented by SMQ/CMQ and PT (when selection is based on SMQs/CMQs) and by SOC and PT (when selection is based on the e-CRF tick box or HLGT/HLT). The summaries will be sorted by decreasing incidence of PT within each SOC/SMQ (in the Cohort 3, all doses combined).

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

- Intensity of the event (mild, moderate, severe);
- Number of events divided by the number of OLDFI IMP injections , or the number of open-label injections received for the OLDFI/OLE combined period depending on the analysis period;
- Time from first OLDFI IMP injection to first injection site reaction;
- Description of the highest intensity of each symptom recorded in the specific e-CRF page;
- The use of the analgesic will be assessed with regards to the occurrence of pain;

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

Analysis of pre-treatment and post-treatment adverse events

- All pre-treatment AEs by primary SOC and PT, sorted by the internationally agreed SOC order and decreasing incidence of PTs (in the Cohort 3, all doses combined) within each SOC;
- All pre-treatment AEs leading to treatment discontinuation by primary SOC and PT, sorted by the sorting order defined above;
- All post-treatment AEs by primary SOC and PT, sorted by the internationally agreed SOC order and decreasing incidence of PTs (in the Cohort 3, all doses combined) within each SOC;
- All post-treatment SAEs by primary SOC and PT, sorted by the sorting order defined above;

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

If applicable, similar summaries of TEAEs as those described above will be also provided on the safety subgroup population of patients with two consecutive results of calculated LDL-C <50 mg/dL (respectively calculated LDL-C <25 mg/dL) (as defined in Section 2.1.4.7). Only TEAE for which it will be confirmed or unclear that they occurred, worsened or became serious the day or after the first level of LDL-C <50 mg/dL (or LDL-C <25 mg/dL) will be considered. In case very few cases are observed, individual data listings of TEAEs will be provided on this subgroup of patients instead.

In addition, for the OLDFI/OLE combined period, the following summary tables will be provided:

- The event rate per patient year (the number of patients with an event in question divided by total patient-years) will be provided for all TEAEs by SOC and PT. For a patient with event, patient year is censored at time of first event; for patient without event, it corresponds to length of OLDFI/OLE combined TEAE period
- Kaplan-Meier curves will be provided, when appropriate, for time from first dose of ODLFI IMP to the first occurrence of selected TEAEs. Patients without any event will be censored at the end of the OLDFI/OLE combined TEAE period.

2.4.5.2 Deaths

The following summaries of deaths will be generated:

- Number (%) of patients from the safety population who died by period (on-study, on-treatment, post-study);
- TEAEs leading to death (death as an outcome on the AE as reported by the Investigator) by primary SOC, HLGT, HLT, and PT sorted by internationally agreed SOC order, with HLGT, HLT, and PT presented in alphabetical order within each SOC, for the safety population. TEAEs leading to death are TEAEs that led to death regardless of timing of

death in relation to IMP injection (ie, death occurring in the TEAE period or during the post-treatment period).

In addition deaths in included but not treated patients will be summarized.

2.4.5.3 Analyses of laboratory variables

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

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

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

For parameters for which no PCSA criteria are defined for children ie, red blood cell count, albumin, monocytes and basophils, similar table(s) using the normal range could be provided.

Cortisol and ACTH

Mean changes from baseline with the corresponding SE will be tabulated by time point for cortisol during treatment period. Cortisol levels obtained at local labs will be excluded.

As the sampling time is a known confounder for the cortisol value, the timing of sample collection as well as the cortisol values by sampling time will be described graphically.

Similar table as for PCSA will be provided using the normal range. The number (%) of patients with at least one:

- Cortisol < LLN,
- Cortisol < LLN and ACTH > ULN

during TEAE period, will be presented.

Gonadal hormone assessments

Mean changes from baseline with the corresponding SE will be tabulated by time point for gonadal assessment (testosterone (boys) and estradiol (girls)) and Pituitary hormones (FSH LH) during treatment period.

Similar table as for PCSA will be provided to summarize:

- For boys: the number (%) of patients with testosterone value <LLN, testosterone value <LLN and LH >ULN, testosterone value<LLN and FSH >ULN, during the TEAE period.
- For girls: the number (%) of patients with estradiol value <LLN, estradiol value <LLN and LH >ULN, estradiol value<LLN and FSH >ULN. Separate results will be provided for girls with menstruation and without menstruation.

The descriptions above may also be performed on the subgroups of samples drawn in the morning (between 7 to 11 AM [(5, 6)]) versus those samples drawn at times other than between 7 to 11 AM.

The correlation of calculated LDL-C with gonadal assessments during treatment period will be explored graphically in all patients combined regardless of cohort and dose, taking into account:

- The worst value of the studied parameter,
- The LDL value obtained on the same day as the worst result of the studied parameter.

This graph may also be performed taking into account samples drawn (respectively not drawn) between 7 to 11 AM.

Fat soluble vitamins (A, D, E, and K)

Mean changes from baseline with the corresponding SE will be tabulated by time point for fat soluble vitamins (A, D, E, and K) and ratio of vitamin E to calculated LDL-C, during treatment period.

Similar table as for PCSA will be provided using the normal range. This table will summarize the number (%) of patients with value < LLN during the TEAE period (except for ratio of vitamin E to calculated LDL-C).

The correlation of calculated LDL-C with fat soluble vitamins (A, D, E, and K) during the treatment period will be explored graphically in all patients combined regardless of cohort and dose, taking into account:

- The worst value of the studied parameter,
- The LDL value obtained on the same day as the worst result of the studied parameter.

Drug-induced liver injury

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

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

logarithmic scale. The graph will be divided into 4 quadrants with a vertical line corresponding to 3 x ULN for ALT and a horizontal line corresponding to 2 x ULN for total bilirubin.

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

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

2.4.5.4 Analyses of vital sign variables

The summary statistics (including number, mean, median, Q1, Q3, SD, minimum and maximum) of all vital signs variables in sitting position (raw values and changes from baseline) will be calculated for each visit or study assessment (baseline, each post-baseline value of the treatment period, last on-treatment, worst on-treatment value and follow-up visit).

Vital signs without position filled in will only be used for the PCSA analysis described below.

The incidence of PCSAs at any time during the TEAE period will be summarized.

2.4.5.5 Analyses of electrocardiogram variables

Not Applicable.

2.4.5.6 Tanner stages measurement

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

2.4.5.7 Analyses of other safety endpoints

Binary endpoints defined in Section 2.1.4.7 will be described using count and percentage. Kaplan-Meier curves will be provided for the "Time to" variables. Patient without event will be censored at the end of the treatment period. For the analysis of the time to the first of the two consecutive LDL-C as defined in Section 2.1.4.7, patients without post-baseline LDL-C result or with only one post-baseline LDL-C result will not be included.

2.4.6 Analyses of anti-alirocumab antibodies variables

The following summaries will be performed on the ADA population taking into account all samples regardless of timing in relation to injections.

- ADA results (negative or positive) by time point;

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

2.4.7 Analyses of pharmacokinetic and pharmacodynamic variables

Concentrations of total alirocumab in serum (Ctrough and CFollow-up), free and total PCSK9 concentrations will be summarized on the PK population by visit using descriptive statistics. Ctrough,av will be summarized on the PK population using descriptive statistics.

Time profiles for Ctrough concentration, total and free PCSK9 will be also provided by alirocumab dose group using graphs (mean ± SE or Median, as appropriate).

Concentrations of total alirocumab in serum and PCSK9 levels might be used for population PK modeling if considered necessary and the results of population PK modeling will be reported separately from the study report.

2.4.8 Analyses of quality of life/health economics variables

Not Applicable.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

The following formulas will be used for computation of parameters.

Date of birth / Age

In case of partial date of birth, the date of birth will be imputed as follows:

If day only is unknown, it will be replaced by 15 (so estimated date of birth will be 15/ real month / real year). If day and month are unknown, they will be replaced by 30JUN (so estimated date of birth will be 30/ JUN / real year).

The age will be calculated using the imputed date of birth.

At screening, age will be put equal to minimum (age using imputed date of birth; 17.9) for patients without exclusion criterion E01 "Age less than 8 or greater than 17 years at the time of signed informed consent".

Time from diagnosis of heFH

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

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

Date of last dose of IMP (for OLDFI and for OLE)

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

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

Renal function formulas

eGFR value will be derived using the Schwartz equation:

GFR (mL/min/1.73 m2) = (0.41 × Height in cm) / Creatinine in mg/dL

Lipids variables, laboratory safety variables

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

Pharmacokinetic variables

Data below the LLOQ are set to zero.

2.5.2 Data handling conventions for secondary efficacy variables

See Section 2.1.3.

2.5.3 Missing data

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

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

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

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

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

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

If the last injection date of OLDFI or OLE period is missing, then this date is imputed to the earliest between

- the last day of the month and year, when applicable or else the 31st of December of the year,
- the date of the end of treatment visit of the period (OLDFI period: Week 8 visit for patients from Cohorts 1 to 3, Week 12 visit for patients from Cohort 4, who completed the OLDFI study treatment period as per protocol, early end of treatment visit for patients who prematurely discontinued the IMP; OLE period: last visit for patients who completed the OLE study treatment period as per protocol, early end of treatment visit for patients who prematurely discontinued the IMP),
- and the date of the last contact,

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

Handling of medication missing/partial dates

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

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

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

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

When the date and time of the first IMP administration is missing, all AEs that occurred on or

after the day of inclusion will be considered as TEAEs.

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

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

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

Handling of potentially clinically significant abnormalities

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

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

For a PCSA defined on a threshold and/or a normal range, this PCSA will be derived using this threshold if the normal range is missing.

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

2.5.4 Windows for time points

Data analyzed by time point (including efficacy, laboratory safety data, vital signs, physical examinations, ADA, PK) will be summarized using the analysis windows given in Table 3 and in Table 4. These analysis windows will be applicable for all analyses, and they are defined to provide more homogeneous data for time point-specific analyses.

Table 3 - Analysis windows definition for OLDFI period

Time point	Targeted study day	Analysis window in study days
Week 4	29	15 to 42
Week 8	57	43 to 63 (for Cohort 4) or 70 (for other cohorts)
Week 10 (for Cohort 4)	71	64 to 77
Week 12 (for Cohort 4)	85	78 to 92
Follow-up (for Cohorts 1 to 3)[a]	Last OLDFI IMP+10 weeks	Last OLDFI IMP+10 weeks ±4 weeks

Study days are calculated from the day of first OLDFI IMP injection, the day of first OLDFI IMP injection being Day 1. For included but not treated patients, Day 1 is the day of inclusion

a For patients from Cohorts 1 to 3. For patients not entering the open-label extension (OLE) period or who prematurely discontinue the OLE period, only for ADA and PK.

Table 4 - Analysis windows definition for the entire study (OLDFI/OLE combined period)

Time point	Targeted study day	Analysis window in study days
Week 4	29	15 to 42
Week 8	57	43 to 63 (for Cohort 4) or 70 (for other cohorts)
Week 10 (for Cohort 4)	71	64 to 77
Week 12 (for Cohort 4)	85	78 to 92
Week 14[a] /Week 16[b]	Number of weeks of the planned visit x 7 +1	Targeted study day-28 to Targeted study day +27
Week 24[c] /Week 26[a] / Week 28[b]	Number of weeks of the planned visit x 7 +1	Targeted study day-28 to Targeted study day +27
Week 36[c]/Week 38[a] / Week 40[b]	Number of weeks of the planned visit x 7 +1	Targeted study day-28 to Targeted study day +27
Week 48[c]/Week 50[a] / Week 52[b]	Number of weeks of the planned visit x 7 +1	Targeted study day-28 to Targeted study day +27
Week 62[a] / Week 64[b]	Number of weeks of the planned visit x 7 +1	Targeted study day-28 to Targeted study day +27
Week 74[a] / Week 76[b]	Number of weeks of the planned visit x 7 +1	Targeted study day-28 to Targeted study day +27
Week 86[a] / Week 88[b]	Number of weeks of the planned visit x 7 +1	Targeted study day-28 to Targeted study day +27
Week 98[a] / Week 100[b]	Number of weeks of the planned visit x 7 +1	Targeted study day-28 to Targeted study day +27
Week 110[a] / Week 112[b]	Number of weeks of the planned visit x 7 +1	Targeted study day-28 to Targeted study day +27
Week 120[a] / Week 124[b]	Number of weeks of the planned visit x 7 +1	Targeted study day-28 to Targeted study day +27
Week 130	911	883 to 938
Follow-up[d]	Last OLE IMP+10 weeks	Last OLE IMP+10 weeks ±4 weeks

Study days are calculated from the day of first OLDFI IMP injection, the day of first OLDFI IMP injection being Day 1. For included but not treated patients, Day 1 is the day of inclusion.

a for Cohort 3; the 3 time points will be combined in the analysis.

b for Cohorts 1 & 2; the 3 time points will be combined in the analysis

c for Cohort 4; the 3 time points will be combined in the analysis

d For Cohorts 1 to 3 patients not entering the open-label extension (OLE) period, or who prematurely discontinue the OLE period, only for ADA.

If multiple valid values of a variable exist within an analysis window, the nearest from the targeted study day will be selected. If the difference is a tie, the value after the targeted study day will be used. If multiple valid values of a variable exist within a same day, then the first value of the day will be selected when time is available, else the scheduled visit will be selected.

PK Concentration will be analyzed as Ctrough, Cmax or Cfollow-up following time windows as defined in Table 5. If the date of the previous injection is unknown, the alirocumab concentration will not be considered for the analysis.

Table 5 - Time windows for PK variables definition

PK variables	Time window (D1 = day of previous injection or day of last injection for $C_{follow-up}$)	
	Q2W regimen	Q4W regimen
Cmax	Day 4 to Day 8	Day 4 to Day 8
Ctrough	Day 9 to Day 22	Day 23 to Day 36
Cfollow-up	Day 23 to last injection + 14 weeks	Day 37 to last injection + 14 weeks

If multiple valid values satisfy the C_{max}, C_{trough} or $C_{follow-up}$ criteria, the nearest from the targeted study day (ie, Day 15/32 for C_{trough} and Day 70 for $C_{follow-up}$, Day 1 being the day of previous injection) will be selected. If the difference is a tie, the value after the targeted study day will be used.

2.5.5 Unscheduled visits

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

2.5.6 Pooling of centers for statistical analyses

No pooling of centers will be performed for safety nor for efficacy analyses.

2.5.7 Statistical technical issues

Not Applicable

3 INTERIM ANALYSIS

There will be no formal interim analysis. However, efficacy and safety analyses will be conducted at the end of OLDFI period (main phase) for Cohorts 1 to 3 and at the end of OLDFI period for Cohort 4 to select the doses that will be used for the Phase 3 study.

Three analyses will be conducted:

- First step analysis of the OLDFI period and first step analysis of the OLDFI/OLE combined period
  - This analysis will be conducted when all patients from Cohorts 1 to 3 have completed the OLDFI period and have all the data up to follow-up period collected and validated.
  - The efficacy analyses of the OLDFI period will support the selection of the dose for the Phase 3 study. Efficacy analyses combining lipid data for OLDFI and OLE periods will be performed for exploratory purposes.
  - The safety analyses for the OLDFI/OLE combined period will not be final at the time of this analysis as it will include all data of the OLE period collected up to the common cut-off date (ie, last follow-up visit of the OLDFI period).
- Final analysis of the OLDFI period and second step analysis of the OLDFI/OLE combined period
  - This analysis will be conducted when all patients from cohorts 4 have completed the OLDFI period and have all the data from OLDFI period collected and validated.
  - The efficacy analyses of the OLDFI period will be the primary analysis of both primary and secondary efficacy endpoints and will include all data from Cohorts 1 to 4. Efficacy analyses combining lipid data for OLDFI and OLE periods will be performed for exploratory purposes.
  - The safety analyses for the OLDFI/OLE combined period will not be final at the time of this analysis as it will include all data of the OLE period collected up to the common cut-off date (ie, last visit of the OLDFI period for Cohort 4).
- Final analysis of the study
  - This analysis will be conducted at the end of OLE period with the data of OLDFI and OLE periods combined and will consist in the final analysis of the combined OLDFI and OLE periods.

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

- Patients without end of treatment visit performed at the time of the cut-off date will be considered as ongoing and exposed up to the cut-off date. Therefore:

  - Patients who did not complete treatment period nor prematurely discontinued the study treatment at cut-off date will be analyzed as "ongoing" in the disposition summary.
  - Their OLDFI/OLE combined TEAE period, treatment period and on-study observation period will end at the cut-off date.
  - Their treatment duration will be derived by considering date of cut-off as last injection date.

- Analyses of number of injections, mean injection frequency, percentage of days with under/above-planned dosing and compliance will be performed up to the last injection reported in the e-CRF up to the cut-off date.
- AEs occurring, worsening or becoming serious after the cut-off date will not be included in the analyses. However, any available outcome before database lock, regardless of timing in relation to the cut-off date, of an adverse event starting prior to the cut-off date will be taken into account. Medications, treatment discontinuations/completions and deaths occurring after the cut-off date will not be included in the analyses.
- Post-treatment period, post-study period are not applicable for ongoing patients. Analyses of post-treatment AEs, post-study deaths and post-treatment medications will be performed for patients who either completed or prematurely discontinued the treatment before or at the cut-off date.
- Analysis of status at last study contact and proportion of patients with insufficient follow-up will be provided for patients who completed the follow-up before or at the cut-off date. Follow-up will be considered completed if one of the following conditions is met: cut-off - last injection date >= 77 days OR last contact filled in regardless of contact method OR follow-up visit performed.

4 DATABASE LOCK

Three database locks will be done:

- First database lock (for first analysis): will include all available data on all included patients up to the common cut-off date as defined in Section 3. This database lock is planned to be done approximately 4 weeks after last follow-up visit of OLDFI period.
- Second database lock (for final analysis of OLDFI period including Cohort 4): will include all available data on all included patients up to the common cut-off date as defined in Section 3. This database lock is planned to be done approximately 4 weeks after last visit of OLDFI period for patients from Cohort 4.
- Final database lock (for final analysis): will include all data of the OLDFI and OLE periods. This database lock is planned to be done approximately 4 weeks after last patient last visit.

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS version 9.2 or higher.

6 REFERENCES

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