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STATISTICAL ANALYSIS PLAN

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

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

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

1 OVERVIEW AND INVESTIGATIONAL PLAN

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

1.1 STUDY DESIGN AND RANDOMIZATION

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

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

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

Note: Patients who had previously participated in the DFI14223 study and had received alirocumab administration during the open-label extension of the DFI14223 study required a wash-out period of at least 10 weeks between the last injection of alirocumab and the screening lipid assessment at the entry of the screening period. However, as these patients had already met the LDL-C requirement of at least 130 mg/dL (3.37 mmol/L) when they were screened for the DFI14223 study, they were not excluded based on the LDL-C value obtained during the screening for the EFC14643 study.

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

The study is comprised of 4 periods as described below:

- A run-in period (if needed) up to 4 weeks (+2 days) in duration.
- A screening period up to 2 weeks (+5 days) in duration.
- A 24-week double-blind treatment period.
- A 80-week open-label treatment period.

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

Double-blind treatment period:

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

Q2W dosing regimen cohort:

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

For patients randomized to receive alirocumab the following doses based on BW will be initially administered:

- 40 mg for BW <50 kg or,
- 75 mg for BW ≥50 kg.

At Week 12 patients randomized to alirocumab will either, in a blinded manner:

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

Q4W dosing regimen cohort:

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

For patients randomized to alirocumab the following doses based on BW will be initially administered:

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

At Week 12, patients randomized to alirocumab will either, in a blinded manner:

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

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

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

Open-label treatment period

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

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

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

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

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

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

Lipid levels will be communicated to the Investigator during the OL treatment period from the second visit (ie, Week 32) onwards. From this visit, the Investigator is responsible, based on his/her own judgment related to the patient's LDL-C levels and the safety profile, to up-titrate, down-titrate, maintain the dose of alirocumab or discontinue alirocumab throughout the study.

From Week 32 onwards:

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

The following up-titration or down-titration of alirocumab doses will be possible:

Up-titration:

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

Down-titration:

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

For Q4W dosing regimen cohort:

Dose adjustment will be possible, as follows:

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

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

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

1.2 OBJECTIVES

1.2.1 Primary objectives

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

1.2.2 Secondary objectives

- To evaluate the efficacy of alirocumab versus placebo on LDL-C levels after 12 weeks of double-blind treatment.
- To evaluate the effects of alirocumab versus placebo on other lipid parameters (eg, apolipoprotein B (Apo B), non-high density lipoprotein cholesterol (non-HDL-C), total-cholesterol (Total-C), high-density lipoprotein cholesterol (HDL-C), lipoprotein (a) (Lp[a]), triglycerides (TGs), apolipoprotein A-1 (Apo A-1) levels after 12 and 24 weeks of treatment.
- To evaluate the safety and tolerability of alirocumab after 24 weeks of treatment in comparison with placebo.

- To evaluate the efficacy, safety and tolerability of alirocumab after 80 weeks of open-label treatment.
- To evaluate the development of anti-alirocumab antibodies after 24 weeks of treatment during the double-blind treatment period.

1.2.3 Other Objectives

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

1.2.4 Exploratory objective of the FMD sub-study

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

1.3 DETERMINATION OF SAMPLE SIZE

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

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

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

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

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

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

Calculations were made using nQuery 7.0 Advisor software.

Sample Size Determination for the FMD sub-study:

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

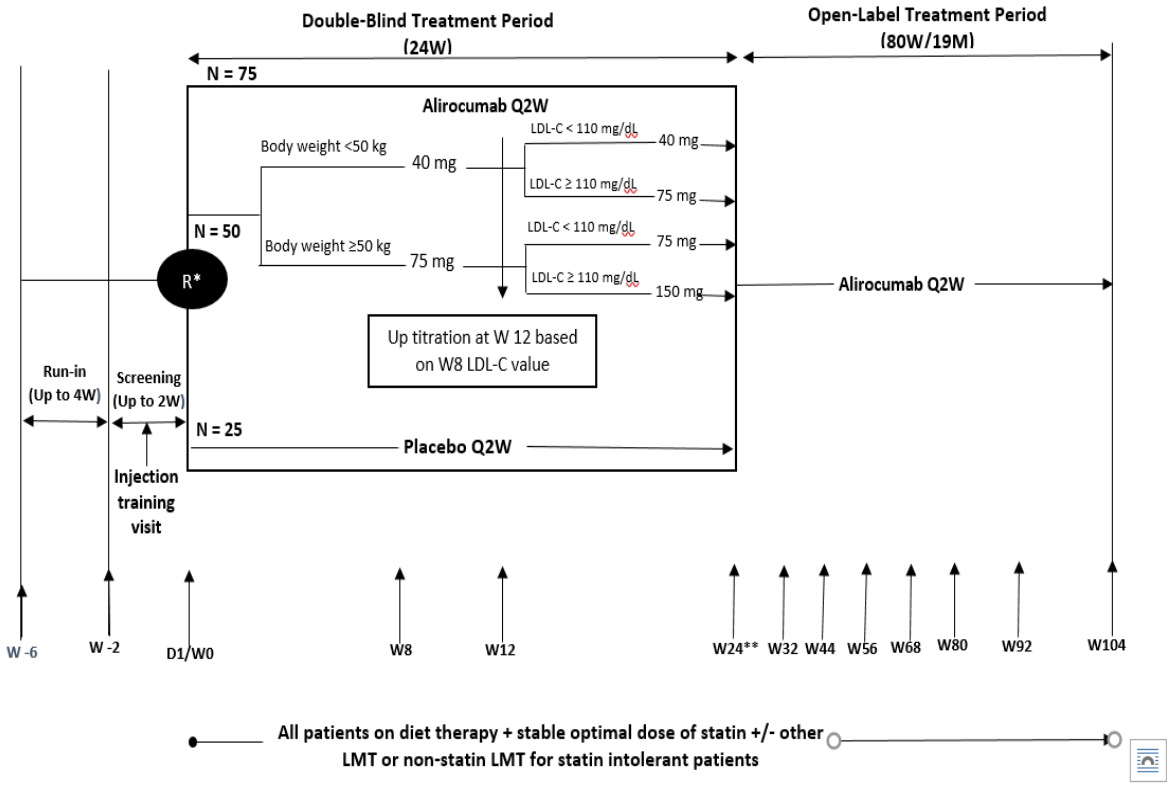
Table 1 - Statistical power according to mean difference and SD of the FMD absolute change from baseline to Week 24

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

1.4 STUDY PLAN

The following figures present the graphical study design:

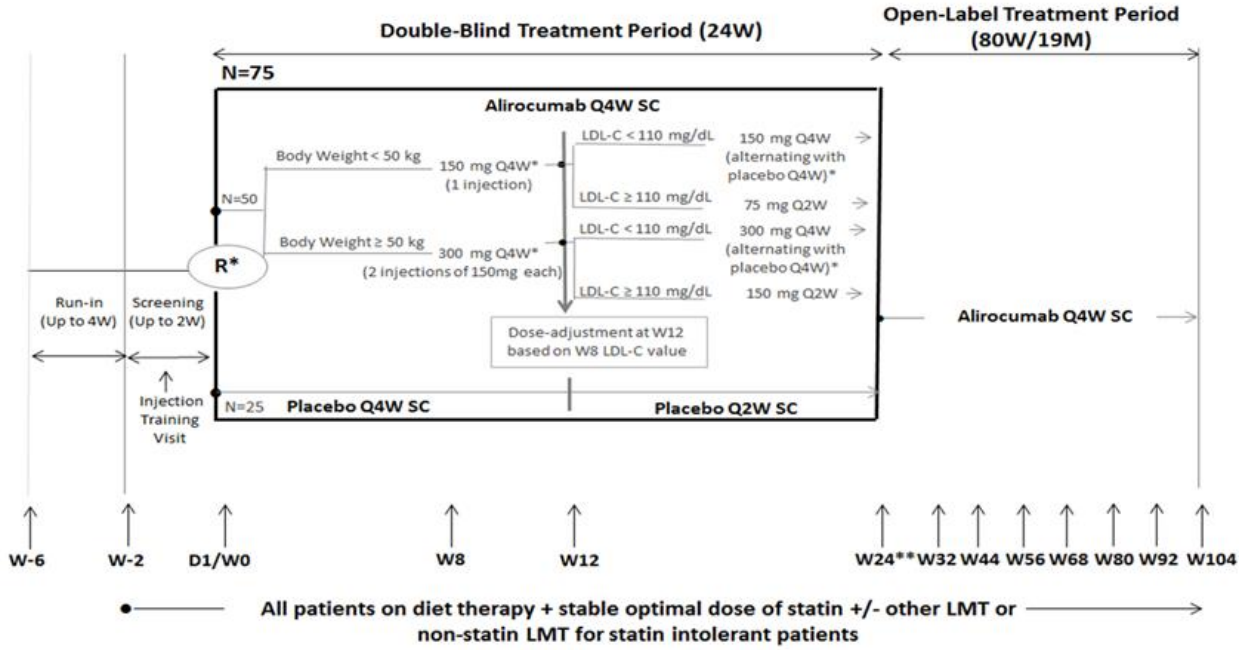
Figure 1 - Graphical study design for Q2W dosing regimen cohort



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

**Primary efficacy endpoint at Week 24

Figure 2 - Graphical study design for Q4W dosing regimen cohort



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

** Primary endpoint at W24.

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

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

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

Table 2 - Protocol amendment statistical changes

Amendment Number	Rationale	Description of statistical changes
2	Revision of the statistical section in accordance with the addition of the Q4W regimen	- Sample size considerations adapted to the addition of the Q4W regimen - In the efficacy analyses, addition of alirocumab Q4W and placebo Q4W to the treatment groups used in the statistical modelling, as well as description of the main comparison (each alirocumab regimen compared to the combined placebo group) - Addition of an analysis exploring the difference in terms of percent change from baseline in LDL-C between the 2 alirocumab dosing regimens - Safety analyses: the summary of safety results will be presented in each alirocumab regimen, in the combined alirocumab group (ie, regardless of the regimen), and in the combined placebo group. - Description of the duration of exposure added for the Q4W dosing regimen - Revision of the handling of multiplicity.
3	Revision of the statistical sections in order to specify analyzing each of the two randomized dosing regimen cohorts separately	- Revision of the 2 main comparisons: in each dosing regimen cohort, the alirocumab group will be compared to its contemporaneously randomized placebo group (ie, of the same dosing regimen cohort). The study power has been updated accordingly. Revision of the statistical models (a separate model will be run for each dosing regimen cohort) Revision of the treatment groups to be displayed in result summaries for safety and other endpoints: alirocumab and placebo within each dosing regimen cohort, and regardless of the dosing regimen cohort (pooled across cohorts)
	To be consistent with the significance level that will be used for tests (2.5% two-sided), 97.5% CI will be computed instead of 95% CI.	- Since two-sided test with a significance level of 2.5% will be performed, 97.5%CI will be computed instead of 95%CI for primary and secondary efficacy endpoints.
	Information omitted by error in the previous version	- Addition of the definition of the treatment period for the Q4W dosing regimen cohort - For the FMD sub-study: addition of the dosing regimen cohort and the treatment-by-dosing regimen cohort effects in the statistical model.
	Revision of the statistical analysis for the FMD sub-study due to its very exploratory nature	- Removal of the multiple imputations process

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

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

Table 3 - Statistical analysis plan statistical changes

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

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

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

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

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

Demographic characteristics

Demographic variables include:

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

Medical or surgical history

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

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

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

- Family history of Myocardial Infarction (MI) (below 50 years of age in 2nd degree relative or below 60 years of age in 1st degree relative).
- Family history of raised cholesterols (>7.5 mmol/L [290 mg/dL] in adult 1st or 2nd degree relative or >6.7 mmol/L [260 mg/dL] in child or sibling under 16 years of age).
- Tendon xanthoma in family (in 1st or 2nd degree relative).
- Familial defective apo B-100.
- DNA-based evidence of an LDL receptor mutation (of the subject).
- Tendon xanthoma (of the subject).
- Subject history of raised Total-C: Total-C >6.7 mmol/l (260 mg/dL) in a child under 16 years of age OR >7.5 mmol/l (290 mg/dL) above 16; Levels either pre-treatment or highest on treatment.
- Subject history of raised LDL cholesterol: LDL cholesterol > 4.0 mmol/l (155 mg/dL) in a child under 16 years OR > 4.9 mmol/l (190 mg/dL) above 16; Levels either pre-treatment or highest on treatment.
- Hypertension (of the subject).
- Type 1 Diabetes (of the subject).
- Type 2 Diabetes (of the subject).

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

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

Smoking status and alcohol habits

Smoking status and alcohol habits include:

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

Disease Characteristics and relevant medical data

Specific disease characteristic includes:

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

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

Other baseline characteristics

Other baseline characteristics include:

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

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

2.1.2 Prior or concomitant medications and post-treatment medications

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

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

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

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

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

2.1.3 Efficacy endpoints

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

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

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

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

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

2.1.3.1 Primary efficacy endpoint(s)

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

The LDL-C at Week 24 will be the LDL-C level obtained within the Week 24 analysis window. All calculated and measured LDL-C values (scheduled or unscheduled, fasting or not fasting) may be used to provide a value for the primary efficacy endpoint if appropriate according to the above definition. In case both calculated and measured LDL-C values are provided for the same sampling, the measured LDL-C will be considered.

2.1.3.2 Secondary efficacy endpoint(s)

2.1.3.2.1 Key secondary efficacy endpoints

The key secondary efficacy endpoints are:

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

- Proportion of patients achieving a LDL-C level lower than 110 mg/dL (2.84 mmol/L) at Week 24 (ITT estimand).
- Proportion of patients achieving a LDL-C level lower than 110 mg/dL (2.84 mmol/L) at Week 12 (ITT estimand).
- Percent change in Lp (a) from baseline to Week 24 (ITT estimand).
- Percent change in Lp (a) from baseline to Week 12 (ITT estimand).
- Percent change in HDL-C from baseline to Week 24 (ITT estimand).
- Percent change in fasting TG from baseline to Week 24 (ITT estimand).
- Percent change in Apo A-1 from baseline to Week 24 (ITT estimand).
- Percent change in HDL-C from baseline to Week 12 (ITT estimand).
- Percent change in fasting TG from baseline to Week 12 (ITT estimand).
- Percent change in Apo A-1 from baseline to Week 12 (ITT estimand).

2.1.3.2.2 Other secondary efficacy endpoints

- All primary and key secondary endpoints in the modified ITT (mITT) population (defined in Section 2.3.1.2), using LDL-C values during the treatment period (on-treatment estimand).
- Absolute change in Apo B/Apo A-1 ratio to Week 12 and Week 24 (ITT and on-treatment estimands).
- Proportion of patients achieving at least 30% reduction, 50% reduction in LDL-C at Week 24 (ITT and on-treatment estimands).
- Proportion of patients achieving at least 30% reduction, 50% reduction in LDL-C at Week 12 (ITT and on-treatment estimands).
- Percent change in LDL-C from baseline to Week 104 (ITT and on-treatment estimands).

2.1.3.2.3 Exploratory endpoint of the FMD sub-study

The exploratory endpoint of the FMD sub-study is the absolute change from baseline to Week 24 in flow mediated dilatation of the brachial artery (as determined by the central reading laboratory) regardless of adherence to treatment. The analysis will consist of the comparison of alirocumab to placebo, regardless of the dosing regimen cohort.

On-treatment analysis will be also conducted.

2.1.4 Safety endpoints

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

Observation period for the Q2W dosing regimen cohort,

The observation of safety data will be as follows:

- The pre-treatment period is defined from the signed informed consent up to the first dose of double-blind IMP.
- Double-blind treatment-emergent adverse event (TEAE) period is defined as:
  - the time from the first dose of double-blind IMP to the last dose of double-blind IMP injection +70 days (10 weeks) as residual effect of alirocumab is possible until 10 weeks after the stop of treatment IMP injection. This period will be truncated at the first dose of open-label IMP for patients proceeding into the OL treatment period.

  The double-blind TEAE period will include:

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

Observation period for the Q4W dosing regimen cohort,

The observation of safety data will be as follows:

- The pre-treatment period is defined from the signed informed consent up to the first dose of double-blind IMP.
  - Double-blind treatment-emergent adverse event (TEAE) period is defined as: the time from the first dose of double-blind IMP to the last dose of double-blind IMP injection +70 days (10 weeks) as residual effect of alirocumab is possible until 10 weeks after the stop of treatment IMP injection. This period will be truncated at the first dose of open-label IMP for patients proceeding into the OL treatment period.

  The double-blind TEAE period will include:

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

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

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

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

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

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

2.1.4.1 Adverse events variables

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

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

Adverse event observation period

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

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

Groupings of adverse events

Grouping of adverse events include the following:

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

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

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

- Cataract using HLT “Cataract conditions”.

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

2.1.4.2 Deaths

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

For double-blind period:

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

For open-label period:

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

2.1.4.3 Laboratory safety variables

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

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

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

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

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

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

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

Technical formulas are described in Section 2.5.1.

2.1.4.4 Vital signs variables

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

Body weight was to be measured during:

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

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

Height was to be measured during:

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

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

Heart rate and blood pressure were to be measured during:

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

2.1.4.5 Electrocardiogram variables

Not applicable

2.1.4.6 Tanner stage measurement

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

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

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

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

2.1.4.7 Cogstate battery test

Cogstate battery test was to be administered during:

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

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

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

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

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

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

2.1.5 Other endpoints

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

- The absolute change in HbA_{1c} (%) from baseline to Week 24 in the double-blind period, as well as change from baseline to Week 68 and Week 104 in the OL period. PCSA criteria for HbA_{1c} will be also used (see Appendix A).
- The proportion of patients with 2 consecutives results, spaced out by at least 21 days, of LDL-C <50 mg/dL (<1.30 mmol/L), LDL-C <25 mg/dL (<0.65 mmol/L) , LDL-C <15 mg/dL(0.39 mmol/L) during each treatment period (double-blind or open-label) and the time to the first LDL-C <50 mg/dL (<25 mg/dL, <15mg/dL respectively) for these patients within the relevant treatment period.
- Cardiac function: CPK-MB and cardiac troponin (at Visit 4 [Week 0 / Day 1] and Visit 7 [Week 24]/or early termination) and in case of any clinically relevant cardiovascular effect observed in patients.
- The percent change in hs-CRP from baseline to Week 24 in the double-blind period. Hs-CRP values greater or equal to 10 mg/L will be excluded from analyses in a second approach, since these are suggestive of concurrent infections (1). PCSA (potentially

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

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

2.1.6 Anti-alirocumab antibodies variables

Anti-alirocumab antibodies (ADA) are assessed:

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

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

- ADA response (Positive or Negative).

  For ADA positive:

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

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

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

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

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

2.1.7 Pharmacokinetic variables

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

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

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

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

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

2.2 DISPOSITION OF PATIENTS

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

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

Randomized patients consist of all screened patients, with a double-blind treatment kit number allocated and recorded in the IVRS/IWRS database, regardless of whether the treatment kit was used or not. Patients treated without being randomized or treated with a double-blind treatment kit

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

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

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

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

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

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

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

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

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

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

Additionally, the following populations will be summarized:

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

Definitions of the study populations are provided in Section 2.3.

2.2.1 Randomization and drug dispensing irregularities

Randomization and drug-dispensing irregularities occur whenever:

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

   OR

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

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

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

2.3 ANALYSIS POPULATIONS

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

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

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

2.3.1 Efficacy populations

The primary efficacy analysis population will be the ITT population.

2.3.1.1 Intent-to-treat population

The ITT population is defined as all randomized patients.

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

2.3.1.2 Modified Intent to treat population

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

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

2.3.1.3 FMD sub-study population

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

2.3.2 Safety population

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

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

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

2.3.3 Anti-alirocumab antibody population

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

2.3.4 Pharmacokinetics population

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

2.3.5 Open-label population

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

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

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

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

2.4 STATISTICAL METHODS

General rules

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

Double-blind period

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

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

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

OL period

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

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

2.4.1 Demographics and baseline characteristics

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

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

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

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

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

These parameters will be also summarized in the OL population.

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

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

2.4.2 Prior or concomitant medications

Double-blind period

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

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

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

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

OL period

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

2.4.3 Extent of investigational medicinal product exposure and compliance

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

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

2.4.3.1 Extent of investigational medicinal product exposure

Double-blind period

- Q2W dosing regimen cohort

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

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

- Q4W dosing regimen cohort

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

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

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

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

OL period

- Q2W dosing regimen cohort

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

- Q4W dosing regimen cohort

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

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

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

Combined period (double-blind and OL periods)

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

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

Titration/dose-adjustment

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

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

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

2.4.3.2 Compliance

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

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

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

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

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

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

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

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

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

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

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

2.4.4 Analyses of efficacy endpoints

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

Double-blind period

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

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

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

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

OL period

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

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

Combined period (double-blind and OL periods)

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

2.4.4.1 Analysis of primary efficacy endpoint

2.4.4.1.1 Primary efficacy analysis

Within each dosing regimen cohort, the percent change from baseline in LDL-C to Week 24 as defined in Section 2.1.3.1 will be analyzed in the ITT population using a mixed-effect model with repeated measures (MMRM) model. All post-baseline data available within Week 8 to Week 24 analysis windows will be used and missing data will be accounted for by the MMRM model.

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

For the Q4W dosing regimen cohort, the model will include the fixed categorical effects of treatment group (alirocumab, placebo), randomization strata (baseline body weight [<50 or ≥50 kg]), time point (Week 8, Week 12, Week 24), treatment-by-time point interaction, and strata-by-time point interaction, as well as the continuous fixed covariates of baseline LDL-C value and baseline value-by-time point interaction. Model assumptions for normality will be explored prior to the analysis testing.

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

These 2 separate models will be run using SAS Mixed procedure with an unstructured correlation matrix by treatment group (in case of convergence issue, a common unstructured correlation matrix for both groups will be used) to model the within-patient errors. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Denominator degrees of freedom will be estimated using Satterthwaite's approximation. Throughout MMRM models, least-square (LS) mean and standard error (SE) at Week 24 will be provided for each treatment group within each dosing regimen cohort.

LS means difference at Week 24 will be provided for the comparison of each alirocumab dosing regimen group versus its contemporaneously randomized placebo group (ie, of the same dosing regimen cohort) as follows:

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

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

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

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

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

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

2.4.4.1.2 Model assumption checks

Homogeneity of treatment effect across baseline LDL-C levels

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

- Treatment group * baseline LDL-C.

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

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

Analysis of residuals:

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

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

2.4.4.1.3 Sensitivity to randomization strata

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

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

2.4.4.1.4 Sensitivity to handling of missing data

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

Visual examination:

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

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

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

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

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

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

Multiple Imputations (under MAR assumption):

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

Pattern mixture model (see Appendix C for more details)

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

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

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

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

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

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

2.4.4.1.5 Sensitivity to the impact of COVID-19

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

2.4.4.1.6 Subgroup analyses

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

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

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

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

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

Subgroups of interest are:

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

2.4.4.2 Analyses of secondary efficacy endpoints

2.4.4.2.1 Continuous endpoints anticipated to have a normal distribution

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

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

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

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

2.4.4.2.2 Continuous endpoints anticipated to have a non-normal distribution

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

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

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

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

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

Multiple imputation model

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

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

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

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

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

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

2.4.4.2.3 Binary endpoints

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

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

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

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

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

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

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

2.4.4.2.4 Summary of results per time point

Double-blind period

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

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

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

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

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

OL period

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

Combined period

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

2.4.4.3 Multiplicity issues

The Bonferroni adjustment will be applied to handle multiplicity for the comparison of each alirocumab dosing regimen group versus its contemporaneously randomized placebo group (ie, alirocumab Q2W versus placebo Q2W; alirocumab Q4W versus placebo Q4W) for the primary efficacy endpoint (two-sided 0.025 alpha level will apply for each comparison).

In order to handle multiple key secondary endpoints, the overall type-I error will be controlled by the use of a sequential inferential approach applied independently within each dosing regimen cohort (Q2W and Q4W). Statistical significance of the primary parameter at the two-sided 0.025 alpha level is required before drawing inferential conclusions for that dosing regimen cohort about first key secondary parameter (refer to order of list in Section 2.1.3.2.1. Inferential conclusions about successive key secondary parameters for a given dosing regimen cohort require statistical significance of the prior one in that dosing regimen cohort.

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

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

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

2.4.4.4 Exploratory efficacy analyses

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

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

FMD sub-study

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

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

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

2.4.5 Analyses of safety data

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

General common rules

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

- Safety data in patients who do not belong to the safety population (ie, exposed but not randomized) will be listed separately.
- The baseline value for both double-blind and OL periods is defined as the last available value obtained up to the date and time of the first double-blind IMP injection in EFC14643 study, except otherwise specified.
- PCSA values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests and vital signs, PCSA in children [Appendix A] and PCSA in adults version dated May 2014 [Appendix B]). Considering that the threshold defined in the PCSA list for monocytes and basophils can be below the ULN, the following PCSA criteria will be used for the PCSA analysis of monocytes and basophils:
  - PCSA criterion for monocytes: >0.7 Giga/L or > ULN (if ULN ≥0.7 Giga/L)
  - PCSA criterion for basophils: >0.1 Giga/L or > ULN (if ULN ≥0.1 Giga/L)
- PCSA criteria will determine which patients had at least 1 PCSA during the TEAE period, taking into account all evaluations performed during the TEAE period, including nonscheduled or repeated evaluations.
- The treatment-emergent PCSA denominator by group for a given parameter will be based on the number of patients assessed for that given parameter at least once during the TEAE period.
- All measurements, scheduled or unscheduled, fasting or not fasting, will be assigned to analysis windows defined in Section 2.5.4, Table 5 and Table 6 in order to provide an assessment for Week 4 to Week 104 time points.
- In both the double-blind and the OL periods, for quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results and change from baseline values by visit using analysis windows. Summaries will also include the last on-treatment value and the worst on-treatment value. The last on-treatment value is defined as the last value collected during the treatment period of each study period (see Section 2.1.4). The worst on-treatment value is defined as the nadir and /or the peak value during the treatment period of each study period according to the direction (minimum or maximum) of the abnormality as defined in the PCSA list.
- For exploratory purposes, key safety analyses for the double-blind period could also be provided according to up-titration/dose-adjustment status, ie, according to whether the patients remained on their initial dose or whether the dose was up-titrated/dose-adjusted. These analyses will be exploratory and descriptive (no formal comparison per dose) as it is expected that there could be inherent differences in the baseline characteristics between those patients up-titrating and those remaining on their initial dose. In order to reduce the

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

2.4.5.1 Analyses of adverse events

Generalities

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

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

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

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

Analysis of all treatment-emergent adverse events

The following TEAE summaries will be generated:

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

  - Treatment-related TEAE.

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

Analysis of all treatment emergent serious adverse event(s)

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

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

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

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

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

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

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

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

Analysis of pre-treatment and post-treatment adverse events

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

Analysis of treatment emergent adverse events related to COVID-19

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

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

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

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

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

Analysis according to IVRS/IWRS BW strata

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

Analysis according to previous participation to the Phase 2 DFI14223 study

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

Additional analysis for the OL period

The following summary tables will be added:

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

2.4.5.2 Deaths

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

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

2.4.5.3 Analyses of laboratory variables

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

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

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

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

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

Drug-induced liver injury

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

An evaluation of drug-induced serious hepatotoxicity (eDISH) with the graph of distribution of peak values of ALT versus peak values of total bilirubin will also be presented using post-baseline values during TEAE period. Note that the ALT and total bilirubin values are presented on a logarithmic scale. The graph will be divided into 4 quadrants with a vertical line corresponding to 3 x ULN for ALT and a horizontal line corresponding to 2 x ULN for total bilirubin.

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

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

Gonadal hormones and pituitary hormones

Girls and boys will be described separately.

- For girls

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

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

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

- For boys

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

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

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

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

Adrenal gland hormones

DHEAS:

Girls and boys will be described separately.

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

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

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

Cortisol and ACTH

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

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

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

2.4.5.4 Analyses of vital sign variables

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

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

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

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

- Analyses by visit (unless data warrants further investigation)

2.4.5.5 Analyses of electrocardiogram variables

Not Applicable.

2.4.5.6 Analysis of Tanner stages measurement

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

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

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

2.4.5.7 Analyses of Cogstate Battery test

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

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

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

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

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

2.4.6 Analyses of other endpoints

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

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

HsCRP and HbA_{1c}

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

Patients with low LDL-C

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

Creatine phosphokinase-MB and cardiac troponin

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

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

- <LLOQ;
- ≥LLOQ.

Urinalysis

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

2.4.7 Analyses of anti-alirocumab antibodies variables

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

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

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

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

ADA results (negative or positive) by time point;

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

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

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

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

2.4.8 Analyses of pharmacokinetic and pharmacodynamic variables

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

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

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

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

2.4.9 Analyses of quality of life variables

Not applicable.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

The following formulas will be used for computation of parameters:

Time from diagnosis of heFH

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

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

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

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

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

Renal function formulas

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

Lipids variables, laboratory safety variables, Hs-CRP

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

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

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

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

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

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

Pharmacokinetic variables

Data below the LLOQ are set to zero.

2.5.2 Data handling conventions for secondary efficacy variables

See Section 2.1.3.2.

2.5.3 Missing data

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

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

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

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

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

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

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

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

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

Handling of medication missing/partial dates

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

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

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

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

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

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

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

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

Handling of missing severity of adverse events

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

Handling of potentially clinically significant abnormalities

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

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

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

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

2.5.4 Windows for time points

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

Table 5 - Analysis windows definition for double-blind period

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

Time point	Targeted study day	Analysis window in study days

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

Table 6 - Analysis windows definition for OL period

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

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

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

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

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

Table 7 Time windows for PK variables definition

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

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

2.5.5 Unscheduled visits

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

2.5.6 Pooling of centers for statistical analyses

Not Applicable.

2.5.7 Statistical technical issues

Not Applicable.

3 INTERIM ANALYSIS

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

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

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

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

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

4 DATABASE LOCK

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

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

5 SOFTWARE DOCUMENTATION

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

6 REFERENCES

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7 LIST OF APPENDICES

Appendix A: Potentially clinically significant abnormalities for children

Appendix B: Potentially clinically significant abnormalities for adults

Appendix C: Detailed statistical methodology for pattern mixture model

Appendix D: List of MedDRA terms for CMQs

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

Appendix F: Cogstate normative data

Appendix G: Effect size calculation formula for Cogstate data

Appendix H: Pediatric formula for eGFR and creatinine clearance

Appendix A Potentially clinically significant abnormalities for children

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES

For studies in children

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

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For studies in children

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

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For studies in children

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

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For studies in children

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

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For studies in children

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

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For studies in children

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

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For studies in children

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

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For studies in children

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

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For studies in children

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

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For studies in children

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

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
For studies in children

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

Appendix B Potentially clinically significant abnormalities for adults

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

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

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

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

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

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

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

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

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

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

Appendix C Detailed statistical methodology for pattern mixture model

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

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

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

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

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

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

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

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

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

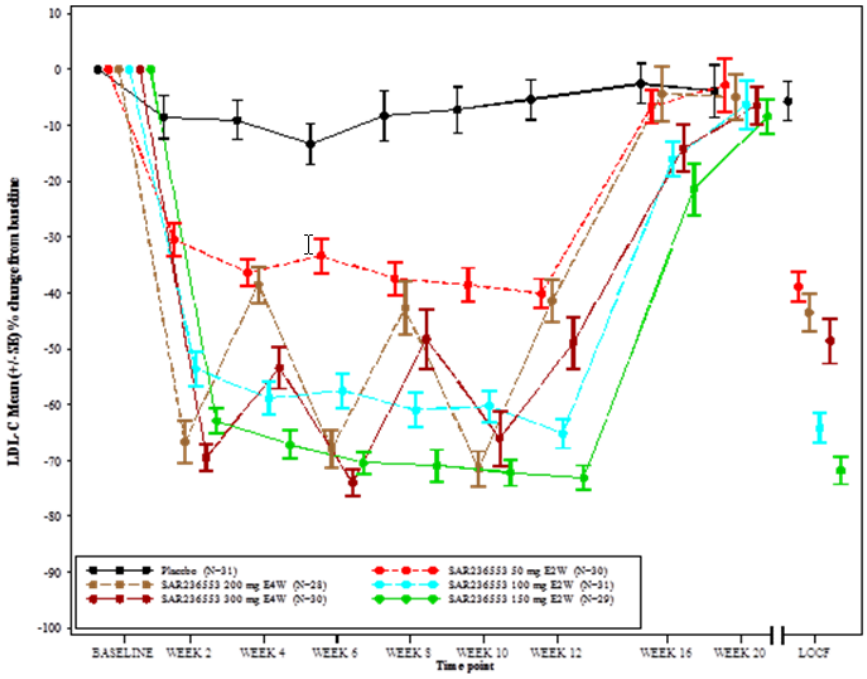
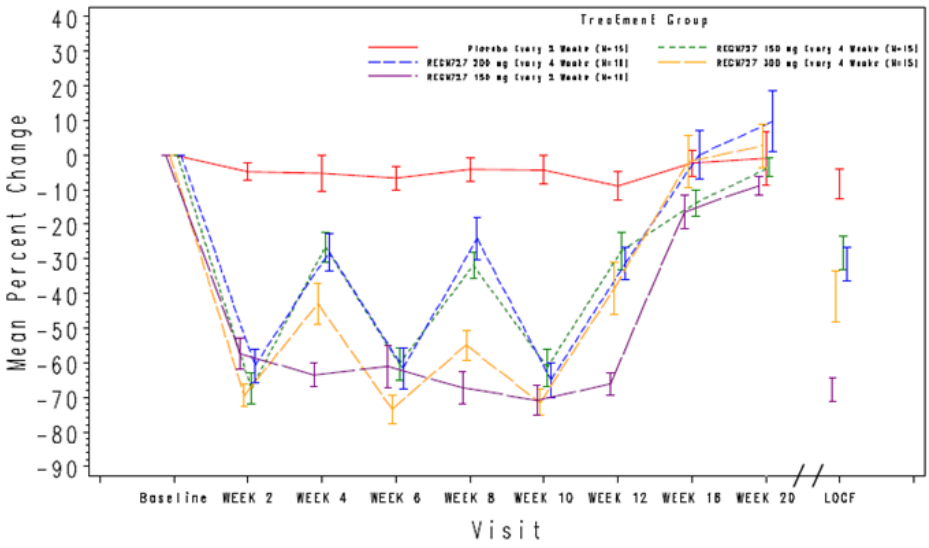


Figure 4 - Study R-727-CL-1003: calculated LDL-C mean (+/- SE) percent change from baseline



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

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

Imputation of missing data during the on-treatment period

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

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

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

A sample SAS code is provided below:

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

        var LDL_BASE   LDL_W8   LDL_W12   LDL_W24  ;

run;
```

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

Imputation of missing data after treatment discontinuation

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

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

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

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

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

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

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

Appendix D List of MedDRA terms for CMQs

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

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

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

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

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

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

Appendix E Z-score calculation formula for Cogstate Battery test

Z-Score: Comparison of Individual Scores to Normative Data

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

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

Where:

t = is the test indicator

i = indexes subject i

j = indexes the jth assessment for subject i

x = cognitive score

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

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

Appendix F Cogstate normative data

Cogstate

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

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

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

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

Cogstate

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

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

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

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

Appendix G Effect size calculation formula for Cogstate data

Effect Size

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

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

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

Where:

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

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

Appendix H Pediatric formula for eGFR and creatinine clearance

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

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