STATISTICAL ANALYSIS PLAN

An open-label study to evaluate the efficacy and safety of alirocumab in children and adolescents with homozygous familial hypercholesterolemia

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA:	anti-alirocumab (drug) antibodies
AE:	adverse event
AESI:	adverse event of special interest
ALP:	alkaline phosphatase
ALT:	alanine aminotransaminase
Apo A-1:	apolipoprotein A-1
AST:	aspartate aminotransferase
ATC:	anatomic therapeutic chemical
BMI:	body mass index
BW:	body weight
CI:	confidence intervals
CMQ:	customized MedDRA queries
CPK:	creatine phosphokinase
CV:	cardiovascular
DBP:	diastolic blood pressure
e-CRF:	electronic case report form
eDISH:	evaluation of drug-induced serious hepatotoxicity
eGFR:	estimated glomerular filtration rate
EOT:	end-of-treatment
HbA_{1c}:	glycated haemoglobin A1c
HDL-C:	high density lipoprotein cholesterol
HLGT:	high level group term
HLT:	high level term
hoFH:	homozygous familial hypercholesterolemia
HR:	heart rate
ie:	id est = that is
IMP:	investigational medicinal product
ITT:	intent-to-treat
IVRS:	interactive voice response system
IWRS:	interactive web response system
LDH:	lactate dehydrogenase
LDL-C:	low-density lipoprotein cholesterol
LLOQ:	lower limit of quantification
LLT:	lowest level term
LMT:	lipid modifying therapy
Lp (a):	lipoprotein a
LS:	least square
MAR:	missing-at-random
MedDRA:	medical dictionary for regulatory activities
MI:	myocardial infarction

MMRM:	mixed-effect model with repeated measures
NMAR:	not missing-at-random
PCSA:	potentially clinically significant abnormality
PCSK9:	proprotein convertase subtilisin/kexin type 9
PK:	pharmacokinetics
PT:	preferred term
Q2W:	every 2 weeks
QQ-plot:	quantile-quantile plot
SAE:	serious adverse event
SAS:	statistical analysis software
SBP:	systolic blood pressure
SC:	subcutaenous
SE:	standard error
SMQ:	standardised MedDRA queries
SOC:	system organ class
TEAE:	treatment emergent adverse event
TG:	triglyceride
ULN:	upper limit of normal
ULOQ:	upper limit of quantification
WHO-DD:	World Health Organization-Drug Dictionary
γGT:	gamma-glutamyl transferase

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

This study is a Phase 3, multi-national, multi-center, open-label study with a treatment period of 48 weeks to evaluate the efficacy and safety of alirocumab in children and adolescents aged 8 to 17 years with homozygous familial hypercholesterolemia (hoFH) confirmed by genetic testing and LDL-C ≥130 mg/dL (3.37 mmol/L) at screening visit, despite treatment with stable lipid modifying therapy (LMT) at optimal doses. Patients who have initiated apheresis treatment for at least 6 months prior to screening and are currently undergoing stable LDL apheresis therapy are also eligible for the study.

The study comprises 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 48-week open-label treatment period.
- A follow-up of 8 weeks (±3 days).

The total duration of the study will be up to 62 weeks for each patient.

During the treatment period, alirocumab will be administered every 2 weeks (Q2W) subcutaneously (SC), starting at Week 0 and continuing up to the end of the open-label treatment period (last injection at Week 46).

The dose of alirocumab will be based on body weight (BW) (75 mg Q2W for BW<50 kg, 150 mg Q2W for BW ≥50 kg). After Week 12, if there is a change in BW, the dose of alirocumab can be adjusted such that the dose corresponds to the patient's BW.

A follow-up call will be planned 10 weeks after the last Investigational medicinal product (IMP) injection, ie, 8 weeks after the end-of-treatment (EOT) visit, for the patients who completed the treatment and for patients who prematurely discontinued for any reason.

Approximately 18 patients are to be enrolled from approximately 20 sites.

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective of this study is to evaluate the efficacy of alirocumab (75 or 150 mg depending on BW), administered every 2 weeks (Q2W), on low-density lipoprotein cholesterol (LDL-C) levels at Week 12 of treatment in children with HoFH 8 to 17 years of age on top of background treatments.

1.2.2 Secondary objectives

The secondary objectives of this study are:

- To evaluate the efficacy of alirocumab after 24 and 48 weeks of treatment on LDL-C levels.
- To evaluate the effects of alirocumab on other lipid parameters (eg, Apo B, non-HDL-C, total-C, HDL-C, Lp (a), triglycerides [TG], apolipoprotein A-1 [Apo A-1] levels) after 12, 24, and 48 weeks of treatment.
- To evaluate the safety and tolerability of alirocumab up to 48 weeks of treatment.

1.2.3 Other objectives

The other objectives of this study are:

- To evaluate the development of anti-alirocumab antibodies (ADA) during 48 weeks of treatment.
- To evaluate the pharmacokinetics (PK) of alirocumab.

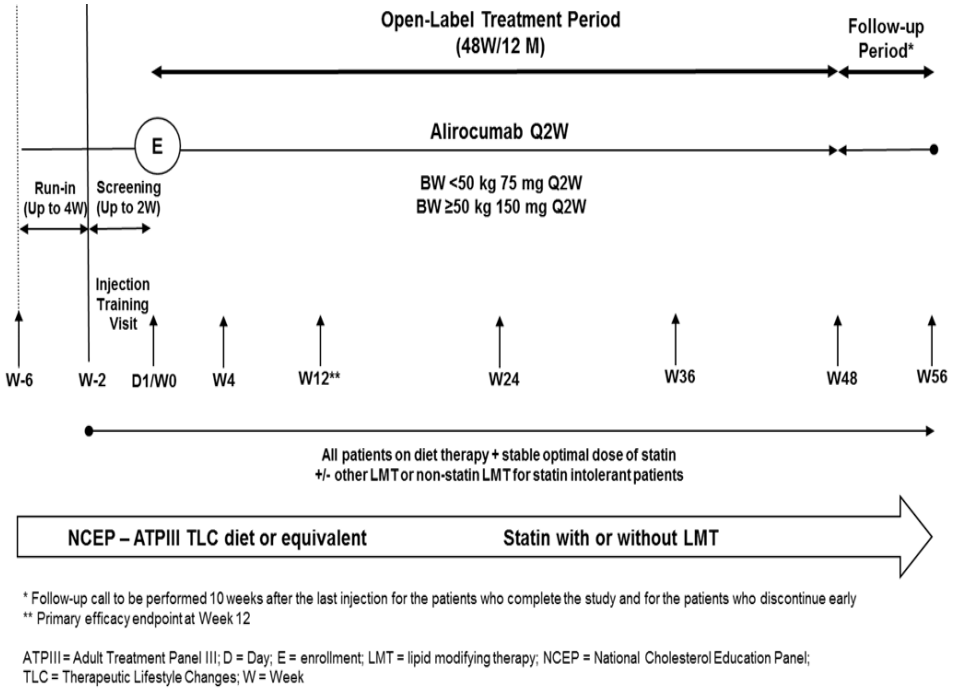
1.3 DETERMINATION OF SAMPLE SIZE

No sample size calculation was performed. Eighteen patients are planned to be enrolled to have at least 15 evaluable patients considering the recruitment constraints in this rare disease population.

1.4 STUDY PLAN

The following figure presents the graphical study design:

Figure 1 - Graphical study design



* Follow-up call to be performed 10 weeks after the last injection for the patients who complete the study and for the patients who discontinue early
** Primary efficacy endpoint at Week 12

ATPIII = Adult Treatment Panel III; D = Day; E = enrollment; LMT = lipid modifying therapy; NCEP = National Cholesterol Education Panel; TLC = Therapeutic Lifestyle Changes; W = Week

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).

As of the date of approval of this statistical analysis plan, the statistical section of the protocol has not been changed in any amendment.

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

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 30 May 2018.

Table 1 - Statistical analysis plan statistical changes

SAP version number	Date approved	Rationale	Description of statistical changes
2	This version	Genotyping data has been collected in order to document the diagnosis of HoFH and verify that patients do not have null mutations on both LDLR alleles.	Description of genotyping data related to HoFH diagnosis added in Section 2.1.1
2	This version	For cardiac troponin T, since expected values should be mainly below the lower limit of quantification (LLOQ) and since no reference ranges are available for healthy children in the central laboratory, quantitative description and description according to normal ranges are replaced by a description by category (<LLOQ, ≥LLOQ) at baseline and Week 12.	Cardiac troponin will be described by category (<LLOQ, ≥LLOQ) at baseline and Week 12. Quantitative analysis and summaries according to normal ranges will not be performed (Cf. Section 2.1.1 and Section 2.4.5.3).
2	This version	To ensure adequate selections of events of interest	Grouping for events of interest updated in Section 2.1.4.1 and in Appendix D based on the last MedDRA version currently in effect at Sanofi at the time of this amendment (version 22.1)
2	This version	To better assess pubertal maturation and the growth development during the study	For pubertal maturation: • Definition of global Tanner puberty classification added (Section 2.1.4.6) • Analysis of change from baseline in Tanner stage based on breast development (girls) or external genitalia (boys) added (Section 2.4.5.6) • Number of post-menarchal girls at baseline and during the study will be described (Section 2.4.5.6) For growth development (Section *2.4.5.4*): • description of % change from baseline in weight added • description of values and absolute change from baseline for BMI added

SAP version number	Date approved	Rationale	Description of statistical changes
2	This version	Post-apheresis LDL-C not considered in the analysis of patients with 2 consecutive low LDL-C values due to the expected transient status of such low values following apheresis. In addition, post apheresis LDL-C values are not related to the administration of the investigational product but directly related to the strength and the length of the apheresis procedure. Therefore they do not provide relevant information on the effectiveness of the IMP and the need to adjust treatment with the IMP.	The analysis of patients with 2 consecutive low LDL-C values (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)) based on post-apheresis LDL-C data will not be provided. Only the analysis using pre-apheresis data will be presented (cf. Section 2.1.5)
2	This version	Clarification that only enrolled patients are part of analyses populations.	• Description of disposition will be performed on enrolled patients instead of treated patients (Section 2.2). • Definition of populations are modified to exclude not enrolled patients from any analysis populations (Section 2.3).
2	This version	Define rule to derive non-HDL-C and calculated LDL-C values when HDL-C 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 values used for lipid quantitative analyses, in case of HDL-C <LLOQ (Section 2.5)
2	This version	Update PCSAs list for children to ensure consistency within the program with another study conducted in children (phase 2 DFI14223 study)	Update of the list of PCSAs for children (Appendix A)

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline value is defined as the last available value obtained up to the date and time of the first open-label IMP administration.

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

Demographic characteristics

Demographic variables are gender (Male, Female), race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, other), ethnicity (Hispanic or Latino, Not-Hispanic or Latino), age in years (quantitative and qualitative variable: <12 and ≥12 to <18 years, as well as <10, ≥10 to <12, and ≥12 to <18 years).

Medical or surgical history

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

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

Disease characteristics at baseline

Specific disease characteristic includes:

- Time from diagnosis of hoFH (years).
- Confirmation of diagnosis (genotyping [Yes, No]).
- HoFH genotype: Mutations affecting LDL receptor function are located on LDLR, LDLRAP1, PCSK9 or APOB genes. Patients are classified according to the mutant alleles and as either “true homozygote” (patients with the same mutation in both alleles of the same gene) , or “compound heterozygote” (patients with different mutation in each allele of the same gene), or “double heterozygotes” (patients with mutations in two different genes) or “Other” (patients not defined as above)
- Statin intolerant status, as per protocol definition [Yes, No]:
  - If Yes, reason the subject is statin intolerant: [Subject is not receiving a daily regimen of statin/Not tolerating daily dose, Subject unable to tolerate statins, having tried at least 2 statins: one statin at the lowest daily starting dose, AND another statin at any dose, due to skeletal muscle-related symptoms],
  - If Not statin intolerant: [Subject treated with maximal dose of statin he can tolerate due to AE at higher dose [Yes, No]].

    If Yes, AE(s) encountered at higher doses: [Skeletal muscle related events, Liver function test abnormalities, Co-morbid conditions such as impaired glucose tolerance/impaired fasting glucose, Other].

    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 lipid modifying therapy at enrollment, as reported in the dedicated prior & concomitant medications e-CRF pages.
- Any statin, eg,
  - 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)
  - Other statin (Yes/No)
- Any LMT other than statins:
  - Any LMT other than nutraceuticals (by chemical class and drug name) including fenofibrate and ezetimibe or other non-Statin LMT,
  - Nutraceuticals (Omega 3 fatty acids (<1000mg/day), Phytosterols, Psyllium/plantago, Policosanol, Other nutraceuticals).

Other baseline characteristics

Other baseline characteristics include body mass index (BMI) in kg/m² (quantitative and qualitative variable using BMI percentiles defined according to age for boys and girls: <P5: Underweight, ≥P5 to <P85: Healthy weight, ≥P85 to <P95: Overweight and ≥P95: Obesity, using the World Health Organization [WHO] growth reference 5-19 years [1, 2, 3]), weight in kg (quantitative and qualitative: <50, ≥50 kg), height in cm, smoking status and alcohol habits.

Glycated haemoglobin A1c (HbA_{1c}) (quantitative and qualitative variable: <5.7%, ≥5.7% to <6.5%, ≥6.5%), cardiac parameters (quantitative for CPK-MB, by category for cardiac troponin T (<LLOQ, ≥LLOQ)) and efficacy lipid parameters (pre-apheresis, if applicable) (quantitative variables for all efficacy parameters and the following qualitative 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

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

- Previous and concomitant statin drugs.
- Previous and concomitant lipid modifying therapy except Statin.
- Other Previous and concomitant medications.
- Medications - Anesthetic for IMP injection.
- Apheresis procedure.

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 IMP administration. Prior medications can be discontinued before first administration or can be ongoing during treatment phase.
- Concomitant medications are any treatments received by the patient concomitantly with the IMP, from first IMP to the last IMP injection +70 days. A given medication can be classified both as a prior medication and as a concomitant medication. Concomitant medications do not include medications started during the post-treatment period (as defined in the observation period in Section 2.1.4).
- Post-treatment medications are those the patient took in the period starting from 71 days after the last IMP injection and ending when the patient terminates the study.

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

Apheresis procedures:

- Apheresis history information such as the rate of patients on apheresis treatment, the time from the first apheresis procedure to the screening visit in years and the frequency (every week/every two weeks/other) for the last 4 apheresis procedures prior to screening.
- The frequency of the apheresis during the treatment period will be also described.

2.1.3 Efficacy endpoints

Efficacy endpoints include lipid parameters (ie, Total-C, LDL-C (calculated or measured), 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. Non-HDL-C is calculated by subtracting HDL-C from the Total-C. If TG values exceed 400 mg/dL (4.52 mmol/L), the LDL-C should be measured by the Central Laboratory (via beta quantification method) rather than calculated.

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 3 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. 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 value is the last available measurement obtained up to the date and time of the first IMP injection (pre-apheresis, if applicable).

2.1.3.1 Primary efficacy endpoint(s)

The primary efficacy endpoint is the percent change in LDL-C (pre-apheresis, if applicable) from baseline to Week 12 in the ITT population, using all LDL-C values (pre-apheresis, if applicable) regardless of adherence to treatment (ITT estimand). Primary endpoint is defined as: 100x (LDL-C value at Week 12 - LDL-C value at baseline) / LDL-C value at baseline.

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. For patients undergoing apheresis, pre-apheresis values will be considered.

2.1.3.2 Secondary efficacy endpoint(s)

The secondary efficacy endpoints are:

- Percent change in LDL-C (pre-apheresis, if applicable) from baseline to Week 12 in the ITT population, using all LDL C values during the treatment period (on-treatment estimand).
- Percent change in LDL-C (pre-apheresis, if applicable) from baseline to Weeks 24 and 48 (ITT and on-treatment estimands).

- Percent change in Apo B, non-HDL-C, Total-C, Lp (a), HDL-C, fasting TG and Apo A-1 (pre-apheresis, if applicable) from baseline to Weeks 12, 24, and 48 (ITT and on-treatment estimands).
- Proportion of patients with ≥15% reduction in LDL-C (pre-apheresis, if applicable) at Weeks 12, 24, and 48 (ITT and on-treatment estimands).
- The absolute change in LDL-C from baseline to Weeks 12, 24, and 48 (ITT and on-treatment estimands).

2.1.4 Safety endpoints

The safety analysis will be based on the reported adverse events and other safety information, such as clinical laboratory data, vital signs and Tanner stage assessment.

Observation period

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

- The PRE-TREATMENT period is defined from the signed informed consent up to the first dose of IMP injection.
- The TEAE period is defined as the time from the first dose of IMP injection to the last dose of IMP injection + 70 days (10 weeks) as residual effect of alirocumab cannot be excluded until 10 weeks after the discontinuation of IMP injection.

  The TEAE period will include:

  - The TREATMENT period: defined as the time from the first dose IMP injection up to the day of last IMP injection +21 days.
- The POST-TREATMENT period is defined as the time starting the day after the end of the TEAE period (ie, 71 days after the day of last dose of 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. 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.

- Treatment-emergent AEs are AEs that developed or worsened or became serious during the TEAE period.
- Post-treatment AEs are AEs that developed or worsened or became serious during the post-treatment period.

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 (i.e. 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 5 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 6 for the list of terms)
- Symptomatic overdose of IMP, selected using appropriate MedDRA codes and the tick boxes “Overdose of alirocumab” and “Symptomatic Overdose” in the overdose adverse event form
- Pregnancy (including male patient’s partner) selected using appropriate MedDRA codes

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

- Hepatic disorder events using SMQ “Hepatic disorder”
- Diabetes mellitus or diabetic complications using 1/ the HLGT “diabetic complications” (including PTs pertaining to the secondary SOC included in the HLGT), 2/ the HLT “diabetes mellitus”, 3/ the HLT “carbohydrate tolerance analyses (incl diabetes)” excluding PTs “blood glucose decreased” and “glycosylated haemoglobin decreased” and 4/ from the HLT "Hyperglyceamic 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 amendment (Version 22.1) 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.

- Death on-study: deaths occurring during the on-study observation period (ie, up to the last planned protocol visit).
- Death on-treatment: deaths occurring during the TEAE period.
- Death post-study: deaths occurring after the last planned protocol visit.

2.1.4.3 Laboratory safety variables

Clinical laboratory data consist of blood analysis, including hematology and clinical chemistry. 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 were to be collected during:

- Screening at Visit 2 (up to Week -2).
- The Open-Label Treatment Period at Visit 4 (Week 0), Visit 5 (Week 4), Visit 6 (Week 12), Visit 7 (Week 24) and Visit 9 (Week 48).

Blood samples for cardiac function were to be collected during:

- The Open-Label Treatment Period at Visit 4 (Week 0) and Visit 6 (Week 12) and in case of any clinically relevant cardiovascular effect observed in patients.

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

- Hematology
  - Red blood cells and platelets: hemoglobin, hematocrit, red blood cell count, platelet count,
  - White blood cells: white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils.
- Clinical chemistry
  - Metabolism: glucose, total protein, albumin, creatine phosphokinase (CPK),
  - Electrolytes: sodium, potassium, chloride, calcium, phosphorus, bicarbonate,

- Renal function: creatinine, eGFR, blood urea nitrogen, uric acid,
- Liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase (γGT), lactate 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).

- Serum pregnancy test: blood test at screening visit and local urine pregnancy test for all other tests.
- Cardiac function: CPK-MB and cardiac troponin.

Technical formulas are described in Section 2.5.1.

2.1.4.4 Vital signs variables

Vital Signs parameters include Height, Weight, BMI, Heart Rate (HR), Systolic and Diastolic Blood Pressure (SBP and DBP) in sitting position.

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 Open-Label Treatment Period at Visit 4 (Week 0), Visit 5 (Week 4), Visit 6 (Week 12), Visit 7 (Week 24), Visit 8 (Week 36) and Visit 9 (Week 48).

Body 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 Open-Label Treatment Period at Visit 4 (Week 0), Visit 5 (Week 4), Visit 6 (Week 12), Visit 7 (Week 24) and Visit 9 (Week 48).

Heart rate and blood pressure were to be measured during:

- Run-in (if applicable) at Visit 1(up to Week -6).
- Screening at Visit 2 (up to Week -2) and Visit 3 (up to Week -1; injection training visit as needed).
- The Open-Label Treatment Period at Visit 4 (Week 0), Visit 5 (Week 4), Visit 6 (Week 12), Visit 7 (Week 24), Visit 8 (Week 36) and Visit 9 (Week 48).

2.1.4.5 Electrocardiogram variables

Not applicable.

2.1.4.6 Tanner stages measurement

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

- Run-in (if applicable) at Visit 1 (up to Week -6) OR Screening at Visit 2 (up to Week -2).
- The Open-Label Treatment Period at Visit 6 (Week 12), Visit 7 (Week 24) and Visit 9 (Week 48).

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 of kids the first signs of puberty is breast development for girls and external genitalia for boys (4, 5, 6).

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 HbA1c (%) from baseline to Week 12, 24 and 48. Out of ranges value for HbA1c will also be used.
- 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) (pre-apheresis only).
- The time to the first LDL-C <50 mg/dL (<25 mg/dL, <15 mg/dL respectively) for these patients (pre-apheresis only).

2.1.6 Anti-alirocumab antibodies variables

Anti-alirocumab antibodies (ADA) (pre-apheresis, if applicable) are assessed during:

- The Open-Label Treatment Period at Visit 4 (Week 0), Visit 6 (Week 12), Visit 7 (Week 24) and Visit 9 (Week 48).

ADA measurements (pre-apheresis, if applicable) will be assigned to the same analysis windows as defined for efficacy endpoints (Table 3). ADA collected post-apheresis (if any) will be described separately.

The following variables will be described:

- 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,

    OR
  - Patients with a positive ADA response at baseline and at least a 4-fold increase in titer in the post-baseline period.

  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 after the last visit for patients with titer ≥240 at their last visit will be listed.

2.1.7 Pharmacokinetic variables

Concentrations of total alirocumab, total and free PCSK9 in serum are assessed before IMP (pre-dose) (pre apheresis and post-apheresis, if applicable) at baseline (Week 0), Week 12, Week 24, and Week 48. Concentrations will be described separately for patients on apheresis and for patients not on apheresis. For patients on apheresis, pre and post-apheresis concentrations will be analyzed separately.

Pharmacokinetic variable is the total alirocumab concentration at each time point. Depending on the timing of the sample versus the previous injection, C_{trough}, C_{max} and $C_{Follow\text{-}Up}$ will be defined as follows:

- C_{max}: alirocumab concentration sample taken 5 days ±2 days after previous injection of alirocumab.
- C_{trough}: alirocumab concentration sample taken between 8 and 21 days after previous injection of alirocumab (may be just prior the next injection).
- $C_{Follow\text{-}up}$: alirocumab concentration sample taken more than 21 days after last injection of alirocumab and no more than 14 weeks after last injection of alirocumab.

Alirocumab concentration and total and free PCSK9 concentrations will be described over time following time windows as defined in Section 2.5.4, Table 3.

2.1.8 Pharmacodynamic/genomics endpoints

Not Applicable.

2.1.9 Quality-of-life endpoints

Not Applicable.

2.1.10 Health economic endpoints

Not Applicable.

2.2 DISPOSITION OF PATIENTS

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

Screened patients are defined as any patient who originally met all the inclusion criteria and none of the exclusion criteria and signed the informed consent.

Enrolled patients consist of all screened patients, with a treatment kit number allocated and recorded in the IVRS/IWRS database, regardless of whether treatment kit was used or not.

For patient study status in the open label treatment period, the total number of patients in each of the following categories will be presented:

- Screened patients.
- Screen failure patients and reasons for screen failure.
- Treated and not enrolled
- Enrolled patients.
- Enrolled and treated patients.
- Enrolled and not treated patients and reason for not being treated.
- Patients who completed the open label treatment period as per protocol (as per e-CRF end-of-treatment form).
- Patients who did not complete the open label treatment period as per protocol (as per e-CRF end-of-treatment form).
- Patients who discontinued the open label treatment by main reason for permanent treatment discontinuation.

- Patients who completed the open label study period as per protocol (as per e-CRF end-of-study form).
- Patients who did not complete the open label study period as per protocol (as per e-CRF end-of-study form).
- Patients who discontinued the open label study by main reason for permanent study discontinuation.
- Status at last study contact.

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

Any critical or major protocol deviations (automatic or manual) will be summarized by deviation category in the enrolled population. 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. These deviations are listed in the centralized monitoring plan.

Additionally, the following populations will be summarized:

- Efficacy population: ITT population.
- Safety population.
- Pharmacokinetics population.
- Anti-alirocumab antibody population.

Definitions of the study populations are provided in Section 2.3.

2.2.1 Enrollment and drug dispensing irregularities

Enrollment and drug-dispensing irregularities occur whenever:

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

   OR

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

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

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

2.3 ANALYSIS POPULATIONS

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

2.3.1 Efficacy populations

The efficacy analysis population will be the ITT population.

The ITT population is defined as all enrolled patients who received at least one dose or partial dose of IMP.

2.3.2 Safety population

Safety analyses will be performed on the safety population, which will consist of enrolled patients receiving at least one dose or partial dose of IMP.

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

2.3.3 Anti-alirocumab antibody population

The anti-alirocumab antibody (ADA) analyses will be performed on all enrolled and treated patients (safety population) with a blood sample on Week 0 (baseline) and at least one evaluable blood sample for antibodies post first IMP injection.

2.3.4 Pharmacokinetics population

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

2.4 STATISTICAL METHODS

Unless otherwise specified, analyses will be performed overall and according to the dose received at study start (alirocumab 75 mg Q2W and alirocumab 150 mg Q2W).

2.4.1 Demographics and baseline characteristics

Parameters described in Section 2.1.1 will be summarized on the ITT population.

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

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

2.4.2 Prior or concomitant medications

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

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

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

The tables for concomitant and post-treatment medications will be sorted by decreasing frequency of ATC followed by therapeutic class based on the overall incidence. 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.

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

- Statin.
- Only LMT other than statin.
- No LMT.

The LMTs intensity at enrollment is defined as:

- Statin.
- Only LMT other than statin.

Apheresis procedures will be summarized at baseline and during the treatment period.

2.4.3 Extent of investigational medicinal product exposure and compliance

The extent of IMP exposure and compliance will be summarized for the safety population.

2.4.3.1 Extent of investigational medicinal product exposure

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

- Duration of IMP injection exposure in weeks defined as (date of last IMP injection + 14 days - date of first IMP injection) / 7, 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.
- The total number of IMP injections by patient.

Duration of IMP injection exposure will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum) and categorically using the following categories: ≥1 day to <4 weeks, ≥4 to <8 weeks, ≥8 to <12 weeks, ≥12 to <24 weeks, ≥24 to <36 weeks, ≥36 to <46 weeks and ≥ 46 weeks.

In addition, dose adjustments will be described.

2.4.3.2 Compliance

Compliance will be assessed using the following parameters:

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

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

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

and >20% days with above-planned dosing and numbers and percentages of patients with 0%, >0% and ≤5%, >5% and ≤10%, >10% and ≤20%, and >20% days with under-planned dosing.

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

2.4.4 Analyses of efficacy endpoints

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

Since there is no control group in this study, there will be no formal statistical test for the efficacy endpoints.

Efficacy endpoints analyzed with the ITT and on-treatment estimands will be analyzed in the ITT population.

2.4.4.1 Analysis of primary efficacy endpoint(s)

Unless otherwise specified, efficacy analyses will be performed overall only (all doses combined).

2.4.4.1.1 Primary efficacy analysis

The percent change from baseline in LDL-C at Week 12 as defined in Section 2.1.3.1 will be analyzed in the ITT population using a mixed-effect model with repeated measures (MMRM) approach. All post-baseline data available within the Week 4 to Week 48 analysis windows will be used and missing data will be accounted for by the MMRM model. The model will include the fixed categorical effect of time point (Weeks 4, 12, 24, and 48), as well as the continuous fixed covariate of baseline LDL-C value.

This model will be run using SAS mixed procedure with an unstructured correlation matrix to model the within-patient errors. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Denominator degrees of freedom will be estimated using Satterthwaite's approximation.

This model will provide baseline adjusted least-squares means estimates at Week 12 with their corresponding standard errors (SEs) and 95% confidence intervals (CI).

The MMRM model 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 2.4.4.1.3).

2.4.4.1.2 Model assumption checks

The analysis of the residuals of the MMRM 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:
  - Time point (Week 4, Week 12, Week 24, week 36, Week 48).

If the primary endpoint has a non-normal distribution, it will be analyzed using multiple imputation approach for handling of missing values as described for non-normally distributed endpoints with log-transformation (see Section 2.4.4.2.2 for details about multiple imputations).

2.4.4.1.3 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).

Pattern mixture model (see Appendix C for more details):

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 IMP injection up to the day of last injection +21 days) versus LDL-C values missing after treatment discontinuation (ie, after the day of last injection +21 days) based on the following assumptions:

- Patients within 21 days of their last 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.

Missing LDL-C values will be imputed 100 times to generate 100 complete data sets. The percent change from baseline to Week 12 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 95% CIs will be provided through the SAS MIANALYZE procedure using Rubin's formulae (8).

2.4.4.2 Analyses of secondary efficacy endpoints

2.4.4.2.1 Continuous endpoints anticipated to have a normal distribution

Continuous secondary variables defined in Section 2.1.3.2 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 model as for the primary endpoint with fixed planned post-baseline time points up to Week 48, as well as, the continuous fixed covariate of corresponding baseline value.

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

2.4.4.2.2 Continuous endpoints anticipated to have a non-normal distribution

Continuous secondary efficacy variables defined in Section 2.1.3.2 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. The percent change from baseline at time point of interest will be derived from observed and imputed lipid values at this time point. Multiple imputations will be followed by robust regression model (9) with endpoint of interest as response variable using M-estimation (using SAS ROBUSTREG procedure) with baseline value as effect. Combined means estimates with their corresponding SEs, 95% CIs will be provided through the SAS MIANALYZE procedure.

Multiple imputation model

Since in general the missing pattern is anticipated not to be 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 models for Step 1 and Step 2 will include the values of the analyzed parameter at baseline and time-points up to Week 48.

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.

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 in these models.

2.4.4.2.3 Binary endpoints

Binary secondary efficacy endpoints defined in Section 2.1.3.2 (ie, proportion of patients with ≥15% reduction in LDL-C at Weeks 12, 24, 48) 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 imputations).

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

The binary endpoint at time point of interest will be derived from observed and imputed lipid values at this time point. Combined proportion with their corresponding 95% CIs will be provided through the SAS MIANALYZE procedure.

Binary secondary efficacy endpoints analyzed with the on-treatment estimand will be analyzed using the same imputation model, but only including on-treatment values in this model.

2.4.4.2.4 Summary of results per time point

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, non-HDL-C, Total-C, Lp (a), HDL-C, fasting TG, Apo B, Apo A-1 and ratio Apo-B/Apo-A1 (absolute change from baseline) (pre-apheresis, if applicable) at Week 12, Week 24 and Week 48 time points will be summarized in the ITT population (ITT and on-treatment estimands) 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, absolute changes from baseline, or percent changes 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, absolute change from baseline and % change from baseline) will be presented for all lipids using observed (ie, non-missing) data. Post-apheresis data will be described separately. In addition, binary variables for LDL-C will be also described. These analyses will be done overall and by dose.

Descriptive summaries for value at visit, absolute change from baseline and % change from baseline for LDL-C using observed data will also be presented separately for patients on apheresis and without apheresis.

2.4.4.3 Multiplicity issues

Not applicable.

2.4.4.4 Additional efficacy analysis(es)

Not applicable.

2.4.5 Analyses of safety data

The summary of safety results will be presented on the safety population. No formal inferential testing will be performed. Summaries will be descriptive in nature.

General common rules

All safety analyses will be performed using the following common rules:

- The baseline value is defined as the last available value obtained up to the date and time of the first IMP injection.
- PCSA values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests and vital signs (PCSA in children [Appendix A] and PCSA in adults version dated May 2014 [Appendix B], for patients who become adults during the study ie, aged 18 years or greater during the study). 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 3 in order to provide an assessment for Week 4 to Week 48 time points.
- For quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results and change from baseline values by visit, using analysis windows. Summaries will also include the last on-treatment value and the worst on-treatment value. The last on-treatment value is defined as the last value collected during the treatment period (see Section 2.1.4). The worst on-treatment value is

defined as the nadir and /or the peak value during the treatment period according to the direction (minimum or maximum) of the abnormality as defined in the PCSA list.

2.4.5.1 Analyses of adverse events

Generalities

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

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

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

Sorting within tables ensures the same presentation for the set of all AEs within the observation period (pre-treatment, 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.
- All TEAEs by primary SOC, HLGT, HLT, and PT.
- All TEAEs by primary SOC and PT, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC (in the overall population). 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 overall population).

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 overall population) 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 overall population) within each SOC.
- All post-treatment SAEs by primary SOC and PT, sorted by the sorting order defined above.

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

Individual data listings of TEAEs in patients with two consecutive results of LDL-C <50 mg/dL (respectively LDL-C <25 mg/dL or LDL-C <15 mg/dL) (as defined in Section 2.1.5) will be provided.

Subgroups of patients with treatment-emergent ADA positive response

Individual data listings of TEAEs in patients with treatment-emergent ADA positive response will be provided.

2.4.5.2 Deaths

The following summaries of deaths will be generated:

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

2.4.5.3 Analyses of laboratory variables

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

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

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

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

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 as AESI during TEAE period by baseline status will be displayed for each parameter.

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

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

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

Creatine phosphokinase-MB and cardiac troponin

Creatine phosphokinase-MB (value and percent change from baseline) at Week 12 will be summarized on the safety population using number of available data, mean, SD, median, Q1, Q3, minimum, and maximum. In addition, similar table 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.

Cardiac troponin at Week 12 will be summarized on the safety population according to the following categories:

- < LLOQ;
- ≥ LLOQ

2.4.5.4 Analyses of vital sign variables

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

2.4.5.5 Analyses of electrocardiogram variables

Not Applicable.

2.4.5.6 Analyses 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 time point using count and percentage.

The change from baseline in Tanner stage based on development of external genitalia for boys, and breast development for girls, at Week 12, at Week 24 and Week 48 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 course of the study will be summarized.

2.4.6 Analyses of other endpoints

HbA_{1c} (value and absolute change from baseline) will be summarized by analysis visit using number of available data, mean, SD, median, minimum, and maximum for each dose during the treatment period. The time profile will be also plotted with the means and the corresponding SEs. Similar table 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.

Binary endpoints defined in Section 2.1.5 will be described using count and percentage. The "Time to" variables will be summarized using number of available data, mean, SD, median, minimum, and maximum.

2.4.7 Analyses of anti-alirocumab antibodies variables

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

- ADA results (negative or positive) by time point.
- Neutralizing status (negative or positive) by time point for positive ADA.
- ADA titers using descriptive statistics (median, minimum and maximum) for positive ADA by time point.
- Number (%) of patients with pre-existing ADA and number (%) of patients with treatment-emergent ADA positive response.

- Number (%) of patients with persistent/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.
- Time to onset of treatment-emergent persistent ADA positive response using descriptive statistics, beginning from the first IMP administration.
- Number (%) of patients with at least one neutralizing ADA.

2.4.8 Analyses of pharmacokinetic and pharmacodynamic variables

Concentrations of total alirocumab in serum ($C_{trough,}$ C_{max} and $C_{follow\text{-}up}$), free and total PCSK9 concentrations will be summarized on the PK population by visit using descriptive statistics. $C_{trough,av}$ will be summarized on the PK population using descriptive statistics.

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

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

2.4.9 Analyses of quality of life/health economics variables

Not applicable.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

The following formulas will be used for computation of parameters.

Time from diagnosis of hoFH

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

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

Renal function formulas

eGFR value will be derived using the Schwartz equation:

eGFR (mL/min/1.73 m^2) = (0.41 × Height in cm) / Creatinine in mg/dL

Lipids variables, laboratory safety variables

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

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 reported in the database, with the values that will be used in quantitative analyses for each parameter.

Table 2 - Example of lipid data for a "dummy" patient

Parameter	Value reported 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
TRIG	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 will be set to zero.

2.5.2 Data handling conventions for secondary efficacy variables

See Section 2.1.3.

2.5.3 Missing data

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

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

If the time of the first 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 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 if investigational medicinal product end of treatment date is missing

If the last injection date 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 (Week 48 visit 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, worsening, seriousness

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

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

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

When the time of the first IMP administration is missing, all AEs that occurred on the day of the first 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 will be assumed as possibly related in the frequency tables, but no imputation will be done at the data level.

Handling of potentially clinically significant abnormalities

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

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

For a PCSA defined on a threshold and/or a normal range, this PCSA will be derived using this threshold if the normal range is missing. 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, physical examinations, ADA, PK) will be summarized using the analysis windows given in Table 3. These analysis windows will be applicable for all analyses, and they are defined to provide more homogeneous data for time point-specific analyses.

Table 3 - Analysis windows definition for open-label treatment period

Time point	Targeted study day	Analysis window in study days
Week 4	29	8 to 49
Week 12	85	64 to minimum (98; study day corresponding to first the injection with IMP from kit allocated at Week 12 re-supply IVRS contact)
Week 24	169	148 to 189
Week 36	253	232 to 273
Week 48	337	309 to 364
Follow-up	Last IMP + 10 weeks	Last IMP+10 weeks ±4 weeks

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

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

PK Concentration will be analyzed as C_{max}, C_{trough} or $C_{follow-up}$ using definitions as defined in Table 4. If the date of the previous injection is unknown, the alirocumab concentration will not be considered for the analysis.

Table 4 - Time windows for PK variables definition

PK variables	Time window (D1 = day of previous injection or day of last injection for $C_{follow-up}$)
C_{max}	Day 4 to Day 8
C_{trough}	Day 9 to Day 22
$C_{follow-up}$	Day 23 to last injection + 14 weeks

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

If multiple valid values satisfy the C_{max}, C_{trough} or $C_{follow-up}$ criteria, the nearest from the targeted study day (ie, Day 6 for C_{max}, Day 15 for C_{trough} and Day 70 for $C_{follow-up}$, Day 1 being the day of previous injection) will be selected. If the difference is a tie, the value after the targeted study day will be used.

2.5.5 Unscheduled visits

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

2.5.6 Pooling of centers for statistical analyses

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

2.5.7 Statistical technical issues

Not Applicable.

3 INTERIM ANALYSIS

No formal interim analysis for efficacy is planned.

4 DATABASE LOCK

The database is planned to be locked at approximately 4 weeks after last patient last visit.

5 SOFTWARE DOCUMENTATION

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

6 REFERENCES

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7 LIST OF APPENDICES

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/1.73 m^2) (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.
HbA_{1c}	>8%	
Albumin	≤25 g/L	
CRP	>2 ULN or >10 mg/L (if ULN not provided)	FDA Sept 2005.

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

Parameter	PCSA	Comments
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.
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.

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

Parameter	PCSA	Comments
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

As a sensitivity analysis of the primary efficacy endpoint (ie, percent change from baseline to Week 12 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 injection +21 days) and missing LDL-C values after treatment discontinuation (ie, after the day of last injection +21 days) based on the following assumptions:

- Patients within 21 days of their last 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.

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 2 and Figure 3).

Figure 2 - Study DFI11565: calculated LDL-C mean (+/- SE) percent change from baseline

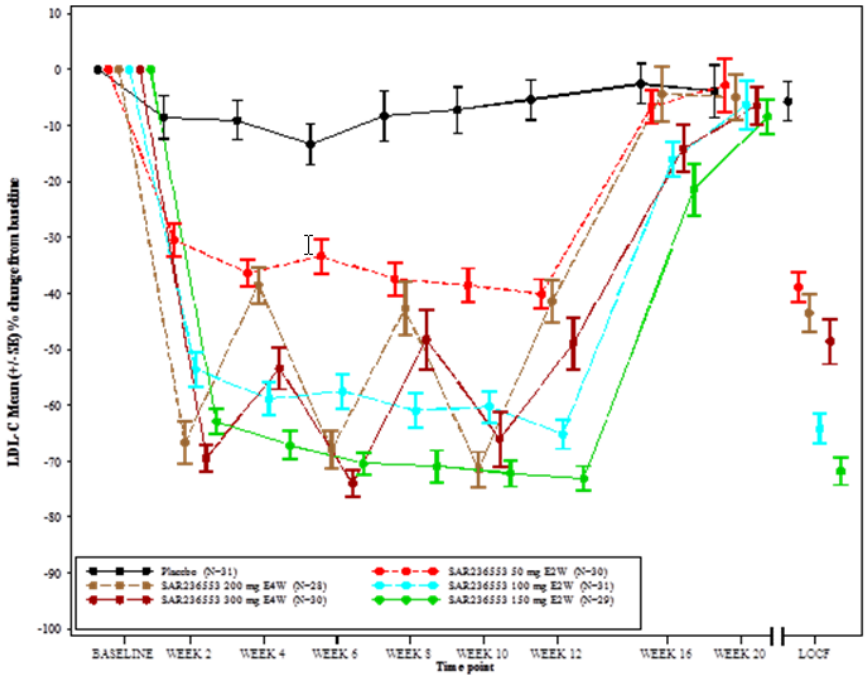
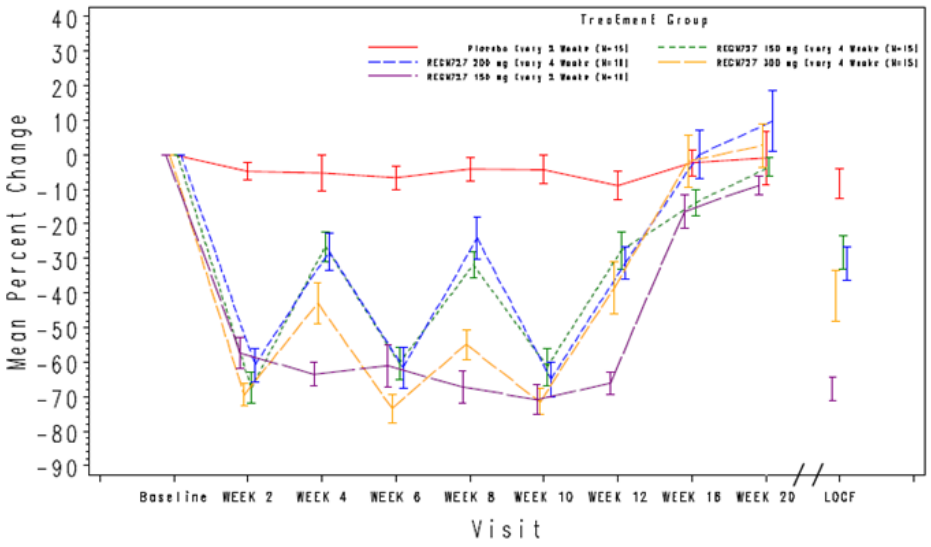


Figure 3 - Study R-727-CL-1003: calculated LDL-C mean (+/- SE) percent change from baseline



Missing LDL-C values will be imputed 100 times to generate 100 complete data sets. The percent change from baseline to Week 12 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 95% 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_W4   LDL_W12   LDL_W24   LDL_48;
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 5 - 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 6 - 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

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