STATISTICAL ANALYSIS PLAN

A Multi-Country, Multicenter, Single-Arm, Open-Label Study to Document the Safety, Tolerability and Effect of Alirocumab on atherogenic lipoproteins in High Cardio-Vascular Risk Patients With Severe Hypercholesterolemia Not Adequately Controlled With Conventional Lipid-Modifying Therapies

SAR236553-LPS14245

STATISTICIAN: [redacted]

DATE OF ISSUE: 11-Oct-2018

NCT02476006

Total number of pages: 59

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE:	adverse event
AESI:	adverse event of special interest
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
ATC:	anatomical therapeutic chemical
CHD:	coronary heart disease
CI:	confidence interval
CV:	cardiovascular
CVD:	cardiovascular disease
DBP:	diastolic blood pressure
ECG:	electrocardiogram
eCRF:	electronic case report form
eGFR:	estimated glomerular filtration rate
EOS:	end-of-study
EOT:	end-of-treatment
FDA:	Food and Drug Administration
FH:	familial hypercholesterolemia
HbA1c:	glycated hemoglobin A1c
HDL-C:	high density lipoprotein cholesterol
heFH:	heterozygous familial hypercholesterolemia
HLGT:	high level group term
HLT:	high level term
HR:	heart rate
IMP:	investigational medicinal product
IVRS:	interactive voice response system
IWRS:	interactive web response system
LDL-C:	low density lipoprotein cholesterol
LMT:	lipid modifying therapy
LTT:	lowest level term
Max:	maximum
MDRD:	modification of the diet in renal disease
MedDRA:	Medical Dictionary for Regulatory Activities
MI:	myocardial infarction
Min:	minimum
mITT:	modified intent-to-treat
PAD:	peripheral arterial disease
PCSA:	potentially clinically significant abnormality
PT:	preferred term
Q1:	first quartile
Q2W:	every 2 weeks

Q3:	third quartile
RBC:	white blood cells, red blood cells
SAE:	serious adverse event
SBP:	systolic blood pressure
SC:	subcutaneous
SD:	standard deviation
SE:	standard error
SIAQ©:	self-injection assessment questionnaire
SMQ:	standardized MedDRA query
SOC:	system organ class
TEAE:	treatment-emergent adverse event
TG:	triglyceride
Total-C:	total cholesterol
ULN:	upper limit of normal range

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN

This trial is to be conducted as a multi-country, multi-center prospective, single arm, open-label, phase IIIb clinical trial.

After enrollment, patients received study treatment (alirocumab) 150 mg subcutaneous (SC) once every 2 weeks (Q2W) or 75 mg SC Q2W. The dose could be adjusted according to the investigator, based on treatment response.

Alirocumab was administered on top of stable maximally tolerated statin therapy ± other lipid modifying therapy (LMT) over a period of at least 12 weeks and until the product becomes commercially available and reimbursed but for a period not exceeding 30 months of treatment.

In each country, patient recruitment was scheduled to end when alirocumab became commercially available and reimbursed. In this case, study treatment could be switched to the commercial product (or another LMT) once the patient had completed the minimum of 12 weeks of study treatment. As a consequence, the total duration of study depend on countries with a minimum of 12 weeks in each participating country and the number of patients at each time point beyond 12 weeks of study treatment is likely to be very variable.

During the course of the study, the investigator managed, based on his/her own clinical judgment and low density lipoprotein cholesterol (LDL-C) value, adjustment of alirocumab doses (either up-titration from 75 to 150 mg Q2W or down-titration from 150 to 75 mg Q2W, or maintenance of the dose). In case a modification of the current dose was decided, the patient was contacted by the site staff and an unscheduled visit was planned to dispense the new treatment kit and retrieve the current one.

The study consists of:

- A screening period of up to 3 weeks, including a training injection during which the patient or another designated person (such as spouse, relative, etc) was trained to self-inject/inject. An optional dedicated visit could be scheduled as needed.
- An open-label treatment period with alirocumab of at least 12 weeks and until the product becomes commercially available and reimbursed. However, the open label treatment period cannot exceed 30 months.
- An end-of-treatment (EOT)/end-of-study (EOS) visit taking place at least 2 weeks after the last study treatment injection.

Note that the original version of protocol included a post-treatment follow-up visit taking place 10 weeks after the last injection for patients who prematurely discontinued alirocumab for any reason as well as for those who switched to another LMT. For those patients who participated in the study under the original version of protocol, the EOT visit and the EOS visit did not occur at the same time (see Section 1.5).

The end of the study per patient is the last protocol planned visit or the resolution/stabilization of all serious adverse events (SAEs) and adverse events of special interest (AESIs), or death, whichever comes last.

During the screening and inclusion visits, it was checked that patients were not adequately controlled with a maximally tolerated dose of statin* with or without other LMT, all at stable doses for at least 4 weeks prior to the screening visit and could be classified in at least one of the following groups to be included in the study:

- A. Patients suffering from heterozygous familial hypercholesterolemia (heFH) with LDL-C concentrations ≥160 mg/dL (4.2 mmol/L) despite treatment.
- B. Patients suffering from heFH with LDL-C concentrations ≥130 mg/dL (3.4 mmol/L) despite treatment and two or more cardiovascular (CV) risk factors among this list:
  - Baseline LDL-C >6.46 mmol/L (250 mg/dL) at the time of the familial hypercholesterolemia (FH) diagnosis (before treatment).
- Family history of premature-onset coronary heart disease (CHD)
  - CHD (first-degree male relative with onset before age 55 years; first-degree female relative with onset before age 65 years),
  - Metabolic syndrome (cf. definition in protocol),
  - High density lipoprotein cholesterol (HDL-C) <1.03 mmol/L (0.40 g/L),
  - Hypertension (blood pressure [BP] >140/90 mmHg or drug treatment),
  - Lp(a) ≥0.50 g/L (1.78 µmol/L),
  - Tendon xanthoma.
- C. Patients suffering from heFH with LDL-C concentrations ≥130 mg/dL (3.4 mmol/L) despite treatment and one of the following characteristics:
  - **established CHD or other cardiovascular disease (CVD)** (history of acute myocardial infarction [MI], ischemic stroke, peripheral arterial disease [PAD], coronary or peripheral arterial revascularization, stable or unstable angina, transient ischemic attack, carotid artery stenosis ≥50%, aortic abdominal aneurysm),
  - **drug treated type 2 diabetes mellitus or type 1 with target organ damage**
  - **family history of first or second degree relative with very premature onset CHD** (first or second degree male relative onset before age 45; first or second degree female relative onset before age 55).
- D. **Non-FH patients suffering from established CHD or other CVD** (history of acute MI, ischemic stroke, PAD, coronary or peripheral arterial revascularization, stable or unstable angina, transient ischemic attack, carotid artery stenosis ≥50%, aortic abdominal aneurysm) **and with LDL-C concentrations ≥130 mg/dL (3.4 mmol/L).**
- E. **Patients suffering from progressive cardiovascular disease (**coronary artery disease, or peripheral arterial occlusive disease or cerebrovascular disease as documented clinically or by imaging techniques), **with a subsequent CV event** (*acute MI, ischemic stroke, ischemia driven revascularization, unstable angina, transient ischemic attack*) **occurring despite stable doses of maximally tolerated lowest level term (LTT) with LDL-C concentrations ≥100 mg/dL (2.59 mmol/L).**

* Definition of maximally tolerated dose (any of following):

- Rosuvastatin 20 mg or 40 mg daily
- Atorvastatin 40 mg or 80 mg daily
- Simvastatin 80 mg daily (if already on this dose for >1 year)

1.2 OBJECTIVES

1.2.1 Primary objective

The primary objective of this study for patients with severe hypercholesterolemia at risk for subsequent CV events and not adequately controlled with currently available LMT is to provide access to alirocumab ahead of commercial availability and to document the overall safety and tolerability of alirocumab in this patient population.

1.2.2 Secondary objectives

The secondary objectives are:

- To document the effect of alirocumab on LDL-C levels as well as non-HDL-C, total cholesterol (Total-C), HDL-C, triglyceride (TG) levels after 12 weeks of treatment.
- To document patient acceptability of self-injection (Self Injection Assessment Questionnaire [SIAQ©] throughout the study.

1.3 DETERMINATION OF SAMPLE SIZE

No formal sample size calculation has been done. The Safety analyses of this study will be descriptive. The table below provides the precision (95% Confidence Interval [CI]) associated to a variety of AE rates for an anticipated sample size of around 1300 patients:

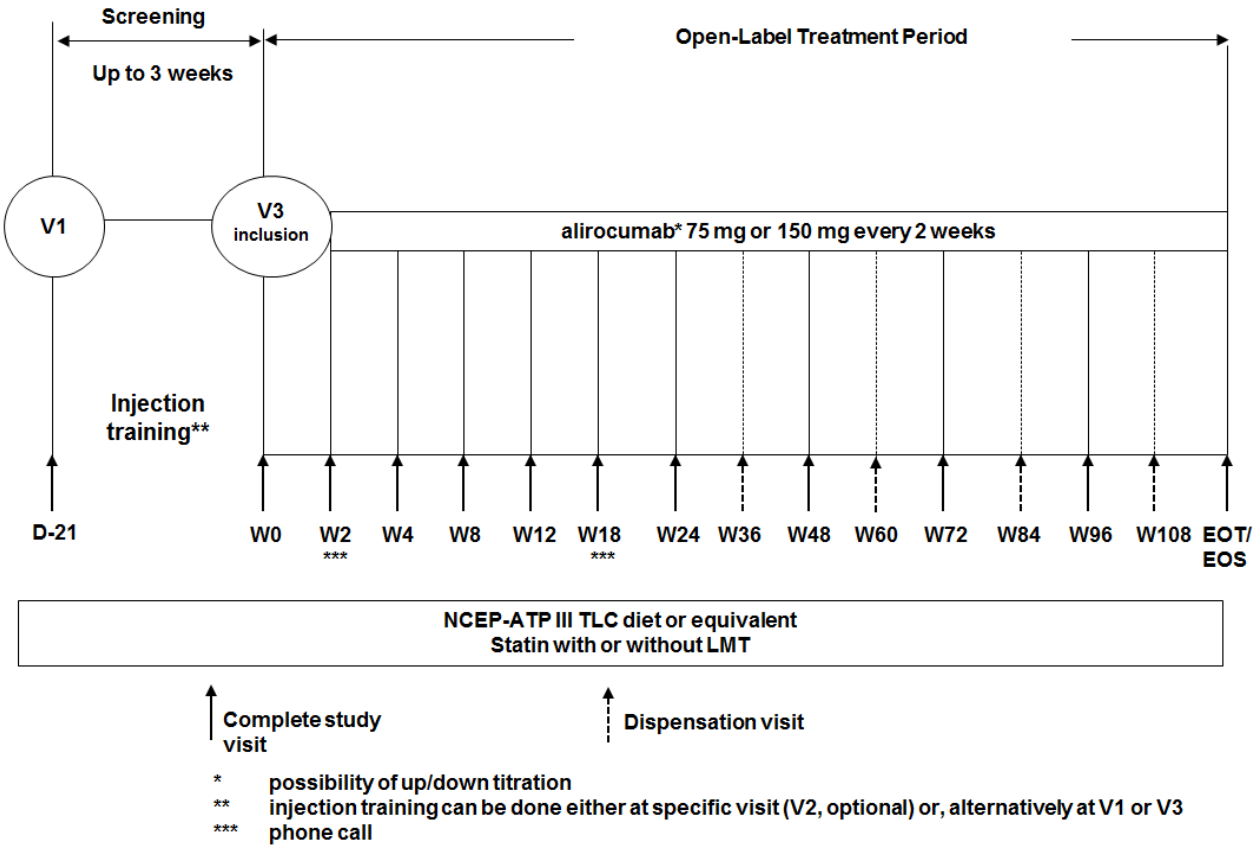
Table 1 - Expected 95% CI for various event rates

Adverse event rates	10%	20%	30%	40%	50%
95% CI	[8.4%; 11.6%]	[17.8%; 22.2%]	[27.5%; 32.5%]	[37.3%; 42.7%]	[47.3%; 52.7%]

For a rare non observed event, by using the rule of three, it can be estimated that the upper limit of the 95% CI of the event rate is approximately equal to 3 divided by the expected number of patients, ie, 0.23%.

1.4 STUDY PLAN

The study duration includes up to 3 weeks of screening period, a minimum of 12 weeks and up to a maximum 30 months of open label study treatment period and an end-study visit at least 2 weeks after the last study treatment injection. Note that the graphical study design displayed below corresponds to the amended protocol (see Section 1.5 for further details about the modifications with respect to the initial version of the protocol).



1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

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

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

The first patient was enrolled on 08 July 2015.

There was one global protocol amendment to the study protocol, introduced after the first patient was enrolled. The major change was about the final on-site visit.

In the newly amended version of the protocol, only one final on-site visit called "EOT/EOS" is required, for all enrolled patients. It has to be performed at least 14 days after the last study treatment injection. However, Investigators should continue to follow-up related SAE or AESI that are ongoing at this final visit until their resolution or stabilization.

In the original version of the protocol, a follow up on-site visit was required to take place:

- Either 2 weeks after last treatment injection for patients who would switch to commercial alirocumab.
- Or 10 weeks after last treatment injection for patients who would prematurely discontinue the treatment irrespective of the reason and for those who would switch to another compound.

Table 2 - Protocol amendment statistical changes

Amendment Number	Date Approved	Rationale	Description of statistical changes
Clinical Trial Amendment no. 5 (ie, the first global protocol amendment)	01Mar2016	Reassessment of the number of patients planned to be enrolled from 1100 initially planned to 1300	Modifications of the table of expected 95% CI for various adverse events rates
		Streamlining of the requirements for the end of study	Only one final on-site visit called "EOT/EOS Visit" is required
		Standardization across the protocols for observational studies	Modification of the list of the AE of special interest
		Clarification regarding the LDL-C assessment given that efficacy is a secondary endpoint and that no central lab is utilized in this study	The Friedewald formula to assess LDL-C will be used even in case TG is elevated (>400 mg/dL)
		Although there is no formal interim analysis, some statistical analyses might be performed before the end of the study in order to support a dossier of reimbursement if required by health authorities in some countries	Some statistical analyses might be performed before the end of the study

In addition to the medical history of specific interest to be described such as quoted in the protocol (CHD, CHD risk equivalents…), the multiple manifestations of CV disease (see Section 2.1.1) was added due to the very high risk of CV event profile of patients enrolled in this study.

Some secondary efficacy analyses were added compared to the original version of the protocol, mainly regarding the occurrence of very low LDL-C level and the associated changes in treatment (see Section 2.4.4.4) in order to better characterize these cases.

Additional descriptive analyses were added to document the adherence to statins according to alirocumab dose and the achieved LDL-C.

Two subgroups that are of particular clinical interest due to the very high risk of CV event profile of these patients were added, namely primary CVD prevention and the subgroup of patients with multiple manifestations of CV diseases.

The definition of the modified intent-to-treat (mITT) population was slightly changed in order to take into account the fact that no imputation will be performed for the missing LDL-C values. Consequently, the availability of a calculated LDL-C value within the analysis window associated to Week 12 is required
(See Section 2.3.1).

In the SIAQ© population is included the condition of the patient who followed the training injection.

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

Not applicable.

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline value is defined as the last value obtained before the date of the first injection of alirocumab.

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

Demographic characteristics

Demographic variables are:

- Gender (Male, Female)
- Race (White/Caucasian, Black, Asian/Oriental, Multiracial, other)
- Ethnicity (Hispanic, Not Hispanic)
- Age in years (quantitative and qualitative variable: <45, ≥45 to <65, ≥65 to <75, and ≥75 years)

Medical history

Medical history of specific interest includes:

- Coronary heart disease.
- Coronary heart disease risk equivalents.
- Cerebrovascular disease.
- Cardiovascular risk factors other than hypercholesterolemia (hypertension, type 2 diabetes, type 1 diabetes, family history of premature CHD). Smoking status will be summarized separately.
- Family history of type 2 diabetes.
- Patient's allergies (described using all pre-printed terms collected in the medical allergic history eCRF page).
- Familial allergic history.
- Multiple manifestations of CV disease.
- Primary and secondary CVD prevention.

The CHD, CHD risk equivalents and multiple manifestations of CV disease will be based on items or combination of items pre-printed in the dedicated CV medical history eCRF page and will also be searched in the list of other CV medical history.

CHD (regardless if it is ongoing or not) corresponds to one of the following items:

- Acute myocardial infarction
- Silent myocardial infarction
- Unstable angina
- Coronary revascularization procedures
- Other clinically significant CHD (diagnosed by invasive or non-invasive testing)

CHD risk equivalents (regardless if it is ongoing or not) corresponds to one of the following items:

- Peripheral arterial disease (as defined in Section 2.5.1)
- Ischemic stroke
- Chronic kidney disease
- Known history of diabetes mellitus (type 1 or 2) AND 2 or more additional risk factors among:
  - History of hypertension
  - History of microalbuminuria or macroalbuminuria or proteinura (>2+ at screening)
  - History of diabetic retinopathy
  - Known family history of premature CHD (before 55 years of age in male, 65 years of age in female first degree relatives)

Multiple manifestations of CV disease (regardless if it is ongoing or not) are defined as follows:

- Two arterial beds:
  - CHD and cerebrovascular disease
  - CHD and PAD
  - Cerebrovascular disease + PAD
- Three arterial beds: CHD and cerebrovascular disease and PAD (as defined in Section 2.5.1)

Cerebrovascular disease corresponds to one of the following items: carotid surgery or stenting, hemorrhagic stroke, ischemic stroke.

In addition, patients' status as primary and secondary CVD prevention will be summarized.

Secondary CVD prevention is defined as patients with at least one of the following conditions:

- History of acute myocardial infarction
- Ischemic stroke
- Peripheral arterial disease
- Coronary or peripheral arterial revascularization
- Stable or unstable angina
- Transient ischemic attack
- Carotid artery stenosis ≥50%
- Aortic abdominal aneurysm

All other patients will be classified as primary CVD prevention.

All medical/surgical history information in the eCRF (preprinted terms or terms mentioned in free text) will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

Disease characteristics at baseline

Specific disease characteristics include:

- Type of hypercholesterolemia
  - Heterozygous familial hypercholesterolemia (heFH): patients included in the groups A, B or C and some patients in the group E, at entry in the study (See Section 1.1),
  - Non-familial hypercholesterolemia (non-FH): patients included in the group D and some patients in the group E, at entry in the study (See Section 1.1).

  The type of hypercholesterolemia for any patient will be cross-checked with the answers mentioned in the medical history (1/5) page of the eCRF.
- For heFH patients
  - Time from diagnosis of hypercholesterolemia (years) computed as:
    (Year of inclusion - year of diagnosis) + (Month of inclusion - month of diagnosis)/12
    Confirmation of diagnosis (genotyping (Yes, No), WHO/Simon Broome criteria).
- For non-FH patients
  - Time from diagnosis of hypercholesterolemia (years) computed as:
    (Year of inclusion - year of diagnosis) + (Month of inclusion - month of diagnosis)/12.
- Lipid modifying therapy history, as reported in the "History of Hyperlipoproteinemia" eCRF page:
  - Type of lipid-modifying therapy ever taken (hydroxymethylglutaryl-coenzyme A [HMG CoA] reductases inhibitors [statin], fibrates, bile acid sequestrant, cholesterol absorption inhibitor, nicotin acid and derivatives, omega 3 fatty acid ≥1000 mg/day, other),
  - Number of patients taking at screening high intensity statins (atorvastatin 40 to 80 mg, rosuvastatin 20 to 40 mg or simvastatin 80 mg) daily and, for those not taking one of these agents at one of the specified doses, reasons for being on a lower dose or for not taking a statin ,
  - Number of patients receiving Simvastatin 80 mg/daily for at least 12 months without myopathy,
  - Number of patients with history of down titration of any statin dose due to tolerability issue,
  - Number of patients with history of change to any different statin due to tolerability issue.

Drug utilization: starting dose of alirocumab

The starting dose of alirocumab dispensed by investigator at inclusion will be described (75 mg or 150 mg) as well as who performed the first injection (patient, designated person, site member). It will be checked that any patient who self-injected or any designated person who injected the patient performed the training injection (with placebo).

Other baseline characteristics

Other baseline characteristics include:

- Body mass index (BMI) in kg/m^2 (quantitative and qualitative variable: <30, ≥30)
- Smoking status (Never smoked, Quit smoking, Currently smoker)
- Alcohol habits (Never, Occasionally, at least monthly, at least weekly, at least daily)
- Weight (quantitative and qualitative variable: <50, ≥50 to <70, ≥70 to <100 and ≥100 kg).
- Height (cm)
- Glycated hemoglobin A1c (HbA1c) (quantitative and qualitative variable: <5.7%, ≥5.7% to <6.5%, ≥6.5%)
- Efficacy lipid parameters - Quantitative analysis for all efficacy parameters, including Total-C and non-HDL-C, and the following qualitative categories for LDL-C, HDL-C, non HDL-C and TG:
- Calculated LDL-C: <70, [70-100[, ≥100 to <130, ≥130 to <160, ≥160 to <190, ≥190 mg/dL, ie, <1.81, ≥1.81 to <2.59, ≥2.59 to <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
- TG: <150, ≥150 to <200, ≥200 mg/dL, category ≥150 mg/dL (mixed dyslipidemia) will be also displayed, ie, <1.7 , ≥1.7 to <2.3, ≥2.3 mmol/L
- Non HDL-C: <100, [100-130[, [130-160[, [160-190[, [190-220[, ≥220 mg/dL, ie, <2.59, [2.59-3.37[, [3.37-4.14[, [4.14-4.91[, [4.91-5.7[, ≥5.7 mmol/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 started within 12 weeks before screening visit and until the end of the study include:

- Lipid modifying therapies (including statins)
- Cardiovascular drugs
- Other

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 the first injection of alirocumab. 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 alirocumab, from the first injection of alirocumab up to the last injection +2 weeks. Any given medication can be classified both as a prior medication and as a concomitant medication depending on the timing of administration.
- Post-treatment medications are those used beyond 2 weeks after the last injection up to the end of study.

For medications classified as "LMT", a flag will be created to categorize "Statin" and "other LMTs".

All medications with the following anatomical therapeutic chemical (ATC) codes will be described and considered as **Statin**:

- C10AA, C10BA, and C10BX.

All medications with the following ATC codes will be described and considered as **other LMTs**:

- C10AX06 (Omega-3-triglycerides), C10AX09 (Ezetimibe), C10AD02 (Nicotinic acid), C10AC01 (Colestyramine); C10AC02 (Colestipol); C10AC04 (Colesevelam); C10AB05 (Fenofibrate) and any other (for the rest).

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

2.1.3 Efficacy endpoints

Efficacy endpoints include lipid parameters: calculated LDL-C, Total-C, HDL-C, TG, non-HDL-C. Total-C, HDL-C, TG will be provided by a local Laboratory. LDL-C will be calculated using the Friedewald formula (1) at all site visits (see Section 2.5.1). One of the most important limitations of the Friedewald formula is that it is not appropriate at TG concentrations >400 mg/dL, anyway and in order to simplify the computations this formula will be used regardless of the TG values. Non-HDL-C is calculated by subtracting HDL-C from the Total-C.

Unless otherwise specified, all lipid values (scheduled or unscheduled, fasting or not fasting) may be used to provide a value for the efficacy endpoints. All measurements, scheduled or unscheduled, fasting or not fasting, will be assigned to analysis windows defined in Table 2 in order to provide an assessment from Week 4 to the end of the study.

The main efficacy endpoint will be the LDL-C at Week 12 (change from baseline). Nevertheless, all efficacy endpoints will be described at each time point.

For all post-baseline time points, the value used for the analyses at a given time point will be the value obtained within the corresponding analysis window. The baseline value is defined as the last available measurement obtained before the date of the first injection of alirocumab.

2.1.3.1 Primary efficacy endpoint(s)

No primary efficacy endpoints are defined since the primary objective is dedicated to safety.

2.1.3.2 Secondary efficacy endpoint(s)

The main efficacy secondary endpoint will be:

- The percent change in calculated LDL-C from baseline to Week 12 (on-treatment estimand).

The key secondary efficacy endpoints will include:

- The proportion of patients reaching calculated LDL-C <100 mg/dL (2.59 mmol/L) at Week 12 (on-treatment estimand).
- The proportion of patients reaching calculated LDL-C <70 mg/dL (1.81 mmol/L) at Week 12 (on-treatment estimand).
- The proportion of patients with LDL-C <70 mg/dL (1.81 mmol/L) and/or ≥50% reduction from baseline in calculated LDL-C at Week 12 (on-treatment estimand).
- The percent change in non-HDL-C, total-C, HDL-C, TG from baseline to Week 12 (on-treatment estimand).

The other secondary efficacy endpoints will be:

- The proportion of patients who were up-titrated from 75 mg Q2W to 150 mg Q2W of alirocumab during the observational period based on investigator's judgment (on-treatment estimand).
- The proportion of patients who were down-titrated from 150 mg Q2W to 75 mg Q2W of alirocumab during the observational period based on investigator's judgment (on-treatment estimand).
- The reasons (ie, LDL-C threshold, AE) that triggered a down-titration or an up-titration of alirocumab (on-treatment estimand).
- The percent change in LDL-C from baseline over time, using all LDL-C values during the efficacy treatment period (on-treatment estimand) defined in Section 2.3.1.
- The absolute change in calculated LDL-C (mg/dL and mmol/L) from baseline over time, using all LDL-C values during the efficacy treatment period (on-treatment estimand).
- The proportion of patients reaching calculated LDL-C <100 mg/dL (2.59 mmol/L) over time (on-treatment estimand).
- The proportion of patients reaching calculated LDL-C <70 mg/dL (1.81 mmol/L) over time (on-treatment estimand).
- The proportion of patients with calculated LDL-C <70 mg/dL (1.81 mmol/L) and / or ≥50% reduction from baseline in calculated LDL-C over time (on-treatment estimand).
- The percent change in non-HDL-C, total-C, HDL-C, TG from baseline over time (on-treatment estimand).
- The absolute change in non-HDL-C, total-C, HDL-C, TG (mg/dL and mmol/L) from baseline over time (on-treatment estimand).

Since the study duration for each participating country will depend on when alirocumab becomes commercially available and reimbursed, with a minimum duration of 12 weeks and up to a maximum of 120 weeks, the secondary efficacy endpoints associated to the lipid parameters will be also assessed at the following time points depending on countries: Weeks 4, 8, 12, 24, 48, 72, 96 and 120 (EOT/EOS).

2.1.4 Safety endpoints

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

Observation period

For all enrolled patients, the period of safety observation starts from the time when the patient gives his/her informed consent and is divided into the following periods:

- The PRE-TREATMENT observation period is defined from the signed informed consent up to the first dose of alirocumab.
- The treatment-emergent adverse event (TEAE) period is defined as the time from the first injection of alirocumab up to the day of the last injection of alirocumab + 14 days.
- The POST-TREATMENT period will cover a period from the day after the end of the TEAE period up to the end of the study (defined as last protocol-planned visit or the resolution/stabilization of all SAEs and AEs with pre-specified monitoring as defined in protocol).

The on-study observation period is defined as the time from the day of first dose of alirocumab until the last protocol planned visit of the patient.

2.1.4.1 Adverse events variables

Adverse events, including AESIs, SAEs and product complaints, will be collected from the time the patient signs the informed consent to the completion of the safety observation period. 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 the considered database lock.

Adverse event observation period

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

Adverse events of special interest

An AESI is an AE (serious or non-serious) that needs to be monitored, documented, and managed in a pre-specified manner described in the protocol.

Following an amendment to the initial protocol (See Section 1.5), the AESIs will be analyzed according to the amended protocol.

For this study, the AESIs are the following:

- Increase in alanine aminotransferase (ALT): ALT ≥3 x upper limit of normal range (ULN) (if baseline ALT <ULN) or ALT ≥2 times the baseline value (if baseline ALT ≥ULN), selected using laboratory data (see Appendix F in the protocol).
- **Allergic events that require consultation with another physician** will be described. Events will be selected using the following standardized MedDRA query (SMQ): "hypersensitivity" (broad and narrow) excluding the preferred terms linked to local injection site reactions ("infusion site dermatitis", "infusion site hypersensitivity", "infusion site rash", "injection site dermatitis", "injection site hypersensitivity", and "injection site rash"). The condition "consultation with another physician" will be considered as verified if a dermatology consultation was completed and/or if a description of the rash was provided by the dermatology consultation.
- In addition, an analysis will be performed for any allergic event whether meeting or not AESI criteria meeting the above SMQ criteria.
- **Local injection site reactions that are allergic in nature** deemed to be allergic by the Investigator (or have an allergic component) AND that require consultation with another physician will be selected using the PTs corresponding to local allergic reactions: "Injection site dermatitis", "Injection site hypersensitivity", "Injection site oedema", "Injection site rash", "Injection site urticaria", "Injection site eczema", "Injection site vasculitis", "Injection site swelling", "Infusion site dermatitis", "Infusion site hypersensitivity", "Infusion site oedema", "Infusion site rash", "Infusion site urticaria", "Infusion site swelling". The condition "consultation with another physician" will be considered as verified if a dermatology consultation was completed and/or if a description of the rash was provided by the dermatology consultation.
- An analysis using these PTs will also be performed for any local injection site reaction whether requiring consultation or not.
- In addition, an analysis will be performed for any local injection site reaction not meeting AESI criteria (not allergic and not requiring consultation with another physician) using the HLT "injection site reaction".
- **Pregnancy** of female patients will be selected using the appropriate MedDRA codes.

- **Symptomatic overdose with Alirocumab.** Overdose with alirocumab is defined as at least twice of the intended dose within the intended therapeutic interval (ie, 2 or more injections are administered in <7 calendar days), to be reported using the Term "symptomatic OVERDOSE" (accidental or intentional), indicating the circumstance in parentheses (eg, "symptomatic overdose [accidental]" or "symptomatic overdose [intentional]"). These events will be selected using the AESI category as selected by the site.
- Another analysis will be performed using all overdose cases (whether symptomatic or asymptomatic and whether with alirocumab or another drug) using the HLT "Overdose".
- In addition, an analysis will be performed using all overdose cases (whether symptomatic or asymptomatic) using the HLT "Overdose" with the condition "relationship to investigational medicinal product (IMP)" as YES.
- **Neurologic events that require additional examinations/procedures and/or referral to a specialist** will be selected using SMQ "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".
- An additional analysis will be performed analyzing all events meeting the above SMQ criteria for neurologic events whether or not the criteria for an AESI are met (whether or not requiring additional exams/procedures and/or referral to a specialist).
- **Neurocognitive events** will be selected using the sponsor Company MedDRA Query (CMQ) based on HLGTs "Deliria (incl confusion)", "Cognitive and attention disorders and disturbances", "Dementia and amnestic conditions", "Disturbances in thinking and perception", "Mental impairment disorders".
- In a second approach, neurocognitive events will be analyzed using the CMQ developed using the Food and Drug Administration (FDA) grouping of events based on PTs "Amnesia", "Amnestic disorder", "Anterograde Amnesia", "Neuropsychiatric symptoms", "Change in sustained attention", "Cognitive Disorder", "Confusional State", "Delirium", "Dementia", "Dementia Alzheimer's type", "Dementia with Lewy Bodies", "Disorientation", "Disturbance in attention", "Executive dysfunction", "Frontotemporal Dementia", "Illogical Thinking", "Impaired reasoning", "Incoherent", "Judgement impaired", "Memory Impairment", "Mental Impairment", "Mental Status Changes", "Mini Mental Status Examination Abnormal", "Presenile Dementia", "Retrograde Amnesia", "Senile Dementia", "Thinking Abnormal", "Transient Global Amnesia ", "Vascular Dementia" and the LLTs "Mental State Abnormal Aggravated", "Thinking Slowed".

2.1.4.2 Deaths

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

- Death on-study: deaths occurring during the on-study observation period.
- Death on-treatment: deaths occurring during the TEAE period.
- Death post-study: deaths reported after the last planned protocol visit.

2.1.4.3 Laboratory safety variables

The clinical laboratory data consist of urinalysis and blood analysis.

Blood samples for laboratory tests are drawn at screening visit, Week 4 (except HbA1c), Week 8 (only for liver panel), Week 12, Week 24, Week 48, Week 72, Week 96 and EOT/EOS. Hepatitis B antigen is measured at screening only and Hepatitis C antibody at screening and at EOT/EOS. Serum pregnancy test is performed at screening and urine pregnancy test is performed at inclusion and at the end of study.

- Hematology (red blood cells [RBC] count, hemoglobin, hematocrit, platelets, white blood cells [WBC] count with differential blood count).
- Standard chemistry (fasting plasma glucose, sodium, potassium, chloride, bicarbonate, CPK, calcium, phosphorous, urea nitrogen, creatinine and calculated creatinine clearance using Cockroft-Gault formula or Estimated Glomerular Filtration Rate [eGFR] using modification of the diet in renal disease (MDRD) Study equation, uric acid, total protein, lactic dehydrogenase (LDH), albumin, γ-Glutamyl Transferase [γGT] Hepatitis B antigen, Hepatitis C antibody).
- HbA1c.
- Liver panel (ALT, aspartate aminotransferase [AST], alkaline phosphatase [ALP], and total bilirubin).
- Serum and urine pregnancy test.

Urinalysis - dipstick is performed at site or at the local Laboratory at screening, inclusion, Week 12, EOT/EOS visits and as needed during the study at investigator's discretion. It will assess for WBC, RBC, pH, specific gravity (qualitative/quantitative), and for the presence of blood, protein, glucose, ketones, nitrates, leukocyte esterase, uro-bilinogen and bilirubin.

Technical formulas are described in Section 2.5.1.

2.1.4.4 Vital signs variables

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

2.1.5 Patient reported outcome

The SIAQ©v2 (Self-Injection Assessment Questionnaire) is a Patient Reported Outcome (PRO) designated to assess the benefits and the potential limitations of self-injections of a subcutaneous medication perceived by patients who self-inject. It contains two modules; one to be self-completed before the first self-injection (hereafter "PRE module" or "PRE-SIAQ") and another one to be self-completed after self-injection (hereafter "POST module" or "POST-SIAQ").

- The PRE-SIAQ consists of 7 items grouped into three domains:
  - Feelings about injections (3 items),
  - Self-confidence (3 items),
  - Satisfaction with self-injection (1 item).

- The POST-SIAQ consists of 21 questions corresponding to 27 different items grouped into six domains:
  - Feelings about injections (3 questions/items),
  - Self-image (1 question/item),
  - Self-confidence (3 questions/items),
  - Injection-site reactions (2 questions including 8 items),
  - Ease of use (5 questions/items),
  - Satisfaction with self-injection (7 questions/items).

The PRE-SIAQ is completed only once by patients who self-inject, before the first self-injection and the POST-SIAQ is completed by any patient who self-injects at Week 4, Week 8, Week 12, Week 24, Week 48 and then at Week 72 and at Week 96.

See Appendix B for a more detailed presentation of the SIAQ©.

2.2 DISPOSITION OF PATIENTS

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

- Screened patients are defined as any patient who signed the informed consent.
- Enrolled patients consist of all screened patients, with a treatment kit number allocated and recorded in the interactive voice response system (IVRS)/interactive web response system (IWRS) database, regardless of whether treatment kit was used or not.

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

- Screened patients.
- Screen failure patients and reasons for screen failure.
- Enrolled patients.
- Enrolled but not treated patients and reason for not being treated.
- Enrolled and treated patients.
- Patients who did not complete the study treatment period as per protocol.
- Patients who discontinued the study treatment by main reason for permanent treatment 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 the denominator. A listing of other reasons for treatment discontinuation will be provided.

The incidence of premature treatment discontinuation (irrespective of the reason) and premature treatment discontinuation due to AEs will be presented graphically, using Kaplan-Meier method (provided that the number of patients concerned is not too small).

The disposition of patients will be presented overall and by country or pooled countries.

A patient is considered **lost to follow-up** (LTFU) if the patient has the information box *"Lost to Follow-Up"* ticked in the CRF p.46.

All critical or major deviations potentially impacting efficacy analyses, enrollment, and drug-dispensing irregularities, and other major or critical deviations will be summarized in tables giving numbers and percentages of deviations. The deviations are listed in the data review and surveillance plan.

In addition, the following populations will be summarized overall:

- Modified intent-to-treat population (mITT).
- Safety population.
- Self-injection population: safety population patients who gave themselves at least 1 alirocumab injection during the observational period.

Definition of the study population are given in Section 2.3.

2.2.1 Enrollment and drug dispensing irregularities

This is an open-label study and every patient will receive alirocumab. Treatment kit numbers will be allocated via interactive voice/web response system (IVRS/IWRS).

Each alirocumab treatment kit will be prepared to contain 6 pre-filled pens.

In addition to the alirocumab treatment kits, a training kit containing 1 placebo pre-filled pen will be prepared for the purpose of instructing patients on injection administration. The content of the labelling is in accordance with the local regulatory specifications and requirements.

Enrollment and drug-dispensing irregularities will be monitored throughout the study and reviewed on an ongoing basis. They will be documented in the clinical study report. The irregularities will be categorized and summarized among enrolled patients (number and percentages).

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

- Kit dispensation without IVRS transaction.
- Erroneous kit dispensation.
- Kit not available.
- Enrolled by error.
- Patient enrolled twice.

2.3 ANALYSIS POPULATIONS

2.3.1 Efficacy population

The efficacy population considered for efficacy analyses will be the mITT population.

The modified intent-to-treat population (mITT) also referred as on-treatment in section above, is defined as: all enrolled patients who took at least one dose or part of a dose of alirocumab and had an evaluable efficacy endpoint during the efficacy treatment period. The main efficacy endpoint will be evaluable provided that the 2 following conditions are met:

- Availability of a baseline calculated LDL-C value (last value available prior to the first injection of alirocumab).
- Availability of the calculated LDL-C within the analysis window associated to Week 12.

The efficacy treatment period is defined as the time period from the first injection of alirocumab up to the day of last injection + 21 days.

2.3.2 Safety population

The safety population will consist of the patients who have signed the informed consent form and who have received at least one dose or partial dose of alirocumab.

2.3.3 Other analysis population

The analysis of the SIAQ© will be performed in the patients of the safety population who followed the training injection and had at least one alirocumab self-injection.

2.4 STATISTICAL METHODS

All statistical analyses will be descriptive and no formal statistical test will be performed.

Analyses will be performed overall and on some sub-groups of interest such as:

- Patients included in each of the risk groups at inclusion (see Section 1.1) enrolled patients who did not fulfill inclusion criterion I 03 will not be considered for this subgroup analysis. However, they will be part of the overall analysis.
- Patients with heFH / non-familial FH.
- Type 1 and Type 2 diabetes mellitus / patients without diabetes.
- Established CHD or other CVD (including patients suffering from progressive cardiovascular disease).

Results will be reported globally without regional subgroups.

The results per country if sample size is sufficient (≥30), or by pooled countries if sample size is not sufficient (<30), will not be displayed in this Statistical Analysis Plan but it will be displayed in post-hoc analysis if it is necessary and asked by the medical countries affiliates.

(Since some countries will include a small number of patients, the statistical results for these countries will have to be interpreted with caution. Likewise, some sub-groups might include a very small number of patients and the statistical results will have to be discussed when analysis will be displayed in post-hoc. Suggested pooled countries could be as follows: Denmark with Finland; Germany with Belgium; Slovakia with Czech Republic; and the last one, Slovenia with Hungary, Romania, and Greece).

Final analysis will be performed after the global Data Base Lock.

Efficacy analysis, AEs analysis and demographics description will be displayed overall, and by the sub-groups of interest descripted above.

2.4.1 Demographics and baseline characteristics

Parameters described in Section 2.1.1 (demographic characteristics, medical history including medical history of specific interest, disease characteristics at baseline, starting dose of alirocumab, other baseline characteristics) will be summarized using descriptive statistics.

The number and percentage of patients will be provided for qualitative variables. The following information will be provided for continuous variables: number of patients, mean, standard deviation, median, as well as Min and Max, first quartile (Q1) and third quartile (Q3).

Parameters will be summarized in the safety population. The analyses will also be performed in the mITT population only if the number of patients in the mITT population is below 90% of the number of patients in the safety population.

Medical history of specific interest (see Section 2.1.1) will presented according to the terms pre-listed in the eCRF and will be displayed overall and by groups at inclusion (A, B, C, D, E) using the number and the proportions of patients.

Other relevant medical/surgical history will be presented by primary SOC and PT. The tables will be sorted by SOC internationally agreed order and decreasing frequency of PT based on the overall incidence.

For each type of hypercholesterolemia (heFH/non-FH), the LDL-C value at entry in the study will be described quantitatively and qualitatively (<70, ≥70 to <100, ≥100 to <130, ≥130 to <160, ≥160 to <190, ≥190 mg/dL, ie, <1.81, ≥1.81 to <2.59, ≥2.59 to <3.37, ≥3.37 to <4.14, ≥4.14 to <4.91, ≥4.91 mmol/L, overall and by inclusion criteria, ie, by groups A, B, C, D or E. Note that any patient could contribute to several inclusion groups.

The starting dose of alirocumab at the entry of patients in the study will be described. The number and proportion of patients for whom alirocumab was started at 75 mg (respectively 150 mg) will be summarized:

- Overall.
- by classes of baseline LDL-C level (<70, ≥70 to <100, ≥100 to <130, ≥130 to <160, ≥160 to <190, ≥190 mg/dL, ie,<1.81, ≥1.81 to <2.59, ≥2.59 to <3.37, ≥3.37 to <4.14, ≥4.14 to <4.91, ≥4.91 mmol/L.
- by diagnosis of heterozygous familial hypercholesterolemia.
- by diagnosis criteria, ie, groups A, B, C, D, E at the enrollment in the study.

The LDL-C values will also be quantitatively summarized for each level of starting dose.

The person who gave the injection of alirocumab at inclusion will be described by the number and the proportion of patients in each of the following categories: patient, designated person, site staff. In addition, among patients who self-injected, the proportion of patients who performed themselves their training injection with placebo will be indicated.

2.4.2 Prior or concomitant medications

The prior and concomitant medications will be presented for the safety population.

Medications will be summarized according to the WHO-DD, considering the first digit of the anatomic category (ATC) class (anatomic category) and the first 4 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 several times for the same medication.

The table for prior medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the overall incidence.

The tables for concomitant will be sorted by decreasing frequency of ATC followed by all other therapeutic classes. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

The tables of prior and concomitant medications will be performed by each one of the following categories:

- Lipid modifying therapies (for these tables, the medications will be displayed taking into account the classification of “Statins” and “Other than statins” as well).
- Cardiovascular drugs.
- Other.

2.4.3 Extent of investigational medicinal product exposure and compliance

The extent of study treatment exposure and compliance will be assessed and summarized within the safety population (Section 2.3.2).

2.4.3.1 Extent of investigational medicinal product exposure

The total exposure will be assessed using descriptive statistics for:

- Duration of alirocumab exposure in weeks defined as:
  (last alirocumab injection date + 14 - first alirocumab injection date)/7, regardless of unplanned intermittent discontinuations. Non-integer values will be rounded to one decimal place.
- Total number of alirocumab injections by patient.

These quantitative parameters will be summarized using number, mean, standard deviation (SD), median, Q1, Q3, Min, and Max.

In addition, duration of treatment exposure will also be summarized categorically by number and percentages for each of the following categories and cumulatively according to these categories:

- 1 day ≤ duration <4 weeks
- 4 weeks ≤ duration <8 weeks
- 8 weeks ≤ duration <12 weeks
- 12 weeks ≤ duration <18 weeks
- 18 weeks ≤ duration <24 weeks
- 24 weeks ≤ duration <36 weeks
- 36 weeks ≤ duration <48 weeks
- 48 weeks ≤ duration <60 weeks
- 60 weeks ≤ duration <72 weeks
- 72 weeks ≤ duration <84 weeks
- 84 weeks ≤ duration <96 weeks
- 96 weeks ≤ duration <108 weeks
- duration ≥108 weeks

The number of patients who gave themselves a training injection (with placebo) will also be described.

2.4.3.2 Compliance

Compliance will be assessed using the following parameters:

- The mean injection frequency of alirocumab will be defined for each patient as the average number of days between 2 consecutive injections, that is:
  (last dose date - first dose date)/(number of injections -1) for patients receiving at least 2 injections.
- The overall compliance will be defined for each patient as:
  (number of injections performed during the study period/number of theoretical injections to be performed during the study period)*100. The number of theoretical injections will be defined for each patient as: (last injection date - first injection date)/14.

- Number and percentage of patients who discontinued temporarily, with delayed injections and/or partially administered injections will be described. For patients with temporary discontinuations, the number of injections not performed will be displayed.

These parameters will be summarized descriptively (N, Mean, SD, Median, minimum [Min] and maximum [Max]).

The percentage of patients whose overall compliance for injections is <80% will be also summarized.

According to protocol, cases of overdose are reported in the AE eCRF pages and will be described in the AE analysis (see Section 2.4.5.1).

2.4.4 Analyses of efficacy endpoints

2.4.4.1 Analysis of primary efficacy endpoint(s)

Not applicable.

2.4.4.2 Analyses of secondary efficacy endpoints

Efficacy variables will be analyzed in the mITT population through descriptive statistics. No formal statistical comparisons will be performed for efficacy variables.

Quantitative descriptive summaries (number of available data, mean, SD, median, Min and Max) by planned time points will be presented for all lipids using observed (ie, non-missing) data. Missing data will not be imputed. In addition, standard error (SE) and the 95% CI for the mean will be provided for lipids other than TGs and Q1 and Q3 will be provided for TGs. The computation of the 95% CI will be based on a normal distribution or a Student distribution depending on the number of patients.

For all continuous secondary efficacy endpoints (LDL-C, non-HDL-C, total-C, HDL-C and triglycerides), percent changes from baseline using number of available data, mean, SD, median, Min, and Max will be displayed. For percent changes, 95% CI of the mean will also be provided.

The proportions of patients reaching the different targets defined for LDL-C (see Section 2.1.3.2) will be provided with their corresponding 95% CI. In case of a number of patients deemed insufficient, the Clopper-Pearson algorithm will be used to compute the 95% CI.

All measurements, scheduled or unscheduled will be assigned to analysis windows defined in Section 2.5.4.

Regarding the patterns of up-titration/down-titration, the proportions with their corresponding 95% CI, will be provided for the following categories:

- Patients with at least one up-titration to 150 mg of alirocumab during the observational period. The time from the initiation of alirocumab at 75 mg to the first up-titration to 150 mg will be quantitatively described and the reasons that triggered the change of dosage will be displayed (AE, Lipid values or others).
- Patients with at least one down-titration to 75 mg of alirocumab during the observational period. The time from the initiation of alirocumab at 150 mg to the first down-titration to 75 mg will be quantitatively described and the reasons that triggered the change of dosage will be displayed (AE, Lipid values or others).
- Patients with a dose of alirocumab unchanged at 75 mg during the observational period and the duration of treatment without changes of doses.
- Patients with a dose of alirocumab unchanged at 150 mg during the observational period and the duration of treatment without changes of doses.

In addition, the number and the proportion of patients for which the dose of alirocumab was down-titrated back to 75 mg and for which the dose of alirocumab was up-titrated back to 150 mg will be described.

The last LDL-C value prior to the up-titration/down-titration or prior to the initiation of treatment for patients with a dose unchanged throughout the study will be summarized quantitatively and with the following categories: <15, ≥15 and <25, ≥25 and <50, ≥50 and <70, ≥70 and <100, ≥100 mg/dL. The LDL-C value at least 4 weeks after up-titration/down-titration will also be provided for patients without any additional change of dosage (LDL-C value selected will be the value nearest to the date of titration + 28 days). The 95% CI will be provided. In case of a number of patients deemed insufficient, the Clopper-Pearson algorithm will be used to compute the 95% CI.

2.4.4.3 Multiplicity issues

Not applicable.

2.4.4.4 Additional efficacy analyses

Occurrence of very low LDL-C level

A LDL-C level <25 mg/dL (0.65 mmol/L) will be defined as very low. An alternative definition with a cut-off at 15 mg/dL (0.39 mmol/L) will also be used.

For each definition of very low LDL-C level, the number and percentage of patients who had a very low LDL-C level at least once during the observational period will be provided overall, by the LDL-C level at baseline (<70 mg/dL (1.81 mmol/L), ≥70 mg/dL and <100 mg/dL (2.59 mmol/L), ≥100 mg/dL and <130 mg/dL (3.37 mmol/L), ≥130 mg/dL and <160 mg/dL (4.14 mmol/L), ≥160 mg/dL) and by starting dose of alirocumab.

Among patients with a very low LDL-C level, the number and percentage of patients receiving each level of dose for alirocumab (75 mg and 150 mg) at the time of the corresponding LDL-C test will be provided. The time from the first injection of Alirocumab to the first occurrence of a very low value of LDL-C will also be displayed.

Change in study treatment after the occurrence of very low LDL-C level

For each definition of very low LDL-C level, the following statistics will be calculated:

- Among the patients who had a very low LDL-C level and received a dose of alirocumab at 150 mg at the time of the corresponding LDL-C test:
  - Number and percentage of patients for whom the dose of alirocumab was changed to 75 mg, at least once at any time after the first occurrence of a very low LDL-C level,
  - Number and percentage of patients for whom alirocumab was discontinued at any time after the first occurrence of a very low LDL-C level,
  - Number and percentage of patients for whom the doses of other lipid-lowering drugs were decreased at any time after the first occurrence of a very low LDL-C level,
  - Number and percentage of patients for whom other lipid-lowering drugs were discontinued at any time after the first occurrence of a very low LDL-C level.
- Among the patients who have a very low LDL-C level and received a dose of alirocumab at 75 mg at the time of the corresponding LDL-C test:
  - Number and percentage of patients for whom alirocumab was discontinued at any time after the first occurrence of a very low LDL-C level,
  - Number and percentage of patients for whom the doses of other lipid-lowering drugs were decreased at any time after the first occurrence of a very low LDL-C level,
  - Number and percentage of patients for whom other lipid-lowering drugs were discontinued at any time after the first occurrence of a very low LDL-C level.

For patients who experienced a very low LDL-C several times during the observational period, only the first occurrence will be considered.

The 95% CI will be provided. In case of a number of patients deemed insufficient, the Clopper-Pearson algorithm will be used to compute the 95% CI.

Discontinuation of alirocumab

The following statistics will be calculated:

- Number and percentage of patients for whom alirocumab is discontinued during the observational period
  - Overall,
  - By starting dose of alirocumab.
- Among the patients for whom alirocumab is discontinued
  - Number and percentage of patients on each dose (75 versus 150 mg) prior to discontinuation,
  - Number and percentage of patients who had LDL-C <25 mg/dL (0.65 mmol/L) and <15 mg/dL (0.39 mmol/L) prior to discontinuation, respectively,

- Number and percentage of patients according to each reason for discontinuation, if available,
- Number and percentage of patients who restarted alirocumab in the observational period.

For patients who discontinued alirocumab several times during the observational period, only the first occurrence will be considered.

The 95% CI will be provided. In case of a number of patients deemed insufficient, the Clopper-Pearson algorithm will be used to compute the 95% CI.

In addition, a listing with all patients who experienced at least once a very low LDL-C level during the observational period will be provided with the following parameters: country, date of enrollment, starting dose of alirocumab, LDL-C level at inclusion, LDL-C <25 mg/dL (Y/N), LDL-C <15 mg/dL (Y/N), date corresponding to the lipid test, down-titration (Y/N), date of down-titration, up-titration (Y/N), date of up-titration, discontinuation of alirocumab (Y/N), date of discontinuation.

Concomitant treatment with statins

In order to assess the treatment with statins, the number and percentage of patients with statin dose decreased and statin discontinuation will be provided:

- Overall.
- In patients initiated on alirocumab 75 mg.
- In patients initiated on alirocumab 75 mg and who were up-titrated to 150 mg.
- In patients initiated on 150 mg.
- In patients with at least one value of LDL-C <25 mg/dL.

The 95% CI will be provided. In case of a number of patients deemed insufficient, the Clopper-Pearson algorithm will be used to compute the 95% CI.

2.4.5 Analyses of safety data

General common rules

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

- The baseline value will be defined as the last available value before the first alirocumab injection.
- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests and vital signs (PCSA version dated May 2014, see Appendix A).
- PCSA criteria will determine which patients had at least 1 PCSA during the TEAE period, taking into account all evaluations performed during the TEAE period, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the PCSA percentages.

- The treatment-emergent PCSA denominator for a given parameter will be based on the number of patients assessed for that given parameter in the TEAE on the safety population.
- The worst on-treatment value is defined as the nadir and/or the peak value during the treatment period according to the direction (Min or Max) of the abnormality as defined the PCSA list. The last on-treatment value is defined as the last value collected during the treatment period.
- All measurements, scheduled or unscheduled, fasting or not fasting, will be assigned to analysis windows defined in Section 2.5.4 in order to provide an assessment for all time points.

2.4.5.1 Analyses of adverse events

Generalities

The primary focus of adverse event reporting will be on TEAEs. Pre-treatment adverse events will be described separately. Likewise, the post-treatment adverse events for the patients concerned (see Section 2.1.4) will also be described separately.

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

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

For the TEAEs as well as for the pre-treatment adverse events, the denominator for computation of percentages is the safety population. Instead, for the post-treatment adverse events, the denominator will be a sub-group of the safety population (see Section 2.1.4).

Sorting within tables ensures the same presentation for the set of all adverse events within the observation period (pre-treatment, treatment-emergent, 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 will define the presentation order for all other tables unless otherwise specified.

Analysis of all treatment-emergent adverse events

The following TEAEs summaries will be generated for the safety population.

- Overview of TEAEs, summarizing number (%) of patients with any
  - Treatment-emergent adverse event,
  - Serious TEAE,
  - Treatment-emergent adverse event leading to death,
  - Treatment-emergent adverse event leading to permanent treatment discontinuation.
- All TEAEs by primary SOC, HLGT, HLT, and PT.
- All TEAEs by primary SOC, HLGT, HLT, and PT, showing number (%) of patients with at least 1 TEAE sorted by the SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order.
- All TEAEs by primary SOC and PT, showing the number (%) of patients with at least 1 TEAEs by primary SOC and PT, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC. This sorting order will be applied to all other tables, unless otherwise specified.
- All TEAEs by PT, showing the number (%) of patients with at least 1 TEAE, sorted by decreasing incidence of PTs.
- All TEAEs regardless of relationship (in one column of the table) and related to alirocumab according to investigator's opinion (in a second column) by primary SOC, HLGT, HLT and PT, showing the number (%) of patients with at least 1 TEAE, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order.
- All TEAEs by maximal severity, presented by primary SOC and PT, showing the number (%) of patients with at least 1 TEAE by severity (ie, mild, moderate, or severe), sorted by the sorting order defined above.
- The event rate per patient-year (the number of patients with an event in question divided by total patient-years) will be provided for all TEAEs by SOC and PT. For a patient with event, patient year is censored at time of first event; for patient without event, it corresponds to length of TEAE period.
- Kaplan-Meier curves will be provided, when appropriate, for time from first dose of alirocumab to the first occurrence of selected TEAEs as well as incidence rates at 24 weeks of exposure. Patients without any event will be censored at the end of the TEAE period. Selected TEAEs will be all AESIs (as defined in Section 2.1.4.1).

Analysis of all treatment emergent serious adverse event(s)

- All serious TEAEs by primary SOC, HLGT, HLT, and PT.
- All treatment-emergent SAEs by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients with at least 1 serious TEAE, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order.

- All treatment-emergent SAEs regardless of relationship (in one column of the table) and related to alirocumab according to investigator's opinion (in a second column), by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients with at least 1 treatment-emergent SAE, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order.
- All treatment-emergent SAEs by PT, showing the number (%) of patients with at least 1 TEAE, sorted by decreasing incidence of PTs.
- The event rate per patient-year will be provided for all serious TEAEs by SOC and PT.

Analysis of all TEAEs leading to treatment discontinuation

- All TEAEs leading to treatment discontinuation, by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, and PT) will be presented in alphabetical order.

Analysis of adverse event of special interest (AESI)

- All AESIs 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 SOC and PT (indicating in the footnote if selection is based on SMQ or HLGT/HLT). The summaries will be sorted by decreasing incidence of PT within each SOC.

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 alirocumab injections received.
- Time from first alirocumab injection to first injection site reaction.
- Description of the highest intensity of each symptom recorded in the specific eCRF page.

Besides, description of symptoms and possible etiologies for General Allergic Reaction TEAE reported by investigator will be listed (ie, presented by listing).

Analysis of pre-treatment and post-treatment adverse events

- All pre-treatment AEs by primary SOC and PT, showing number (%) of patients with at least one pre-treatment AE sorted by SOC internationally agreed order and decreasing incidence of PTs within SOC.
- All pre-treatment AEs leading to treatment discontinuation by primary SOC and PT, showing number (%) of patients with at least one pre-treatment AE leading to discontinuation, sorted by SOC internationally agreed order and decreasing incidence of PTs within SOC.
- All post-treatment AEs by primary SOC and PT, showing number (%) of patients with at least one post-treatment AE sorted by SOC internationally agreed order and decreasing incidence of PTs within SOC.
- All post-treatment serious AEs by primary SOC and PT, showing number (%) of patients with at least one post-treatment serious AE sorted by SOC internationally agreed order and decreasing incidence of PTs within SOC.

In case the number of patients with at least one adverse event is very small (analyses per country or pooled countries, post-treatment AEs for example), listings might be an alternative presentation of the results.

Analysis of product complaints

- Number (%) of patients experiencing product complaints.
- Number (%) of patients experiencing product complaints associated with a TEAE.

2.4.5.2 Deaths

The following summaries of deaths will be generated for the safety population.

- Number (%) of patients who died by study period (TEAE, on-study, post-study) summarized on the safety population.
- Treatment-emergent adverse events leading to death (death as an outcome on the AE case report form page as reported by the Investigator) by primary SOC , HLGT, HLT, and PT showing number (%) of patients sorted by internationally agreed SOC order, with HLGT, HLT, and PT presented in alphabetical order within each SOC.

2.4.5.3 Analyses of laboratory variables

The summary statistics (including mean, median, Q1, Q3, SE Min and Max) of some laboratory variables (absolute values and changes from baseline) will be calculated for each visit, last and worst value assessed during the treatment period. Since no central laboratory was used in this study, results obtained from local laboratories will be converted into the units listed in Appendix A. For a given parameter, if no unit is indicated, no quantitative analysis will be performed.

The incidence of PCSA (list provided in Appendix A) at any time during the TEAE period will be summarized by biological function whatever 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, similar table(s) using the normal range will be provided. A listing of patients with at least one post-baseline PCSA will be provided.

The absolute change in HbA1c (%) will be assessed from baseline to Weeks 12, 24, 48, 72, 96 and EOT/EOS.

For parameters HbA1c, FPG and LDL-C plots will be displayed; mean changes from baseline with the corresponding SE will be plotted over time (at same time points).

For the parameters assessed through dipstick urinalysis, no central laboratory was used. As a consequence, the results of statistical analyses on these parameters will have to be interpreted with caution.

Drug-induced liver injury

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

A graph of distribution of post-baseline peak values of ALT versus peak values of total bilirubin will also be presented. Note that the ALT and total bilirubin values are presented on a logarithmic scale. The graph will be divided into 4 quadrants with a vertical line corresponding to 3 x ULN for ALT and a horizontal line corresponding to 2 x ULN for total bilirubin.

2.4.5.4 Analyses of vital sign variables

The summary statistics (including mean, median, Q1, Q3, SE, Min and Max) of all vital signs parameters (raw data and changes from baseline) will be calculated for each visit, last and worst value assessed during the treatment period.

Additionally, the incidence of PCSAs at any time during the TEAE period will be summarized irrespective of the baseline level and/or according to the following baseline status categories:

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

2.4.6 Analyses of SIAQ©

Analysis of the PRE-SIAQ

Analysis of the PRE-SIAQ (see Appendix B) will be only descriptive and will be performed in the patients belonging to the safety population and who self-injected provided that they filled in the questionnaire before the training self-injection with placebo, and regardless of whether they completed the POST-SIAQ after the subsequent self-injections of alirocumab.

Each of the 7 items of the PRE-SIAQ will be qualitatively described (number and percentage of patients for each modality of each item). A quantitative analysis will be provided for each of the 3 domains of the PRE-SIAQ (feelings about injection, self-confidence, satisfaction with self-injection).

It will be checked that all patients who self-injected at least once during the observational period performed a training injection with placebo.

Analysis of the POST-SIAQ

Analysis of the POST-SIAQ (see Appendix B) will also be only descriptive and will be performed in the patients of the safety population who gave themselves at least one alirocumab injection (see Section 2.3.3) regardless of whether they completed the PRE-SIAQ. A descriptive summary will be provided at Weeks 4, 8, 12, 24, 48, 72 and 96.

Each of the 27 items of the POST-SIAQ will be qualitatively described with number and percentage of patients for each modality of each item. A quantitative analysis of the scores by domains will be provided for each of the 6 domains of the POST-SIAQ (feelings about injection, self-image, self-confidence, injection-site injection, ease of use, satisfaction with self-injection).

If questionnaires were completed while the patient did not self-inject or were not performed the same day of an injection, they will not be considered for the analysis.

Comparison of domain scores between PRE-SIAQ and POST-SIAQ

Regarding the analysis of the change in the perception of self-injection between the first self-injection and the subsequent self-injections, only patients with a PRE-SIAQ and at least one POST-SIAQ will be considered. There is no formal method for comparing PRE-SIAQ and POST-SIAQ; only some items are common to the PRE-SIAQ and the POST-SIAQ. For the common items, a histogram will display the scores by domain before the first self-injection and after the injection at Weeks 4, 8, 12, 24, 48, 72 and 96.

Seven items are common between the PRE-SIAQ and the POST-SIAQ. They are grouped into 3 domains (see Appendix B for further details) which will be compared:

- Feeling about injection including 3 items.
- Self-confidence including 3 items.
- Satisfaction with Self-injection including 1 item in common.

See Appendix B for further details about the scoring of each domain of the PRE-SIAQ and of the POST-SIAQ.

These analyses will be performed overall.

2.5 DATA HANDLING CONVENTIONS

Some general rules of data handling conventions are listed below.

2.5.1 General conventions

In general, the baseline value of an analysis variable is defined as the last observation before or on the first dose of the treatment.

Last on-treatment value is defined as the value collected at or just prior to the last study drug intake.

Time from diagnosis

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 01 JANUARY if the year of diagnosis equals the year of informed consent; it will be put equal to 01 JULY otherwise. In case the day of diagnosis would be missing, it will be put equal to 15 if the

consent and the diagnosis did not occur during the same month; it will be put equal to 1 otherwise.

Demographic and baseline characteristics

Age = Integer of ([date of informed consent - date of birth]/365.25)

Medical history

"Peripheral Arterial Disease" corresponds to at least one of the following conditions:

- Intermittent claudication.
- Peripheral revascularization procedure (angioplasty, stenting).
- Thrombolysis for PAD.
- Peripheral revascularization surgery (arterial bypass).
- Critical limb ischemia.

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

The following formulas has been used for below parameter automatic calculation in the eCRF:

eGFR value will be derived using the MDRD equation:
eGFR (mL/min/1.73 m^2) = 175 x (Serum Creatinine converted in mg/dL)$^{-1.154}$ x (Age)$^{-0.203}$
x (0.742 if Female) x (1.212 if African American)

Creatinine Clearance is calculated using the Cockroft-Gault formula:

- If serum creatinine measured in **mg/dL**:
  CrCl = ([140-age] x [Weight in kg] x [0.85 if women])/(72 x Serum Creatinine in mg/dL).
- If serum creatinine measured in **µmol/L**:
  CrCl = ([140-age] x [Weight in Kg] x [1.23 if men and 1.04 if women])/(Serum Creatinine in µmol/L).

Lipid formulas

LDL-C is calculated using the Friedewald formula (1) in all cases, ie, even in case TG are elevated (>400 mg/dL):

- LDL-C = Total-C - HDL-C - (TG/2.17), when all concentrations are expressed in mmol/L.
- LDL-C = Total-C - HDL-C - (TG/5), when all concentrations are expressed in mg/dL.
  In order to convert the result into mmol/L, divide by 39.

2.5.2 Data handling conventions for secondary efficacy variables

See Section 2.1.3.

2.5.3 Missing data

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

The analyses and summaries for variables with continuous scales will be based on observed data only. However, the number of patients with missing observations will be provided.

For data listings, the character date will always be used to present the data collected in the CRF.

Handling of computation of age

Missing birth date conventions:

- missing Day, assume = 15.
- missing Month, assume = 7.
- missing Year, calculations cannot be done.
- Missing Day and Month, assume = 1st of July.

Handling of computation of treatment duration if IMP end of treatment date is missing

For the calculation of the treatment duration, the date of the last dose of alirocumab is the date of last administration reported on the end-of-treatment case report form page. If this date is missing, the exposure duration should be left as missing.

Handling of medication missing/partial dates

No imputation of medication start/end dates will be performed. If a medication date is missing or partially missing, so it cannot be determined whether it was taken prior or concomitantly, it will be considered as a prior **and** concomitant medication.

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

Missing or partial adverse event onset dates will be imputed so that if the partial AE onset date/time information does not indicate that the AE started prior to treatment, the AE will be classified as treatment-emergent. No imputation of AE end dates/times will be performed. 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 IMP administration is missing

When the date of the first alirocumab administration is missing, all AEs that occurred on or after the day of the first dispensation by IVRS should be considered as TEAEs. The exposure duration should be kept as missing.

The last dose administration should be clearly identified in the case report form (on the EOT/EOS page) and should not be approximated by the last returned package date.

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

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

Handling of potentially clinically significant abnormalities

If a patient has a missing baseline 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 or a normal range and the other on a threshold value, with the first condition being missing, the PCSA will be based only on the second condition.

For a PCSA defined on a threshold and/or a normal range, this PCSA will be derived using this threshold if the normal range is missing; eg, for eosinophils the PCSA is >0.5 GIGA/L or >ULN if ULN ≥0.5 GIGA/L. When ULN is missing, the value 0.5 should be used. When PCSA (based on normal range) could not be defined because normal ranges are missing the value should be considered as non-evaluable.

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

Handling of missing data in SIAQ© questionnaire

Domain scores will be calculated only if 50% or more items of the domain are completed.
See Appendix B for further information.

Questionnaire completion date will be the date reported in the eCRF at each visit by the physician.

2.5.4 Windows for time points

Data analyzed by time point (including efficacy, laboratory safety data, vital signs) 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

Time point	Targeted study day	Analysis window in study days
Week 4	29	15 to 42
Week 8	57	43 to 70
Week 12	85	71 to 98
Week 24	169	155 to 182
Week 36	253	239 to 266
Week 48	337	316 to 357
Week 60	421	400 to 441
Week 72	505	484 to 525
Week 84	589	568 to 609
Week 96	673	652 to 693
Week 108	757	736 to 777
Week 120	841	820 to 861
Follow-up[a]	Last injection + 10 weeks	Last injection + 10 weeks ± 4 weeks

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

a For the patients who participated in the study according to the initial protocol and who prematurely discontinued the treatment irrespective of the reason and those who will switch to another LMT

If multiple valid values of a variable exist within a time 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.

2.5.5 Unscheduled visits

Laboratory and vital sign data from unscheduled visits will be used in PCSA analysis. The unscheduled visits will also be assigned to the appropriate analysis time window for the summary of change from baseline by visit. The one closest to the targeted visit date will be used in the presence of multiple measurements within the same time window.

2.5.6 Pooling of centers for statistical analyses

No analysis using pooled center is planned.

2.5.7 Statistical technical issues

Not applicable.

3 INTERIM ANALYSIS

No formal interim analysis is planned for this study. However some descriptive analyses might be performed before the end of the study in order to support the submission of a reimbursement dossier if requested by local health authorities or the submission of preliminary study data to scientific meetings.

4 DATABASE LOCK

The final database is planned to be locked approximately 10 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

1. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972;18:499-502.

7 LIST OF APPENDICES

Appendix A Potentially clinically significant abnormalities criteria (version dated May 2014)

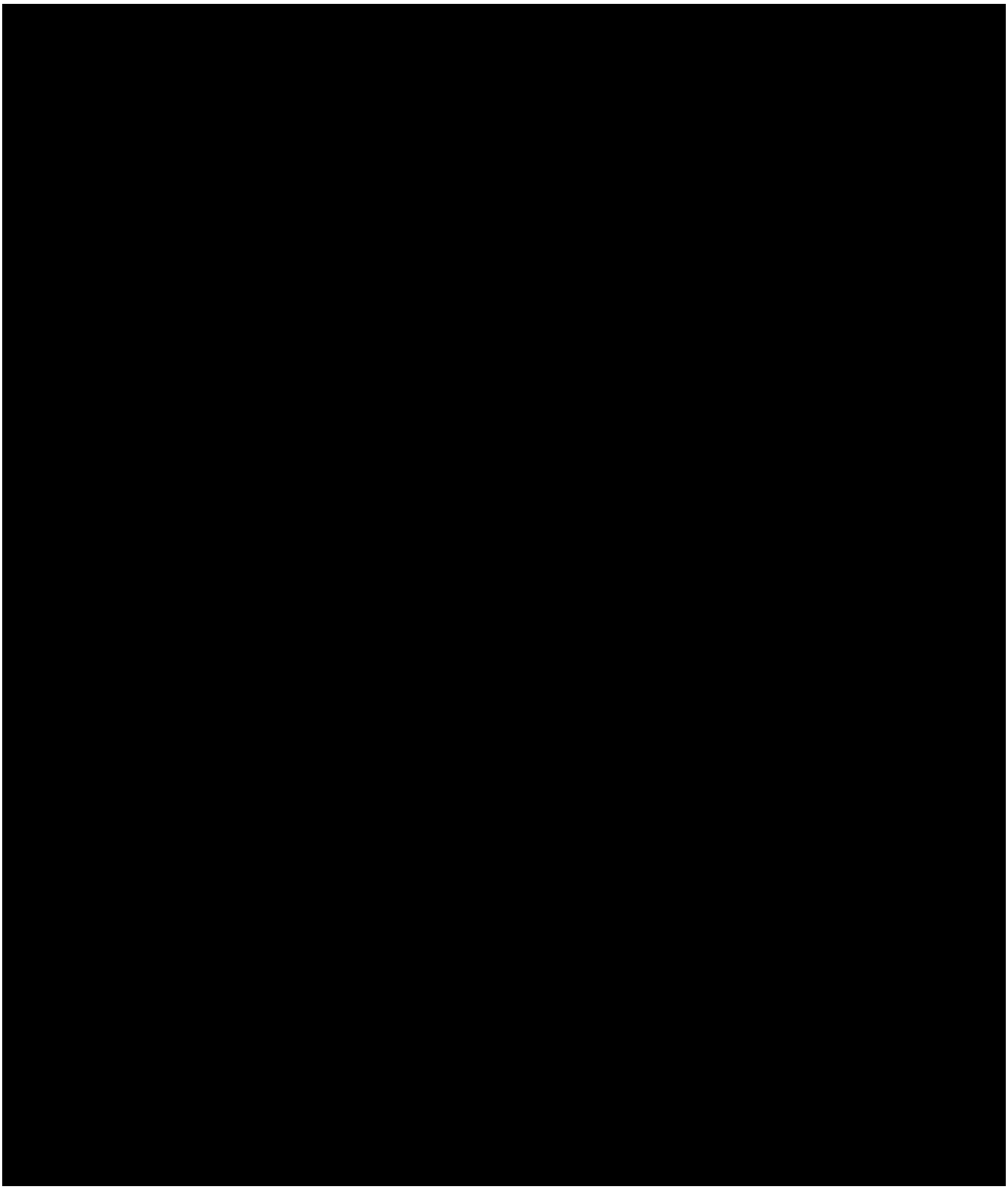
Parameter	PCSA	Comments
Clinical Chemistry		
ALT	By distribution analysis : >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI - FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following 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.

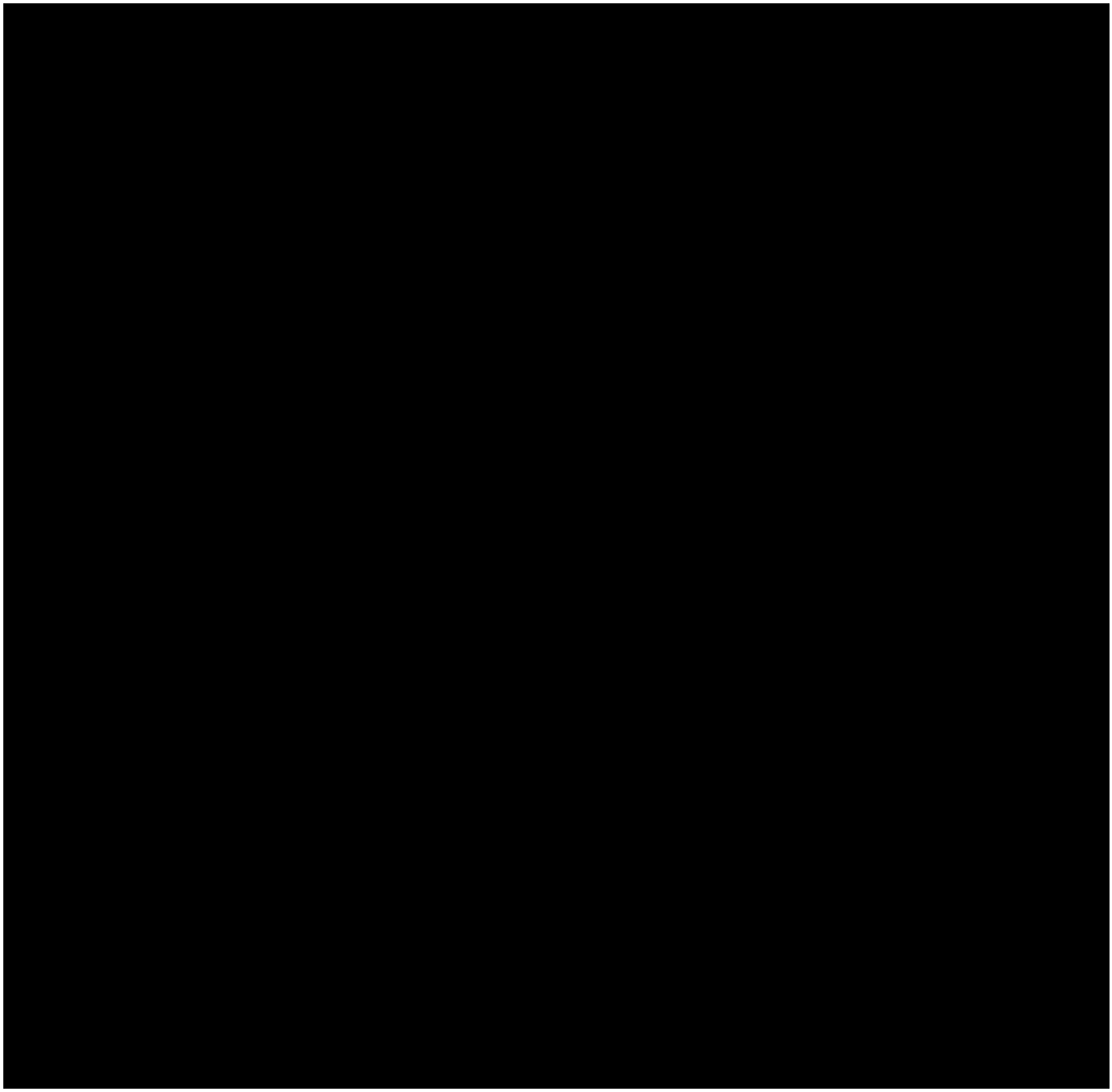
Parameter	PCSA	Comments
CLcr (mL/min) (Estimated creatinine clearance based on the Cokcroft-Gault equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - <60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
eGFR (mL/min/1.73m^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.
HbA1c	>8%	
Albumin	≤25 g/L	
CRP	>2 ULN or >10 mg/L (if ULN not provided)	FDA Sept 2005.
Hematology		
WBC	<3.0 Giga/L (Non-Black); <2.0 Giga/L (Black) ≥16.0 Giga/L	Increase in WBC: not relevant. To be interpreted only if no differential count available.
Lymphocytes	>4.0 Giga/L	

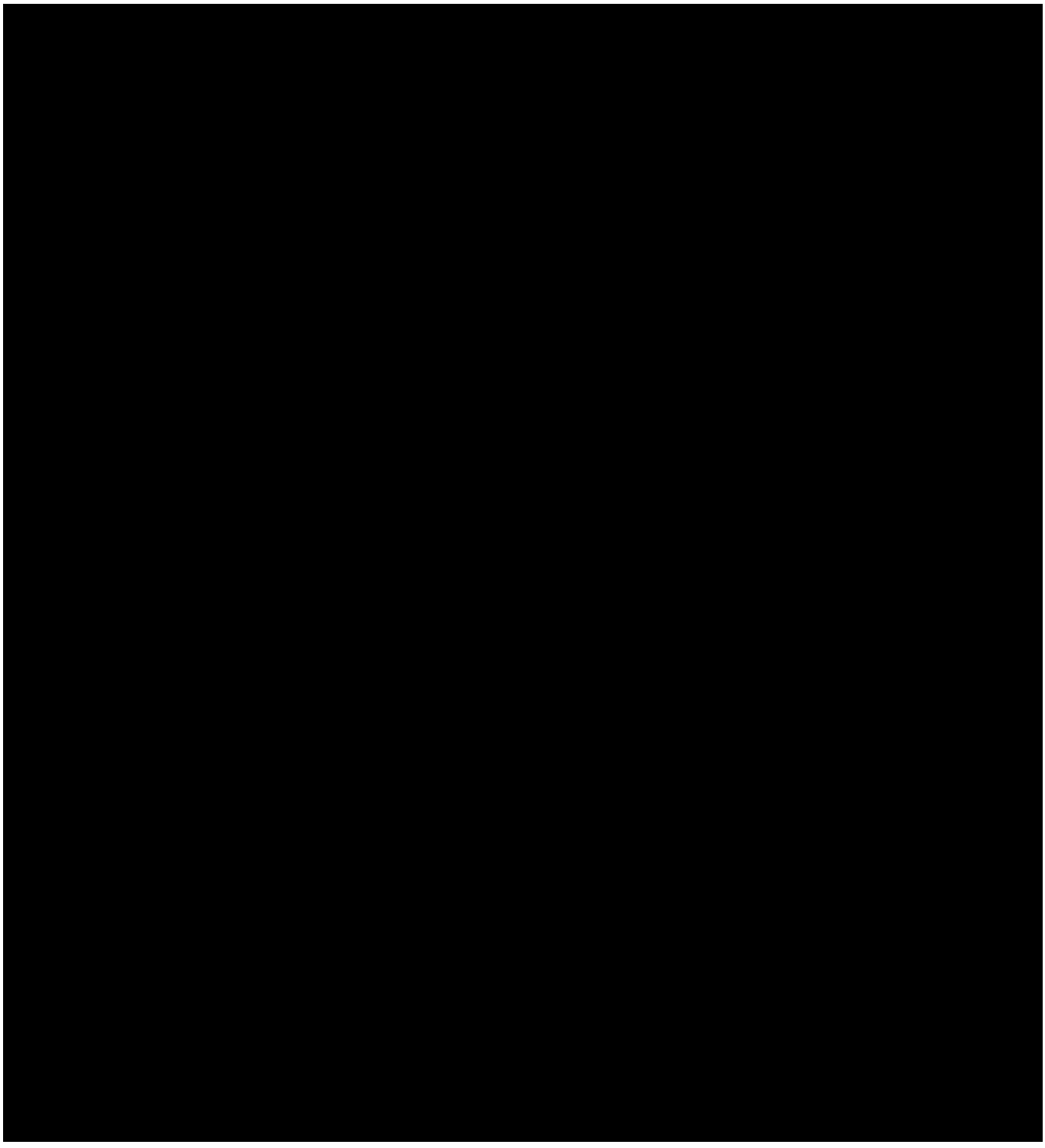
Parameter	PCSA	Comments
Neutrophils	<1.5 Giga/L (Non-Black); <1.0 Giga/L (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
Monocytes	>0.7 Giga/L or >ULN (if ULN ≥0.7 Giga/L)	
Basophils	>0.1 Giga/L	
Eosinophils	>0.5 Giga/L or >ULN (if ULN ≥0.5 Giga/L)	Harrison- 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 ≥20 mmHg ≥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.
Orthostatic Hypotension		
Orthostatic SDB Orthostatic DBP	≤-20 mmHg ≤-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 A; Gintant GA; Kleiman R; Gutstein D; Gottfridsso C, Michelson EL, et al. Am Heart J. 2013;165[4]:489-500)

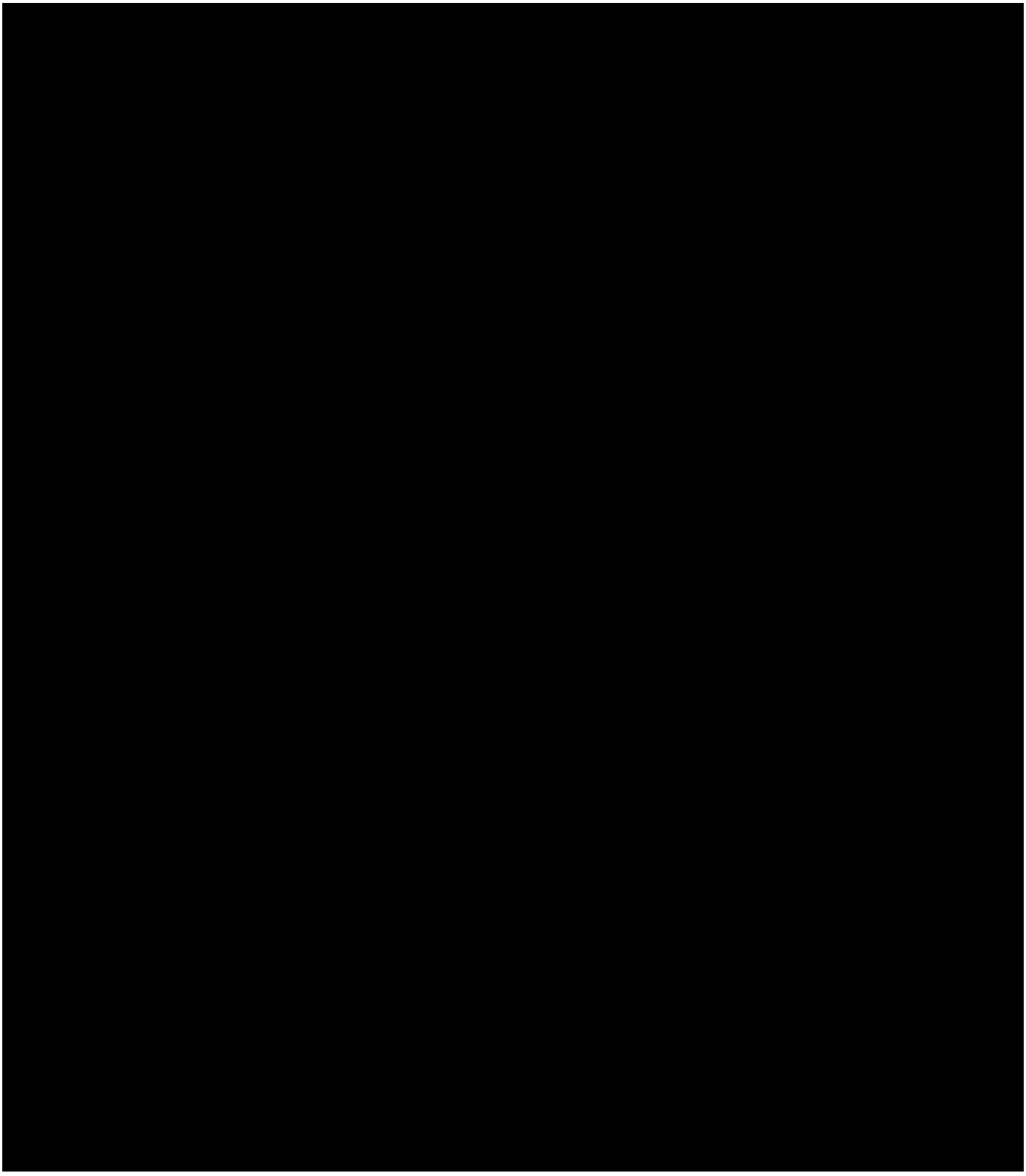
Parameter	PCSA	Comments
HR	<50 bpm	Categories are cumulative
	<50 bpm and decrease from baseline ≥20 bpm	
	<40 bpm	
	<40 bpm and decrease from baseline ≥20 bpm	
	<30 bpm	
	<30 bpm and decrease from baseline ≥20 bpm	
	>90 bpm	Categories are cumulative
	>90 bpm and increase from baseline ≥20 bpm	
	>100 bpm	
	>100 bpm and increase from baseline ≥20 bpm	
	>120 bpm	
	>120 bpm and increase from baseline ≥20 bpm	
PR	>200 ms	Categories are cumulative
	>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%	
QRS	>110 ms	Categories are cumulative
	>110 msec and increase from baseline ≥25%	
	>120 ms	
	>120 ms and increase from baseline ≥25%	
QT	>500 ms	
QTc	Absolute values (ms)	To be applied to any kind of QT correction formula.
	>450 ms	Absolute values categories are cumulative
	>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	

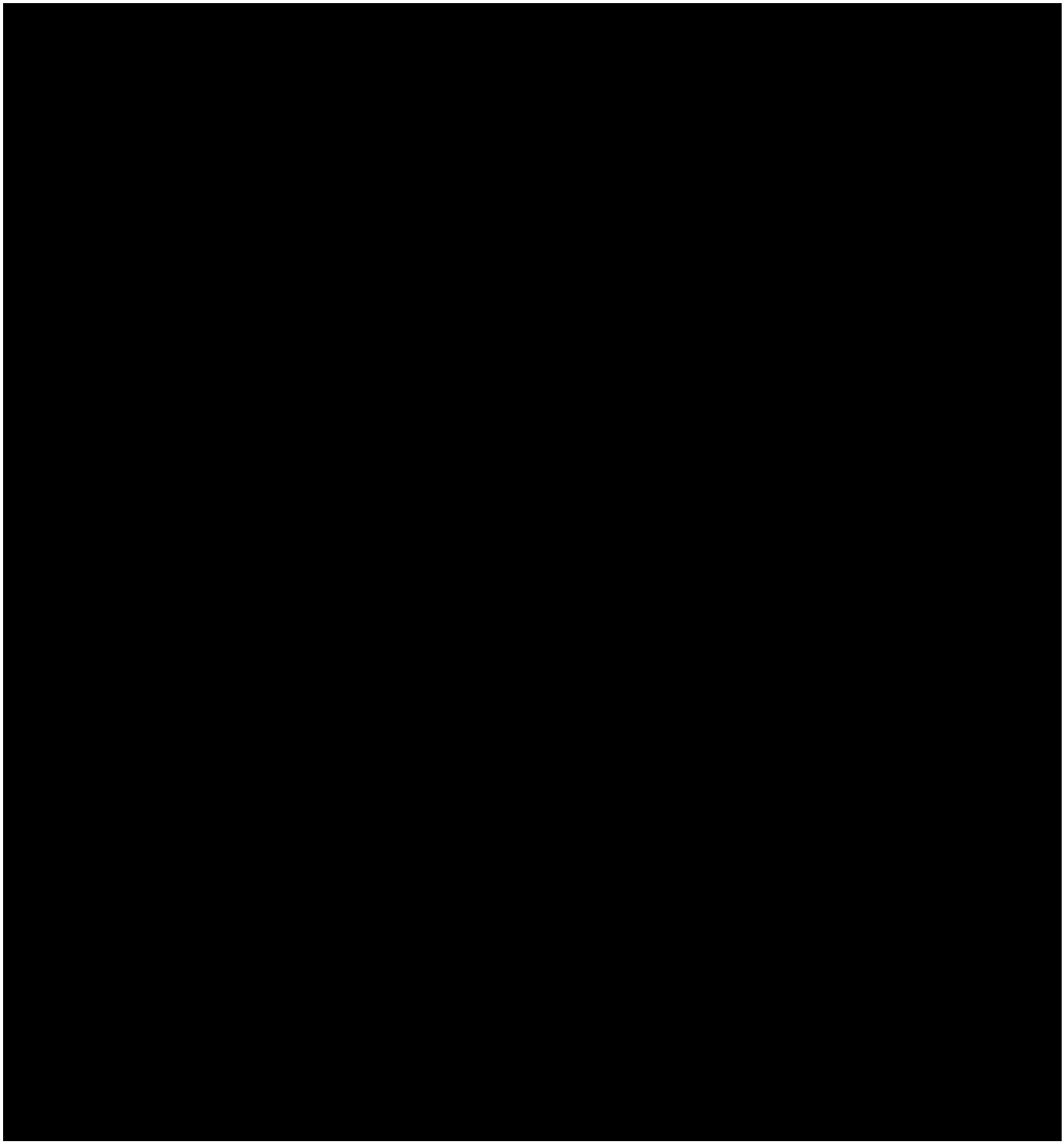
Appendix B Self-injection Assessment Questionnaire (SIAQ©)

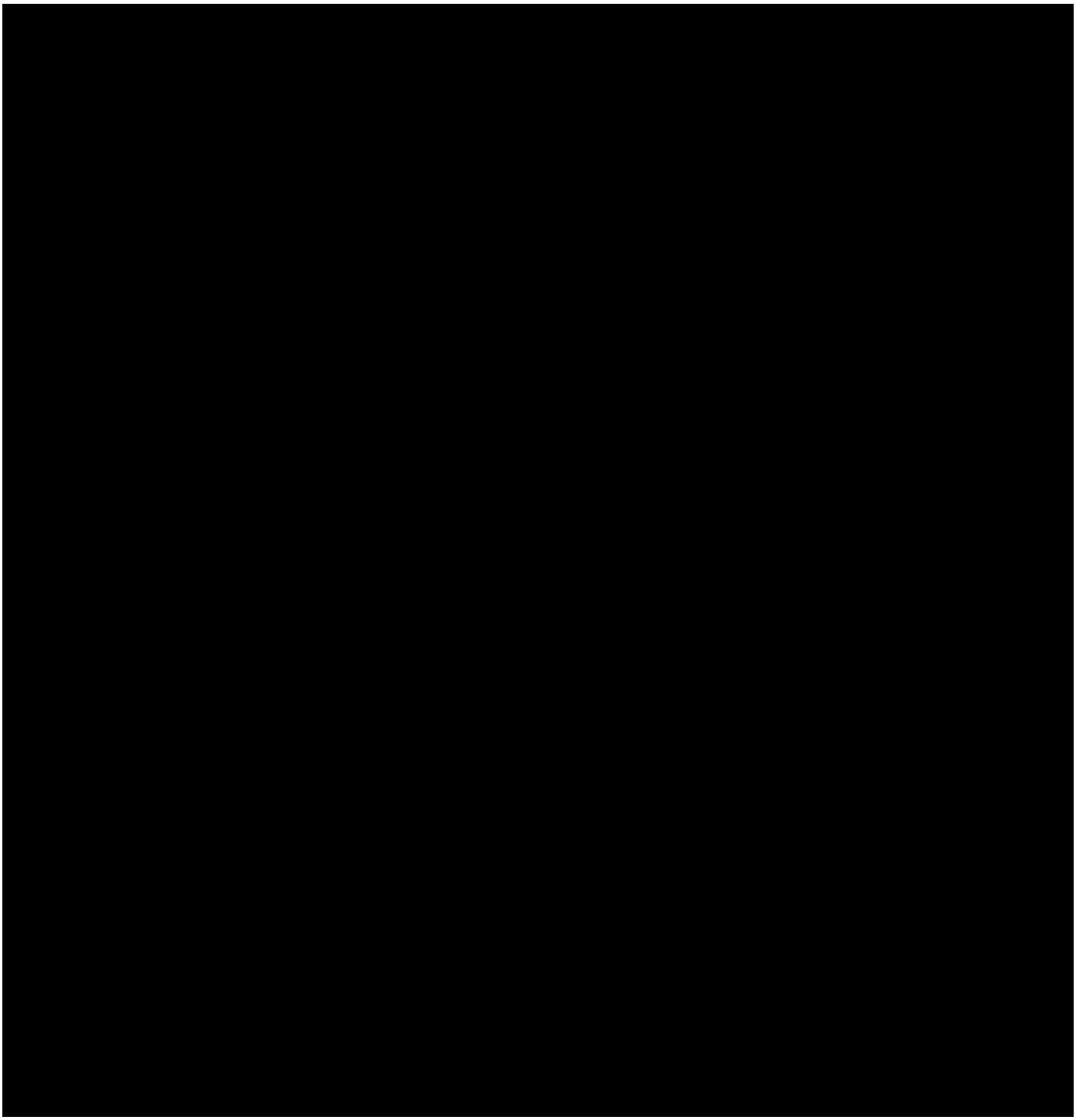


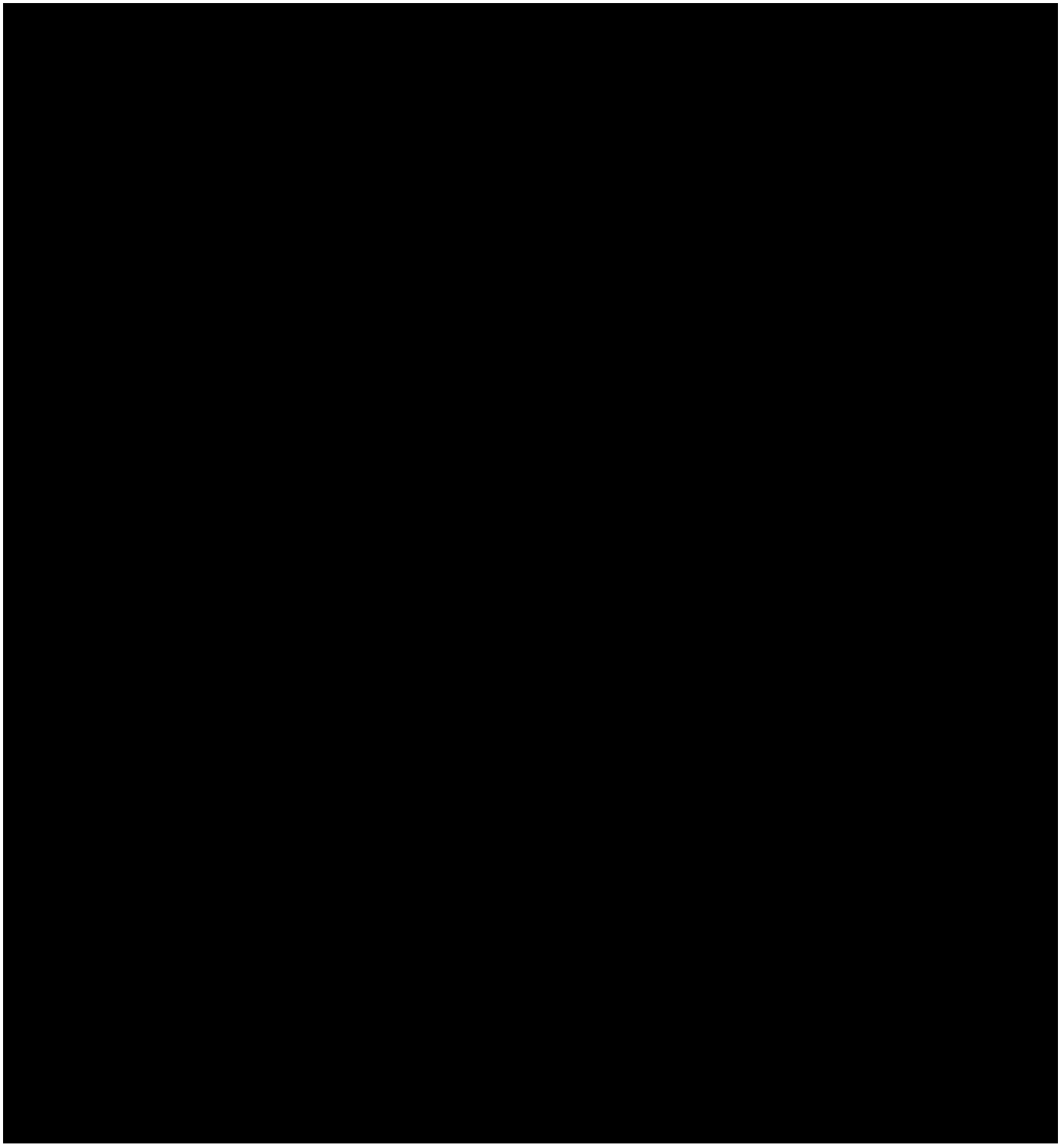












LPS14245 16.1.9 Statistical Analysis Plan

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	Clinical Approval	19-Feb-2019 16:23 GMT+0100
[redacted]	Clinical Approval	21-Feb-2019 13:52 GMT+0100
[redacted]	Clinical Approval	22-Feb-2019 16:41 GMT+0100