STATISTICAL ANALYSIS PLAN

A multicenter, randomized, open-label, parallel-group usability study of the commercial 1 mL alirocumab auto-injector device (AI) and the new 2 mL auto-injector device (SYDNEY) in high or very high cardiovascular risk patients with hypercholesterolemia not adequately controlled with their lipid modifying therapy

SAR236553/REGN727 - MSC14864

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA:	anti-drug (alirocumab) antibodies
AE:	adverse event
AESI:	adverse events of special interest
AI:	auto injector
ALP:	alkaline phosphatase
ALT:	alanine amino transferase
AST:	aspartate aminotransferase
ATC:	anatomic category
AUC0-tau:	area under the curve concentation versus time curve extrapolated to infinity
CHD:	coronary heart disease
CI:	confidence interval
Cmax:	maximum plasma concentration
CMQ:	company MedDRA query
C_{trough}:	trough concentration
e-CRF:	electronic case report form
HDL-C:	high-density lipoprotein cholesterol
heFH:	heterozygous famililal hypercholesterolemia
HLGT:	high level group term
HLT:	high level term
IMP:	investigational medicinal product
LDL-C:	low density lipoprotein cholesterol
LLOQ:	lower limit of quantification
LMT:	lipid modifying therapy
mITT:	modified intent-to-treat
PCSA:	potentially clinically significant abnormality
PCSK9:	proprotein convertase subtilisin/kexin type 9
PK:	pharmacokinetic
PT:	preferred term
PTC:	product technical complaint
Q4W:	every four weeks
SAE:	serious adverse event
SMQ:	standardized MedDRA query
SOC:	system organ class
TEAE:	treatment emergent adverse event
TG:	triglyceride
tmax:	maximum time
Total-C:	total-cholesterol
ULN:	upper limit of normal

1 OVERVIEW AND INVESTIGATIONAL PLAN

This statistical analysis plan (SAP) provides a comprehensive and detailed description of strategy and statistical technique to be used for the clinical study reports of MSC14864 study.

The overall goal of this study, MSC14864, is to assess the usability of SYDNEY (New device).

1.1 STUDY DESIGN AND RANDOMIZATION

This is a multicenter, randomized, open-label, 16-week study conducted in the USA, with 2 parallel arms (parallel-arm period) for the first 4 weeks, and then only one arm (single-arm period) for the subsequent weeks until Week 16.

Eligible patients will be randomly allocated to receive alirocumab 300 mg Q4W, self-administered using either the approved AI or the new investigational AI (SYDNEY) device for the first injection on Day 1. This injection will be performed at the clinical site under supervision and guidance by staff from the site.

Subsequently, all patients will receive alirocumab 300 mg Q4W self-administered using only SYDNEY device for the injections on Week 4 (Day 29), Week 8 (Day 57) and Week 12 (Day 85) respectively.

1.2 OBJECTIVES

1.2.1 Primary objective

To collect 12 weeks of real-use (usability) data assessing the robustness and user interaction of SYDNEY, in unsupervised settings on Weeks 4, 8, and 12.

1.2.2 Secondary objectives

Device related:

- To collect real-use (usability) data assessing the robustness and user interaction of SYDNEY and the current AI 1 mL alirocumab auto-injector device in supervised settings on Week 0 (Day 1).

Pharmacokinetics:

- To compare alirocumab pharmacokinetics 300 mg Q4W administered using SYDNEY and the current AI, from baseline until Week 4.
- To evaluate alirocumab PK 300 mg Q4W administered using SYDNEY, until Week 16.

Anti-drug antibodies:

- To evaluate the development of ADA.

Pharmacodynamics:

- To compare the percent and absolute change in LDL-C from baseline to Week 4 using SYDNEY and the current AI.
- To evaluate the percent and absolute change in LDL-C from baseline to Weeks 8, 12 and 16, using SYDNEY.

Safety:

- To evaluate the safety and tolerability of alirocumab 300 mg Q4W, using both Auto Injector Devices.

1.3 DETERMINATION OF SAMPLE SIZE

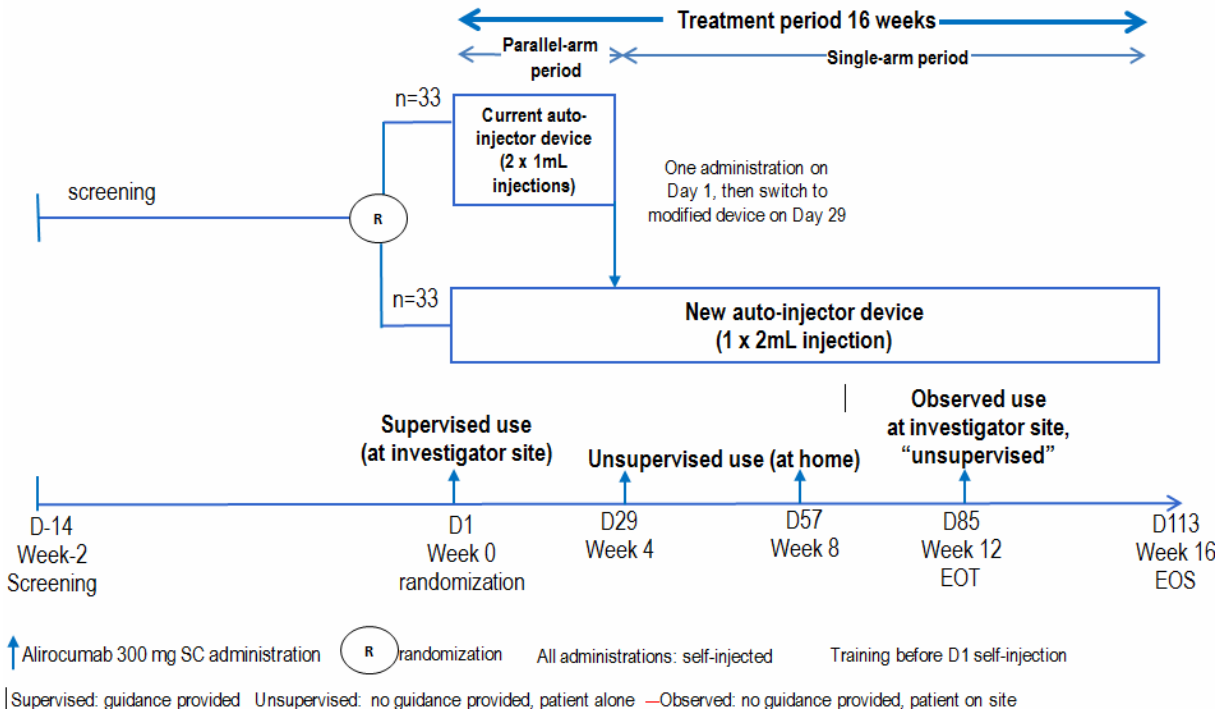
No formal sample size was calculated, the sample size is based on empirical considerations.

Considering a drop-out rate of 10% it is planned to randomize 66 patients overall (33 in each group) in order to ensure 60 evaluable patients overall (30 in each group) resulting in 180 unsupervised planned injections using SYDNEY, including the 2^{nd}, 3^{rd} and 4^{th} unsupervised injections with SYDNEY for patients randomized in the approved AI group who will switch to SYDNEY group just before the second injection.

Expecting a maximum of 3 observed PTC over the 180 injections (observed PTC rate of 1.67%) with SYDNEY, the upper bound of the 2-sided 95% CI calculated with the Wilson score method will be no higher than 5.2%.

1.4 STUDY PLAN

The following figure presents the graphical study design:



1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

Not applicable.

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

Not applicable.

2 STATISTICAL AND ANALYTICAL PROCEDURES

Analyses will be performed in each study phase (parallel arms phase and the single arm phase) separately unless otherwise specified. The results will be presented by treatment arm (SYDNEY, and approved AI) for the parallel arm phase and overall for the single arm phase.

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

For both study phases, the baseline value is defined as the last available value prior to the first dose of study medication planned at Day 1.

All baseline safety and pharmacodynamics parameters (apart from those listed below) will be presented along with the on-treatment summary statistics in the safety and pharmacodynamics sections (Section 2.4.4.2.5 and Section 2.4.4.2.4).

Demographic characteristics

Demographic variables are:

- Gender (Male, Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Island)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Age in years (quantitative and qualitative variable: <65, ≥65 to <75, and ≥75 years)

Medical or surgical history

Medical or surgical history includes:

- CHD
  - Acute myocardial infarction
  - Silent myocardial infarction
  - Unstable angina
  - Coronary revascularization procedure
  - Other clinically significant CHD diagnosed by invasive or non-invasive testing
- Non-CHD Cardiovascular disease
  - Ischemic stroke
  - Peripheral arterial disease

  - Abdominal aortic aneurysm
  - Atherosclerotic renal artery stenosis
  - Carotid artery disease
- Other risk factors
  - Moderate chronic kidney disease (as defined in protocol)
  - Type 1 or type 2 diabetes mellitus.
  - Calculated 10-year fatal Cardiovascular disease risk SCORE ≥5%
- Patient's history of allergies (described using all pre-printed terms collected in the medical allergic history e-CRF page)

Medical or surgical history will be based on items or combination of items pre-listed in the dedicated medical history e-CRF page (unless otherwise specified).

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

Disease characteristics at baseline

Specific disease characteristics include:

- Type of hypercholesterolemia
  - heFH
  - Non-familial hypercholesterolemia
- For heFH patients
  - Time from diagnosis of heFH (years)

  Confirmation of diagnosis (genotyping (Yes, No), clinical criteria (Yes, No))
- For Non-familial hypercholesterolemia patients:
  - Time from diagnosis of hypercholesterolemia (years)
- Background LMT at randomization as reported in dedicated prior and concomitant medications e-CRF pages
  - Atorvastatin daily dose in mg (10, 20, 40,80, Other)
  - Rosuvastatin daily dose in mg (5, 10, 20, 40 Other)
  - Other statins (if any)
  - Any LMT other than statins
    - Any LMT other than nutraceuticals (by therapeutic class and drug name)

- Nutraceuticals (Omega 3 Fatty Acids, Plantago Seed, Phytosterol, Other Nutraceutical)

Other baseline characteristics

Other baseline characteristics include body mass index in kg/m² (quantitative and qualitative variable: <30, ≥30), alcohol habits.

Lipid parameters (quantitative variables for all parameters and the following qualitative variable) will be also summarized at baseline (definitions in Section 2.1.3):

- Calculated LDL-C: <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

Any technical details related to computation, dates and imputation for missing data are described in Section 2.5.3.

2.1.2 Prior or concomitant medications

All medications will be coded using the World Health Organization-Drug Dictionary using the versions currently in effect at Sanofi at the time of database lock.

- Prior medications are those the patient used prior to first IMP intake. Prior medications can be discontinued before first dosing or can be ongoing during treatment phase.
- Concomitant medications during the parallel-arm period are any treatments received by the patient from first IMP injection to first IMP injection +70 days for patients choosing not to continue into the single-arm period. For patients entering in the single-arm period, concomitant medications will be truncated at the day before second IMP injection.
- Concomitant medications during the single-arm period are defined as any treatments received by the patient from the second IMP injection to the last open-label IMP injection +70 days.
- Post-treatment medications are those the patient took in the period starting from 71 days after the last IMP injection.

2.1.3 Primary endpoint

The primary endpoint is the number (%) and types of SYDNEY-associated PTCs at the unsupervised injections on Weeks 4, 8, and 12. In this study, a PTC is defined as any complaint reported on the Patient Complaint form that triggered an investigation by the Device Department and was classified by this department as device-related, patient-related, or undetermined, whether or not associated with an AE. The complaints categorized as not related to device or patient will not be considered as a PTC. This definition will be used for both primary and secondary endpoints.

2.1.4 Secondary endpoints

2.1.4.1 Device-related endpoints

During the parallel-arm period, patients are to receive injection(s) with either SYDNEY device or current AI. During the single arm period, all patients are to receive 3 separate injections with the SYDNEY device only.

The following endpoints will be analyzed:

- For both devices:
  - Number and percentage of patients with SYDNEY or current AI- associated PTCs (overall and by type) at the supervised injections on Day 1
  - Injection experience questionnaire on Day 1
- For SYDNEY only:
  - Number and percentage of patients with a SYDNEY- associated PTC (overall and by type) at the unsupervised injections on Weeks 4, 8, and 12
  - Patient perspective questionnaire
  - Injection-Treatment Acceptance Questionnaire

2.1.4.2 Pharmacokinetic variables

Concentrations of total alirocumab, total and free PCSK9 in serum are assessed at Day 1, Week 1, Week 2, Week 3,Week 4, Week 8 ,Week 12, Week 13, Week 14, Week 15 and Week 16.

The PK parameters will include, but may not be limited to C_{max}, t_{max} and AUC0-tau.

2.1.4.3 Anti-drug antibodies variables

ADA will be assessed at baseline (Day 1), Week 4 and Week 16. The following variables will be described:

- ADA response (Positive or Negative). For ADA positive:
  - Titer levels
- Pre-existing positive ADA defined as patients with positive ADA response at baseline with less than 4-fold increase in titer in the post-baseline period

- Treatment-emergent positive ADA response defined as 1) Patients with no ADA positive response at baseline but with any positive response in the post-baseline period or 2) Patients with a positive ADA response at baseline and at least a 4- fold increase in titer in the post-baseline period. For treatment-emergent positive ADA, the following categories for ADA duration will be applied:
  - A persistent positive response is a treatment-emergent ADA positive response detected in at least 2 consecutive post-baseline samples separated by at least a 12-week period
  - An indeterminate duration positive response is defined as ADA present only at the last sampling time point
  - A transient positive response is defined as any treatment-emergent positive ADA response that is neither considered persistent nor indeterminate

2.1.4.4 Pharmacodynamic variables (lipid variables)

Lipid parameters include LDL-C, Total-C, HDL-C and TG. Each parameter will be assessed at baseline (Day 1), Week 4, Week 8, Week 12 and Week 16 during the treatment period (on-treatment estimand) as defined in Section 2.1.4.5. Post-treatment data will not be considered.

The pharmacodynamic endpoints will be the percent change in LDL-C, Total-C, HDL-C, and TG values from baseline to Week 4, Week 8, Week 12 and Week 16.

All calculated and measured LDL-C, Total-C, HDL-C, and TG values (scheduled or unscheduled, fasting or not fasting) may be used in the analyses if appropriate according to above definition and analysis windows (as defined in Table 1) used to allocate a time point to a measurement. In case both calculated and measured LDL-C are provided for the same sampling, the measured LDL-C will be considered. For TG, only fasting measurements will be used, measurements with missing fasting status will be excluded from the analyses.

2.1.4.5 Safety endpoints

The safety analysis will be based on the reported adverse events including SAE AESIs and other safety information, such as clinical laboratory data and vital signs.

Observation period

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

- The pre-treatment period: defined as the time from the signed informed consent up to the first IMP injection;

- The TEAE period of the parallel-arm period defined as the time from the first IMP injection to the day before the second IMP injection for patients entering into the single arm period or to 70 days after the first IMP injection, whichever comes first;
  - The TEAE period of the parallel-arm period will include the TREATMENT period defined as the time from the first IMP injection to the day before the second IMP injection for patients entering into the single arm period, or to 35 days after the first IMP injection, whichever comes first.
- The TEAE period of the single-arm period is defined as the time from the second IMP injection up to the day of last IMP injection + 70 days.
  - The TEAE period of the single-arm period will include the TREATMENT period defined as the time from the second IMP injection up to the day of last IMP injection + 35 days.
- The post-treatment period: defined as the time starting 71 days after the day of last IMP injection.

The on-study observation period of the parallel-arm period is defined as the time from the day of first IMP injection until the Week 4 visit of the patient, if done, or 4 weeks after the randomization of the patient.

The on-study observation period of the single-arm period is defined as the time from the second IMP injection until the Week 16 visit of the patient, if done, or 16 weeks after the randomization of the patient.

2.1.4.5.1 Adverse events variables

Adverse events (including SAEs and AESIs) are recorded from the time of signed informed consent until the end of study.

All AEs will be coded to a “lowest level term”, “PT”, “HLT”, “HLGT”, and associated primary “SOC”using the version of MedDRA currently in effect at Sanofi at the time of database lock.

Adverse event observation period

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

Adverse events of special interest

AESIs are AEs (serious or non-serious) that need to be monitored, documented, and managed in a pre-specified manner described in the protocol. In this study, AESI are the following (their complete descriptions are provided in the protocol):

- Local injection site reactions, selected using e-CRF specific tick box on the AE page;
- Allergic events:
  - General allergic events will be tabulated. Events will be selected using standardized MedDRA query (SMQ) “hypersensitivity” (broad and narrow) excluding the following PTs linked to local injection site reactions (“infusion site dermatitis”, “infusion site hypersensitivity”, “infusion site rash”, “infusion site urticaria”, “injection site dermatitis”, “injection site hypersensitivity”, “injection site rash”, “injection site urticaria” and “injection site vasculitis”);
  - General allergic events and local allergic reactions at IMP injection site will be described. This selection will be based on the above selection for general allergic event and on the following selection of PT from the symptoms complementary form for local injection site reaction ("Injection site dermatitis", "Injection site hypersensitivity", "Injection site oedema", "Injection site rash", "Injection site urticaria", "Injection site eczema", "Injection site vasculitis", "Injection site swelling", "Infusion site dermatitis", "Infusion site hypersensitivity", "Infusion site oedema", "Infusion site rash", "Infusion site urticaria", "Infusion site swelling")
- ALT ≥3 ULN (if baseline ALT < ULN) or ALT ≥2 times the baseline value (if baseline ALT ≥ ULN), selected using laboratory data
- Neurologic events selected using a CMQ, based on SMQs “demyelination” (broad and narrow), “peripheral neuropathy” (broad and narrow), and “Guillain-Barre syndrome” (broad and narrow) excluding the following PTs “acute respiratory distress syndrome”, “asthenia”, “respiratory arrest” and “respiratory failure” and including selected PTs from SMQ "optic nerve disorders" (see Table 2 for the list of terms)
- Neurocognitive events:
  - Selected using a CMQ, based on the following 5 HLGTs: “deliria (including confusion)”, “cognitive and attention disorders and disturbances”, “dementia and amnestic conditions”, “disturbances in thinking and perception”, and “mental impairment disorders”
  - A second grouping of terms for neurocognitive events was defined based on Regulatory Agency request (see Table 3 for the list of terms)
- Pregnancy occurring in a female patient (including male subject’s partner) selected using appropriate MedDRA codes.
- Symptomatic overdose with IMP, selected using events reported as “Overdose of Alirocumab” and with “symptomatic overdose ticked “Yes” in the “Overdose” e-CRF page;

2.1.4.5.2 Deaths

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

- Death on-study during the parallel-arm period: deaths occurring during the on-study observation period of the parallel-arm period,
- Death on-treatment during the parallel-arm period: deaths occurring during the TEAE period of the parallel-arm period,
- Death on-study during the single-arm period: deaths occurring during the on-study observation period of the single-arm period,
- Death on-treatment during single-arm period: deaths occurring during the TEAE period of the single-arm period,
- Death post-study: deaths occurring after the on-study period.

2.1.4.5.3 Laboratory safety variables

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

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

- Hematology
  - Red blood cells count and platelets: hemoglobin, hematocrit, platelet count, Red blood cells count
  - White blood cells: White blood cells count, White blood cells differential (neutrophils, lymphocytes, monocytes, basophils, eosinophils)
- Clinical chemistry
  - Metabolism: glucose, total protein, albumin, creatine phosphokinase
  - Electrolytes: sodium, potassium, chloride, calcium.
  - Renal function: estimated glomerular filtration rate, creatinine, urea nitrogen
  - Liver function: ALT/ Serum Glutamic-Pyruvic Transaminase, AST/ Serum Glutamooxaloacetate Transferase, ALP, albumin, total bilirubin, Gamma-Glutamyl Transferase.

2.1.4.5.4 Vital signs

Vital signs parameters include heart rate, systolic and diastolic blood pressure measured after 5 minutes in seating resting position.

2.1.5 Other endpoints

The proportion of patients with LDL-C <25 mg/dL (<0.65 mmol/L) within the treatment period of the parallel and single-arm periods (and with two consecutives results below this limit if applicable, spaced out by at least 21 days) and the time to the first LDL-C <25 mg/dL for these patients will be provided. The same analysis will be provided with 15 mg/dL (0.39 mmol/L).

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 met the inclusion criteria and signed the informed consent.

Randomized patients consist of all screened patients with a treatment kit number allocated and recorded in the Interactive Response Technology database, regardless of whether the treatment kit was used. Patients treated without being randomized or treated with a double-blind treatment kit before the randomization will not be considered as randomized and will not be included in any analysis population. For patient study status, the following analyses will be performed in each period separately (by treatment group for parallel-arm period and overall for the single-arm period), if applicable:

- Screened patients
- Screen failure patients and reasons for screen failure
- Nonrandomized but treated patients (if any)
- Randomized patients
- Patients who completed the study treatment period as per protocol
- Patients who prematurely discontinued study treatment by main reason for permanent treatment discontinuation
- Status at last study contact (Alive/ Dead)

All critical or major deviations potentially impacting analyses, randomization, and drug-dispensing irregularities, and other major or critical deviations will be summarized in tables giving numbers and percentages of deviations by treatment group (when applicable).

Additionally, the following populations (for each study periods) will be summarized by treatment group for the populations of the parallel-arm period and overall for the populations of the single-arm period.

- Randomized population
- mITT population
- Safety population
- PKs population
- ADA population

Definitions of the study populations are provided in Section 2.3.

2.2.1 Randomization and drug dispensing irregularities

Randomization and drug-dispensing irregularities occur whenever:

1. A randomization is not in accordance with the protocol-defined randomization method, such as a patient is randomized twice.

   OR

2. A patient is dispensed an IMP kit not allocated by the protocol-defined randomization (which may or may not contain the correct-as-randomized IMP), or b) a nonrandomized patient is treated with IMP reserved for randomized patients.

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

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

Randomization and drug allocation irregularities
Kit dispensation without Interactive Response Technology transaction
Erroneous kit dispensation
Patient randomized twice

2.3 ANALYSIS POPULATIONS

Patients treated without or before being randomized will not be considered randomized and will not be included in any analysis populations. The safety experience of patients treated and not randomized will be reported separately.

Randomized population: includes all randomized patients as defined in Section 2.2.

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

2.3.1 Modified intent-to-treat population

The mITT population of the parallel arms period will consist of all randomized patients who received at least 1 dose or part of a dose of IMP during this period and who had an evaluable value of LDL-C at baseline and an on-treatment LDL-C value within Week 4 analysis window. Patients in this mITT population will be analyzed according to the auto-injector device group allocated by randomization (ie, as-randomized treatment group).

The mITT population of the single arm period will consist of all randomized patients who continued in single arm period and received at least 1 dose or part of a dose of IMP during this period and who had an evaluable value of LDL-C at baseline and at least one on-treatment LDL-C within one of the analysis windows from Week 8 to Week 16.

The treatment periods are defined in Section 2.1.4.5.

2.3.2 Safety population

The safety population of the parallel arms period will consist of all randomized patients who received at least 1 dose or part of a dose of IMP during this period. Patient data will be analyzed according to the auto-injector device actually used.

The safety population of the single-arm period will consist of all randomized patients who continued in the single-arm period and receive at least 1 dose or part of a dose of IMP during this period.

All safety and PTC analyses will be performed on these populations.

In addition:

- Nonrandomized but treated patients (if any) will not be part of the safety population, but their safety data will be presented separately.
- Randomized patients for whom it is unclear whether they took the IMP will be included in the safety population as randomized.

2.3.3 Pharmacokinetic populations

The PK population of the parallel arms period will consist of all randomized patients who received at least 1 dose or part of a dose of IMP (safety population) and had at least one evaluable blood sample for PK during this period. All patients will be analyzed according to the auto-injector device that they actually received.

The PK population of the single arm period will consist of all randomized patients who received at least 1 dose or part of a dose of IMP and had at least one evaluable blood sample for PK during this period.

The PK population will be used for the analyses of alirocumab concentrations and PCSK9 concentrations.

2.3.4 Anti-alirocumab antibody population

The ADA population of the parallel arms period will consist of all randomized patients who received at least 1 dose or part of a dose of IMP during this period (safety population) with an available ADA sample at baseline and at least one post-baseline available ADA sample during this period. All patients will be analyzed according to the auto-injector device that they actually received.

The ADA population of the single arm period will consist of all randomized patients who receive at least 1 dose or part of a dose of IMP during this period (safety population) with an available ADA sample at baseline and at least one post-baseline available ADA sample during this period.

2.4 STATISTICAL METHODS

2.4.1 Demographics and baseline characteristics

Parameters described in Section 2.1.1 will be summarized on the randomized population by treatment group using descriptive statistics.

Continuous data will be summarized using the number of available data, mean, standard deviation (SD), median, minimum, and maximum for each treatment group. Categorical and ordinal data will be summarized using the number and percentage of patients in each treatment group.

Medical and surgical history will be summarized by primary SOC and HLT. The tables will be sorted by internationally agreed order of SOC and by the decreasing frequency of HLT based on the overall incidence across treatment groups. In addition all medical history of specific interest will be presented by treatment group.

2.4.2 Prior or concomitant medications

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

Medications received during the parallel-arm period will be summarized by treatment group and medications received during the single -arm period will be summarized overall. Medications will be summarized according to the World Health Organization-Drug Dictionary, considering the first digit of the ATC class and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized, and patients will be counted once in

each ATC category (anatomic or therapeutic) linked to the medication. Therefore patients may be counted 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 across treatment groups. In case of equal frequency across anatomic or therapeutic categories, alphabetical order will be used.

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

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

2.4.3 Extent of investigational medicinal product exposure and compliance

The extent of IMP exposure and compliance will be assessed and summarized by actual device within the safety population for the parallel-arms period and overall for the single-arm period.

2.4.3.1 Extent of investigational medicinal product exposure

No duration of IMP exposure will be calculated for the parallel-arms period since patients will receive injection(s) at Day 1 only during this period. The proportion of patients having received the first injection(s) will be summarized.

The duration of IMP exposure for the single-arm period is defined as: last IMP injection date - first IMP injection date during this period + 28 days (regardless of unplanned intermittent discontinuations) and will be described quantitatively. The number of injections received during the single-arm period will also be summarized. The number of patients receiving 1, 2 and 3 injections during the single-arm period will be provided.

2.4.3.2 Compliance

No treatment compliance to the IMP will be calculated for the parallel-arms period since patients will receive injection(s) at Day 1 only during this period. For patients randomized to receive the current AI, it will be described whether all patients received the 2 injections as planned.

Treatment compliance to the IMP for the single-arm period will be assessed using the mean injection frequency, defined for each patient, as the average number of days between 2 consecutive injections, that is: (last injection date - first injection date during this period)/(number of injections -1) for patients receiving at least 2 injections during this period.

2.4.4 Analyses of endpoints

2.4.4.1 Analysis of primary endpoint

The primary endpoint (ie, number [%]) and types of SYDNEY-associated PTCs related to the unsupervised injections will be described on the safety population for the single arm period. The number and % of PTCs will be provided with the 95% CI using Wilson score method. If applicable, the number of PTCs per patient will be described. In addition the type of PTCs will be described.

In addition, all the reported complaints (including complaints not confirmed as fulfilling PTC definition) will be described.

2.4.4.2 Analysis of secondary endpoints

2.4.4.2.1 Device-related endpoints

All secondary device-related endpoints will be analyzed on the safety population using descriptive statistics. In addition, 95% CI for the number of PTCs, number and % of patients with any PTCs will be provided using Wilson score method.

Questionnaires will be analyzed with descriptive statistics.

2.4.4.2.2 Pharmacokinetic variables

All analyses for PK variables will be presented by treatment group for the parallel-arms period and overall for the single-arm period.

All the PK analyses will be performed using the PK population in each period.

PK parameters (C_{max}, t_{max}, AUC0-tau and C_{trough}) will be summarized (mean, geometric mean, median, standard deviation, standard error of mean, coefficient of variation, minimum, and maximum).

For the parallel-arms period, log-transformed C_{max}, AUC0-tau and C_{trough}, estimates and 90% CI for the ratio of geometric means (SYDNEY/ AI) will be provided using an ANCOVA model with treatment group (SYDNEY, AI) as fixed effect and baseline body weight as covariate.

2.4.4.2.3 Anti-drug antibodies variables

The following summaries will be performed on the ADA population by treatment group for the parallel-arm period and overall for the single-arm period, taking into account all samples regardless of timing in relation to injections:

- ADA results (negative or positive) by time point
- ADA titers using descriptive statistics (median, minimum, and maximum) for positive ADA by time point
- Number (%) of patients with pre-existing ADA and number (%) of patients with treatment emergent ADA positive response
- Number (%) of patients with persistent/indeterminate /transient treatment-emergent ADA positive response
- Time to onset of treatment-emergent ADA positive response using descriptive statistics.

2.4.4.2.4 Pharmacodynamic variables (lipid variables)

Continuous endpoints anticipated to have a normal distribution

Continuous variables anticipated to have a normal distribution (ie, percent change in LDL-C, Total-C, HDL-C at Week 4) will be analyzed in the mITT population of the parallel-arm period using an ANCOVA model with fixed categorical effect of treatment group (SYDNEY, AI), as well as the continuous fixed covariate of corresponding baseline value. LS means and 95% CI will be provided for both SYDNEY and AI.

Depending on the number of missing LDL-C values at Week 4, a sensitivity analysis may be performed using multiple imputations (with baseline LDL-C and device group factors included in the imputation model) using the MI SAS® procedure to impute missing data followed by ANCOVA model. Results will be combined using Rubin's formulae with the SAS MIANALYZE procedure.

Continuous endpoints anticipated to have a non-normal distribution

Continuous variables anticipated to have a non-normal distribution (ie, percent change in TG at Week 4) will be analyzed in the mITT population of the parallel-arm period using the robust regression model with endpoint of interest as response variable using M-estimation (using SAS ROBUSTREG procedure) with treatment group (SYDNEY, AI) and corresponding baseline value as effects to compare treatment effects. Combined means estimates for both treatment groups with their corresponding 95% CIs will be provided.

Descriptive statistics will be provided for the 4 lipid parameters at Week 8, Week 12 and Week 16 on the mITT population of the single-arm period.

2.4.4.2.5 Safety variables

The summary of safety results will be presented separately for the parallel-arm and single-arm periods. The parallel-arm period will be presented by treatment group and the single-arm period will be presented by overall patients. No formal inferential testing will be performed for either study period. Summaries will be descriptive in nature. All summaries of safety results described in this section will be presented for each study period respectively, unless otherwise noted.

General common rules

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

- Safety data in patients who do not belong to the safety population (eg, exposed but not randomized) will be listed separately.
- The baseline value, for both parallel arms and single arm periods, is defined as the last available value obtained up to the date and time of the first IMP administration.
- The PCSA values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs, and electrocardiogram (PCSA version dated May 2014 [Appendix A]). In case the PCSA threshold is within the normal laboratory ranges, the analysis will be done using "<Low Limit Normal" or ">ULN" threshold instead of "<PCSA threshold" or ">PCSA threshold" respectively.
- PCSA criteria will determine which patients had at least 1 PCSA during the TEAE period, taking into account all evaluations performed during the TEAE period, including nonscheduled or repeated evaluations. The treatment-emergent PCSA denominator for a given parameter will be based on the number of patients assessed for that given parameter at least once during the TEAE period.
- All measurements, scheduled or unscheduled, fasting or not fasting, will be assigned to analysis windows defined in Section 2.5.4 in order to provide an assessment for Week 4 to Week 16 time points.
- For quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results and change from baseline values by visit and treatment group using analysis windows. Summaries will also include the last on-treatment value and the worst on-treatment value. The last on-treatment value is defined as the last value collected during the treatment period of each study period. The worst on-treatment value is defined as the nadir and /or the peak value during the treatment period of each study period according to the direction (minimum or maximum) of the abnormality as defined in the PCSA list.

2.4.4.2.5.1 Adverse events

Generalities

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

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

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

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

Analysis of all treatment-emergent adverse events

The following TEAE summaries will be generated.

- Overview of TEAEs, summarizing number (%) of patients with any
  - TEAE
  - Serious TEAE
  - TEAE leading to death
  - TEAE leading to permanent treatment discontinuation
- All TEAEs by primary SOC, HLGT, HLT, and PT
- All TEAEs by primary SOC and PT
- All TEAEs by treatment group regardless of relationship in one column and, in the same table a second column with TEAEs related to alirocumab according to investigator's opinion by primary SOC, HLGT, HLT and PT
- All TEAEs by maximal intensity (ie, mild, moderate or severe), presented by primary SOC and PT

Analysis of all treatment emergent serious adverse event(s)

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

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

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

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

- All grouping of TEAEs including AESI as listed in Section 2.1.4.5.1 will be analyzed using selections defined in Section 2.1.4.5.1 and will be presented by SMQ/CMQ and PT (when selection is based on SMQs/CMQs) and by SOC and PT (when selection is based on the e-CRF tick box or HLGT/HLT). The summaries will be sorted by decreasing incidence of PT within each SOC/SMQ (in the SYDNEY group for tables performed on the parallel-arm period)

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

- Intensity of the event (mild, moderate, severe)
- Number of events divided by the number of IMP injections received
- Time from first IMP injection to first injection site reaction
- Description of the highest intensity of each symptom recorded in the specific e-CRF page

Analysis of TEAE(s) linked to PTC:

- All TEAEs related to PTC by primary SOC, HLGT, HLT, and PT

Analysis of pre-treatment and post-treatment adverse events

- All pre-treatment AEs by primary SOC and PT
- All pre-treatment AEs leading to treatment discontinuation by primary SOC and PT
- All post-treatment AEs by primary SOC and PT
- All post-treatment SAE by primary SOC and PT

2.4.4.2.5.2 Deaths

The following summaries of deaths will be generated.

- Number (%) of patients who died by study period (on-study, on-treatment, post-study) Deaths in nonrandomized patients or randomized but not treated patients.

- TEAEs leading to death (death as an outcome on the AE 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 .
- TEAEs leading to death (death as an outcome on the AE as reported by the Investigator) by primary SOC, HLGT, HLT, and PT. TEAEs leading to death are TEAEs that led to death regardless of timing of death in relation to IMP injection (i.e. death occurring in the TEAE period or during the post-treatment period).

2.4.4.2.5.3 Laboratory variables

The summary statistics (including number, mean, median, standard deviation, minimum and maximum) of all laboratory variables (central laboratory values and changes from baseline) will be calculated for each visit or study assessment (baseline, each post-baseline time point, last on-treatment and worst on-treatment value).

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

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

For parameters for which no PCSA criteria are defined, similar table(s) using the normal range will be provided.

Drug-induced liver injury

The liver function tests, namely AST, ALT, ALP, and total bilirubin, are used to assess possible drug-induced liver toxicity. The proportion of patients with PCSA values or ALT increase as defined in Adverse Events of Special Interests section (see Section 2.1.4.5.1) during TEAE period by baseline status will be displayed for each parameter.

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

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

The incidence of liver-related TEAEs will be summarized by treatment group. The selection of PTs will be based on SMQ Hepatic disorder (see Section 2.1.4.5.1).

2.4.4.2.5.4 Vital sign variables

The summary statistics (including number, mean, median, standard deviation, minimum and maximum) of all vital signs variables (central laboratory values and changes from baseline) will be calculated for each visit or study assessment (baseline, each post-baseline time point, last on-treatment, worst on-treatment value).

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

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

2.4.4.3 Analysis of other endpoints

Other endpoints defined in Section 2.1.5 will be described using count and percentage.

2.4.5 Multiplicity issues

Not applicable.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

The following formulas will be used for computation of parameters.

Time from diagnosis

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

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

Date of last dose of IMP (for single-arm period)

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

Renal function formulas

eGFR value will be derived using the Modification of the Diet in Renal Disease equation:175 × (creatinine in µmol/L / 88.4)-1.154 × (age in years)-0.203 (x 0.742 if female, x 1.212 if race is "black or African American").

Lipids variables, laboratory safety variables, hs-CRP

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

Pharmacokinetic variables

Data below the LLOQ are set to zero.

2.5.2 Data handling conventions for secondary variables

See Section 2.1.4.

2.5.3 Missing data

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

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

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

Handling of computation of treatment duration if last IMP injection date is missing

If the last IMP injection date is missing, the exposure duration will be left as missing.

Handling of analysis periods if last IMP injection date is missing

If the last IMP injection date is missing, then this date will be imputed to the earliest between

- the last day of the month and year, when applicable or else the 31st of December of the year,
- the date of the end of treatment visit (Week 12 visit for completers, early end of treatment visit for patients who prematurely discontinued the IMP),
- and the date of the last contact,

to determine the analysis periods end.

Handling of medication missing/partial dates

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

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

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

Handling of adverse events when date and time of first IMP injection is missing

When the date of the first IMP injection is missing, all adverse events that occurred on or after the day of randomization will be considered as TEAEs.

Handling of missing assessment of relationship of AEs to IMP

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

Handling of missing severity of AEs

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

Handling of potentially clinically significant abnormalities

Patients with missing baseline value will be grouped in the category “normal/missing at baseline.”

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

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

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

2.5.4 Windows for time points

Data analyzed by time point (except PK and PCSK9 variables) will be summarized using the analysis windows given in Table 1. These analysis windows will be applicable for all analyses, and they are defined to provide more homogeneous data for time point-specific analyses. For PK, since measurements are planned every week, e-CRF visits will be used instead of analysis windows.

Table 1 - 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 16	113	99 to 126

Study days are calculated from the day of first IMP injection, the day of first open-label IMP injection being Day 1. For randomized but not treated patients, Day 1 is the day of randomization.

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

2.5.5 Unscheduled visits

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

2.5.6 Pooling of centers for statistical analyses

Not applicable.

2.5.7 Statistical technical issues

Not applicable.

3 INTERIM ANALYSIS

No interim analysis is planned.

4 DATABASE LOCK

The database is planned to be locked approximately 28 days 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

Not applicable.

7 LIST OF APPENDICES

Appendix A Potentially clinically significant abnormalities criteria

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

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

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

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

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

Parameter	PCSA	Comments
Glucose		
Hypoglycaemia	≤3.9 mmol/L and <LLN	ADA May 2005.
Hyperglycaemia	≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)	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	
Neutrophils	<1.5 Giga/L (Non-Black);<1.0 Giga/L (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
Monocytes	>0.7 Giga/L	
Basophils	>0.1 Giga/L	
Eosinophils	>0.5 Giga/L or >ULN (if ULN≥0.5 Giga/L)	Harrison- Principles of internal Medicine 17th Ed., 2008.
Hemoglobin	≤115 g/L (Male); ≤95 g/L (Female) ≥185 g/L (Male); ≥165 g/L (Female) Decrease from Baseline ≥20 g/L	Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
Hematocrit	≤0.37 v/v (Male) ; ≤0.32 v/v (Female) ≥0.55 v/v (Male) ; ≥0.5 v/v (Female)	
RBC	≥6 Tera/L	Unless specifically required for particular drug development, the analysis is redundant with that of Hb. Otherwise, consider FDA criteria.
Platelets	<100 Giga/L ≥700 Giga/L	International Consensus meeting on drug-induced blood cytopenias, 1991.

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

Parameter	PCSA	Comments
Urinalysis		
pH	≤4.6 ≥8	
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Orthostatic Hypotension		
Orthostatic SDB	≤-20 mmHg	
Orthostatic DBP	≤-10 mmHg	
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.

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

Parameter	PCSA	Comments
ECG		Ref.: ICH E14 guidance (2005) and E14 Q&A (2012), and Cardiac Safety Research Consortium White Paper on PR and QRS (Nada et al. Am Heart J. 2013; 165(4) : 489-500)
HR	<50 bpm <50 bpm and decrease from baseline ≥20 bpm <40 bpm <40 bpm and decrease from baseline ≥20 bpm <30 bpm <30 bpm and decrease from baseline ≥20 bpm	Categories are cumulative
	>90 bpm >90 bpm and increase from baseline ≥20bpm >100 bpm >100 bpm and increase from baseline ≥20bpm >120 bpm >120 bpm and increase from baseline ≥20 bpm	Categories are cumulative
PR	>200 ms >200 ms and increase from baseline ≥25% > 220 ms >220 ms and increase from baseline ≥25% > 240 ms > 240 ms and increase from baseline ≥25%	Categories are cumulative
QRS	>110 ms >110 msec and increase from baseline ≥25% >120 ms >120 ms and increase from baseline ≥25%	Categories are cumulative
QT	>500 ms	

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

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

Appendix B List of MedDRA terms for CMQ

Table 2 - Selected PTs from SMQ "Optic nerve disorders" including in the CMQ for neurologic

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

MedDRA Term Label	Preferred Term Code
Quadranopia	10075427
Visual acuity reduced	10047531
Visual acuity reduced transiently	10047532
Visual acuity tests abnormal	10047534
Visual field defect	10047555
Visual field tests abnormal	10047567
Visual impairment	10047571
Visual pathway disorder	10061411

Table 3 - CMQ "Neurocognitive disorders – FDA's recommendation"

MedDRA level	MedDRA Code	MedDRA Term Label
PTCD	10001949	Amnesia
PTCD	10061423	Amnestic disorder
PTCD	10002711	Anterograde Amnesia
PTCD	10066842	Behavioural and Psychiatric Symptoms of Dementia
PTCD	10008398	Change in sustained attention
LLTCD	10009843	Cognitive Deterioration
PTCD	10057668	Cognitive Disorder
LLTCD	10010300	Confusion
LLTCD	10048321	Confusion Aggravated
PTCD	10010305	Confusional State
PTCD	10012218	Delirium
PTCD	10012267	Dementia
PTCD	10012271	Dementia Alzheimer's type
LLTCD	10012290	Dementia Nos
LLTCD	10012291	Dementia Nos Aggravated
LLTCD	10012292	Dementia of the Alzheimer's type NOS
PTCD	10067889	Dementia with Lewy Bodies
PTCD	10013395	Disorientation
PTCD	10013496	Disturbance in attention
PTCD	10070246	Executive dysfunction
PTCD	10068968	Frontotemporal Dementia
LLTCD	10058669	Global Amnesia

MedDRA level	MedDRA Code	MedDRA Term Label
PTCD	10021402	Illogical Thinking
PTCD	10071176	Impaired reasoning
PTCD	10021630	Incoherent
PTCD	10023236	Judgement impaired
PTCD	10027175	Memory Impairment
PTCD	10027374	Mental Impairment
LLTCD	10027376	Mental Impairment Nos
LLTCD	10048345	Mental State Abnormal Aggravated
PTCD	10048294	Mental Status Changes
PTCD	10065424	Mini Mental Status Examination Abnormal
PTCD	10036631	Presenile Dementia
PTCD	10038965	Retrograde Amnesia
PTCD	10039966	Senile Dementia
LLTCD	10039967	Senile Dementia Nos
LLTCD	10040602	Short-term Memory Loss
PTCD	10043431	Thinking Abnormal
LLTCD	10043438	Thinking Slowed
PTCD	10044380	Transient Global Amnesia
PTCD	10057678	Vascular Dementia

MSC14864 16.1.9 Statistical Analysis Plan

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	Clinical Approval	27-Mar-2018 16:09 GMT+0200
[redacted]	Clinical Approval	27-Mar-2018 16:49 GMT+0200