NCT03694197

STATISTICAL ANALYSIS PLAN

VERSION: FINAL

Title: **Long Term Safety Study of PRALUENT in Patients with Heterozygous Familial Hypercholesterolemia or with Non-Familial Hypercholesterolemia at High and Very High Cardiovascular Risk and Previously Enrolled in the Neurocognitive Function Trial**

Protocol: **R727-CL-1609**

Investigational Product: **PRALUENT® (REGN727/SAR236553)**

Sponsor: **Regeneron Pharmaceuticals, Inc.**

Statistician: [redacted]

Clinical Trial Manager: [redacted]

Clinical Study Director: [redacted]

Version/Date: **V1.0 / July 16, 2020**

The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACB	Anticholinergic burden
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
Apo	Apolipoprotein
AST	Aspartate aminotransferase
CANTAB	Cambridge Neuropsychological Test Automated Battery
CHD	Coronary heart disease
CI	Confidence interval
CPK	Creatine phosphokinase
CRF	Case report form (paper or electronic)
CT	Computed tomography
CTFG	Clinical Trial Facilitation Group
CRO	Contract research organization
CVD	Cardiovascular disease
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic data capture
eGFR	Estimated Glomerular Filtration Rate
FH	Familial hypercholesterolemia
GCP	Good Clinical Practice
GDS-S	Geriatric Depression Scale short form
HbA1c	Hemoglobin A1c
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
heFH	Heterozygous familial hypercholesterolemia
HIV	Human immunodeficiency virus
hs-CRP	High-sensitivity C-reactive protein
ICF	Informed consent form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
ITT	Intent-to-treat

IVRS	Interactive voice response system
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LDLR	Low-density lipoprotein receptor
LMT	Lipid-modifying therapy
LOCF	Last observation carried forward
Lp(a)	Lipoprotein a
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
MMRM	Mixed-effect model with repeated measures
MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
NCEP ATP	National Cholesterol Education Program-Adult Treatment Panel
Non-HDL-C	Non-high-density lipoprotein cholesterol
PAL	Paired Associates Learning
PCSA	Potentially clinically significant abnormal value
PCSK9	Proprotein convertase subtilisin/kexin type 9
PRN	Pro re nata
PT	Preferred term
Q2W	Every 2 weeks
RBC	Red blood cell
Regeneron	Regeneron Pharmaceuticals, Inc.
RTI	Reaction Time
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis Software
SC	Subcutaneous
SOC	System organ class
SWM	Spatial Working Memory
TEAE	Treatment-emergent adverse event
TG	Triglyceride
Total-C	Total cholesterol
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal

VHP	Voluntary Harmonization Procedure
WBC	White blood cell

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying the statistical approaches for the analysis of study data prior to database lock. The SAP is intended to be a comprehensive and detailed description of the strategy and statistical methods to be used in the analysis of data collected in the R727-CL-1609 study.

This plan may be revised during the study to accommodate protocol amendments and adapt to unexpected issues in study execution that may affect planned analyses. These revisions will be based on data review of the study data, and a final plan will be issued prior to the database lock.

1.1. Background/Rationale

This study is an open-label extension (OLE) to the neurocognitive function study (R727-CL-1532) in which all patients will be treated, in a single arm, with PRALUENT. The study will be conducted on patients who completed treatment and the end of study (EOS) visit in the neurocognitive function study (R727-CL-1532), with no premature discontinuation of study drug or placebo. This will allow for patient exposure to PRALUENT of approximately 6 years.

At the time of inclusion into the OLE study, knowledge of the treatment arm in the neurocognitive function study (R727-CL-1532) will not be available to the investigator or the sponsor. Patients eligible to participate in the OLE study will initiate treatment with PRALUENT at the starting dose of 75 mg once every 2 weeks (Q2W), regardless of the treatment group to which they were randomized in the neurocognitive function study (R727-CL-1532).

The study duration of approximately 192 weeks, in addition to the 96-week exposure in the neurocognitive function study (R727-CL-1532), will enable the assessment of long-term exposure to PRALUENT.

Following a Type II variation for Praluent submitted on 14 August 2019 to modify the EU RMP, the missing information “clinical impact of very low LDL-C for extended period of time” was removed from the RMP in the CHMP opinion dated Jan. 16,2020. The EMA agreed to release the R727-CL-1609 study as there is no expectation that this study can further characterize the safety profile of alirocumab beyond what has already been learned from other long-term, controlled studies. Therefore, the study was terminated early by sponsor on January 31, 2020. Given this early termination, all analyses will be considered descriptive.

PRALUENT is also referred to as alirocumab, REGN727 or SAR236553. In the context of the R727-CL-1609 SAP, it will be referred to as PRALUENT.

1.2. Study Objectives

1.2.1. Primary Objectives

The primary objective of the study is to describe the long-term safety of PRALUENT in patients with heterozygous familial hypercholesterolemia (heFH) or non-familial hypercholesterolemia (FH) patients at high or very high cardiovascular risk who completed the neurocognitive function study (R727-CL-1532).

1.2.2. Secondary and Exploratory Objectives

The secondary objectives of the study are:

- To describe the effect of PRALUENT on low-density lipoprotein cholesterol (LDL-C)
- To describe the effect of PRALUENT on other lipid parameters
- To describe the effect of PRALUENT on gonadal steroid hormones

1.2.3. Modifications from the Statistical Section of Protocol Amendment 2

Because this study was terminated early by the Sponsor, all analyses will be considered descriptive.

1.2.4. Modifications from the Approved Statistical Analysis Plan

This is the first version of the Statistical Analysis Plan (SAP).

2. INVESTIGATING PLAN

2.1. Study Design

This is a phase 4, OLE, uncontrolled, multi-center, long-term, safety study to be performed in patients who have completed the neurocognitive function study (R727-CL-1532). The observation period for PRALUENT treatment in the OLE study is planned to be approximately 192 weeks.

Patients who completed treatment and the EOS visit in the neurocognitive function study (R727 CL-1532) may enroll in the OLE study. The EOS visit of the double-blind neurocognitive function study (R727-CL-1532) corresponds to visit 1 (day 1) of the OLE study. The first SC injection of PRALUENT will be administered in the clinic (day 1, visit 1).

After visit 1, patients have the option to either self-administer study drug, or have another designated person (such as a spouse or caregiver) administer study drug for them.

The starting dose of PRALUENT will be 75 mg administered SC Q2W (regardless of treatment assigned in the neurocognitive function study R727-CL-1532), that may be modified to 150 mg administered SC Q2W, and can be maintained or modified from 150 mg Q2W to 75 mg Q2W. Low-density lipoprotein cholesterol levels must be measured at 8 weeks after initiating study treatment, or at least 4 weeks after dose modification, to assess response and to adjust the dose, if needed.

The investigator will be blinded to the treatment received in the neurocognitive function study (R727-CL-1532) until that study is complete and the database is locked. Lipid profile values from samples obtained after inclusion will be blinded until week 8, in order to prevent any potential unblinding of the neurocognitive function study (R727-CL-1532).

2.2. Sample Size and Power Considerations

No formal sample size was calculated for this study. The anticipated number of patients is based on the previously observed drop-out rate in the ODYSSEY program.

2.3. Study Plan

From week 8 in the OLE study, lipid measurements will be collected and will be known by the investigator in real time. The investigator will manage the PRALUENT dose at his/her discretion based on LDL-C levels, starting at week 12, by either modifying the dose from 75 mg Q2W to 150 mg Q2W, maintaining the dose, modifying the dose from 150 mg Q2W to 75 mg Q2W, or discontinuing treatment with PRALUENT at any time during the treatment period. If a dose is missed, the patient should administer the injection as soon as possible and thereafter resume treatment from the day of the missed dose (ie, resume on the next originally

planned date). The statin dose should not be modified to adjust the degree of LDL-C lowering.

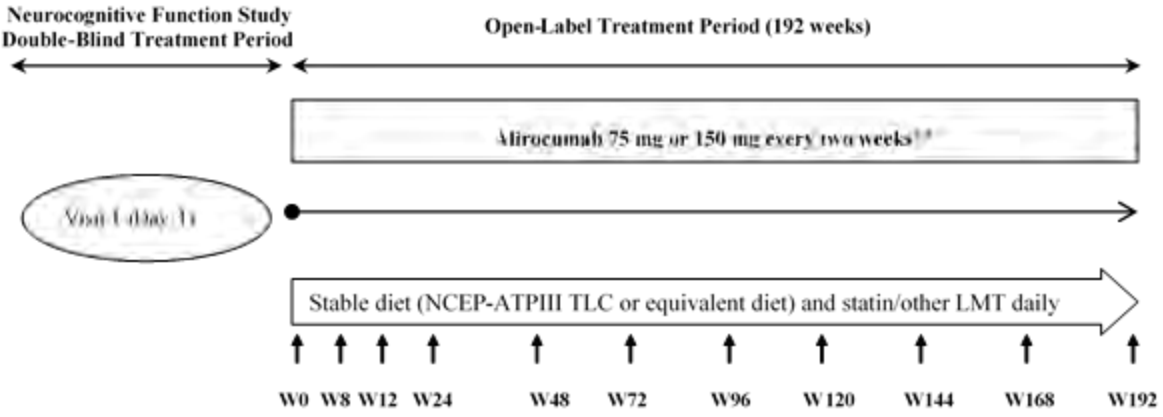
Background LMT will be prescribed as per clinical practice and should remain the same as in the neurocognitive function study (R727-CL-1532). Lipid modifying therapy, including statins, should not be changed during the course of the study. However, if clinically necessary, background LMT may be adjusted at the investigator's discretion. Any adjustment will be documented in the electronic case report form (CRF). Patients not treated with a statin (eg, statin intolerant patients, or patients in whom statin treatment was stopped during the neurocognitive function study [R727 CL 1532] for a safety reason) may still participate in the OLE study.

The investigator should refer to the label for information on PRALUENT and other LMTs.

Patients should continue a National Cholesterol Education Program-Adult Treatment Panel III Therapeutic Lifestyle Changes (NCEP-ATPIII TLC) diet or equivalent throughout the entire study duration.

Visits are planned at weeks 0, 8, 12, 24, 48, 72, 96, 120, 144, 168, and 192. At each visit, except at the EOS visit at week 192, study drug will be dispensed to the patient. If at any time during the study after the week 8 visit, the investigator, based on lipid results or safety issues, decides to modify the dose of PRALUENT, an unscheduled kit dispensation visit will be performed.

Figure 1: Study Flow Diagram



*The end of study visit in the neurocognitive function study (R727-CL-1532) will correspond to visit 1 (day 1) of this study.
**Starting dose is 75 mg Q2W. The first LDL-C assessment is at week 8. At any time after week 8, the investigator will be responsible to manage the PRALUENT dose by either modifying from 75 mg Q2W to 150 mg Q2W, maintain the dose, modifying from 150 mg Q2W to 75 mg Q2W or discontinuing the treatment with PRALUENT at any time during the treatment period.

3. ANALYSIS POPULATIONS

In accordance with guidance from the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (ICH, 1998), below are the patient populations defined for statistical analysis.

3.1. Safety Analysis Sets

3.1.1. Safety Population

Since this is a single-arm, open-label study, treatment allocated and the actual treatment received will be the same. Therefore, a single analysis set (ie, the safety analysis set [SAF]) will be used for safety and efficacy analyses. The SAF includes all patients who received any study drug in this study. All safety and efficacy variables will be analyzed using the SAF.

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristic Variables

The baseline value is generally defined as the baseline value in the neurocognitive function study (R727-CL-1532), i.e., the last available value before the first dose of double-blind study treatment in that study.

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

The following variables will be summarized:

Demographic Characteristics

- Sex (Male, Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Age in years (quantitative and qualitative variable: <45, ≥45 to <65, ≥65 to <75, and ≥75 years; and <65, and ≥65 years)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown)

Baseline Characteristics

- Baseline Weight (kg)
- Baseline Height (cm)
- Baseline Body mass index (BMI) in kg/m² (quantitative and qualitative variable defined as <30, ≥30)
- Tobacco Use (current, past, never)
- Alcohol Use (current, past, never)
- LMT at Baseline
- Female Menopausal Status

Baseline Disease Characteristics

- Lipid parameters - quantitative variables for all efficacy parameters

- LDL-C: <70, ≥ 70 to <100, ≥100 to <130, ≥130 to <160, ≥160 to <190, ≥190 mg/dL (<1.81, ≥1.81, <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 (<1.04, ≥1.04 mmol/L)

- Fasting TG: <150, ≥150 to <200, ≥200 mg/dL, and category ≥150 mg/dL for mixed dyslipidaemia (<1.7, ≥1.7 to <2.3, ≥2.3 mmol/L, and category ≥ 1.7 mmol/L),

- Lp(a): <30, ≥30 to <50, ≥50 mg/dL, and category ≥30 mg/dL (<0.3, ≥0.3 to <0.5, and ≥0.5 g/L)

- HbA1c both quantitative variable and qualitative variable defined as: <5.7%, ≥5.7% to <6.5%, ≥6.5%

- hs-CRP

- Hepatitis B surface antigen

- Hepatitis C antibody

4.2. Medical History and Disease Characteristics

Medical history is not collected in this study. The medical history data collected in the neurocognitive function study (R727-CL-1532) will be used for the patients enrolled in this study.

As applicable, patient medical history, pre-listed or not in the e-CRF, will be dictionary coded by primary system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), specifically the MedDRA version in effect at the time of database lock for the analysis. Medical history of interest will be assessed through cardiovascular history and risk factors (dedicated and pre-listed e-CRF variables of acute myocardial infarction, silent myocardial infarction, etc., with outcome of occurred/not occurred), subject medical allergic history (dedicated and pre-listed e-CRF variables of allergic rhinitis, chronic sinusitis, etc., with outcome of occurred/not occurred), and family medical allergic history (dedicated and pre-listed e-CRF variables of allergic rhinitis, chronic sinusitis, etc., with outcome of occurred/not occurred). Additional other medical history (i.e., not already collected in the pre-printed e-CRFs) and surgical history will also be coded and reported.

Medical history of specific interest includes:

- Coronary heart disease (CHD)

- CHD risk equivalents

- Cardiovascular (CV) 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 e-CRF page).

Further for medical history variables, CHD, CHD risk equivalents, and CV risk factors are defined below, and will be based on items or combinations of items pre-listed in the dedicated medical history e-CRF page (unless otherwise specified). Patient status for primary and secondary CVD prevention is also defined below.

CHD (regardless if it is ongoing or not) is defined as at least one of the following events:

- Acute myocardial infarction

- Silent myocardial infarction

- Unstable angina

- Coronary revascularization procedure

- Other clinically significant CHD diagnosed by invasive or non-invasive testing

CHD risk equivalent (regardless if it is ongoing or not) is defined as at least one of the following events:

- Peripheral arterial disease: See definition below.

- Ischemic stroke

- Chronic kidney disease

- Known history of diabetes mellitus (type 1 or 2) AND 2 or more additional risk factors among:

  – History of ankle-brachial index ≤ 0.90

  – History of hypertension

  – History of microalbuminuria or macroalbuminuria or dipstick urinalysis at screening (week-2) with >2+ protein

- History of pre–proliferative or proliferative diabetic retinopathy or laser treatment for diabetic retinopathy
- Known family history of premature CHD

As listed above, "Peripheral arterial disease" history is defined as follows, using combinations of the corresponding pre-listed medical history items of the e-CRF page "Cardiovascular history and cardiovascular risk factors":

- Intermittent claudication (linked to PAD) TOGETHER WITH ankle-brachial index ≤ 0.90;

Or

- Intermittent claudication (linked to PAD) TOGETHER WITH peripheral revascularization procedure (angioplasty, stenting) for PAD or peripheral revascularization surgery (arterial bypass) for PAD;

Or

- Critical limb ischemia TOGETHER WITH peripheral revascularization procedure (angioplasty, stenting) for PAD or thrombolysis for PAD or peripheral revascularization surgery (arterial bypass) for PAD.

Secondary CVD prevention is defined as patients with any of the following history of CVD (other patients will be classified as primary CVD prevention):

- History of CHD (as defined above)
- History of ischemic stroke
- History of PAD with severity criteria defined as one of the following events:
  - Intermittent claudication and ankle brachial index ≤ 0.90
  - Peripheral revascularization procedure (angioplasty, stenting) for PAD
  - Thrombolysis for PAD
  - Peripheral revascularization surgery (arterial bypass) for PAD
  - Critical limb ischemia

CV Risk Factors are defined for this study as high risk and very high risk below.

- Very high CV risk patients are defined as patients with CHD or CHD risk equivalents (ASCVD).

- High CV risk patients are defined as all other patients.

Hyperlipoproteinemia disease history will be assessed through diagnosis of HeFH, time from diagnosis to study randomization (years), confirmation of diagnosis (genotyping [Yes/No], clinical diagnosis [Yes/No], lipid modifying therapies history and received at randomization in the neurocognitive function study (R727-CL-1532) as detailed below.

- Lipid modifying therapy history, as reported in the "History of Hypercholesterolemia/Statin Use" e-CRF page

  - Type of lipid-modifying therapy taken at screening (statin, fibrates, bile acid sequestrant, cholesterol absorption inhibitor, nicotinic acid and derivates, omega 3 fatty acids ≥1000 mg/day, other).

  - Number of patients at screening on a maximal tolerated dose of stain. For those not on not statin or not taking the maximum tolerated dose, reason for not statin or not taking a maximum tolerated dose.

  - Number of patients with a history of down-titration of statin dose due to tolerability issues

  - Number of patients with a history of changing to a different statin due to tolerability issues

Lipid modifying therapies received at randomization in the neurocognitive function study (R727-CL-1532) will be derived from the prior and concomitant medication e-CRF pages by selecting medications with the type of lipid lowering medication tick box checked ("Statin" or "Other lipid modifying therapy").

- Background lipid modifying therapy at randomization as reported in the dedicated prior and concomitant medication e-CRF pages

  - Number of patients taking atorvastatin 40 to 80 mg, rosuvastatin 20 to 40 mg daily

  - Atorvastatin daily dose in mg (10, 20, 40, 80, Other)

  - Rosuvastatin daily dose in mg (5, 10, 20, 40, Other)

  - Simvastatin daily dose in mg (10, 20, 40, 80, Other)

  - Other statins

- Any LMT other than statins
- Any LMT other than nutraceuticals (by chemical class and drug name)
- Nutraceuticals (Omega 3 fatty acids (<1000mg/day), Phytosterols, Psyllium/plantago, Policosanol, Other nutraceuticals)

Details (i.e. statin names, doses) for patients who had received at least 2 statins the day of randomization in the neurocognitive function study (R727-CL-1532) will be listed.

4.3. Prior and Concomitant Medications

All medications (including statin, non-statin LMT, CV, and Other) taken from the time of informed consent to the end of the study, including medications that were started before the study and are ongoing during the study, will be reported in the Concomitant Medications CRF.

All medications will be dictionary coded using the World Health Organization-Drug Dictionary (WHO-DD) to both an anatomic category and a therapeutic category, with the version in effect at the time of the database lock. Drug names will be matched to respective Anatomical-Therapeutic-Chemical (ATC) classification, although a drug can be matched to more than one ATC classification (i.e. patients can be counted in several categories for the same medication).

Definitions for deriving prior medications, concomitant and post-treatment medications are described below, with the understanding that a given medication can be simultaneously classified both as a prior and concomitant medication.

- Prior medications are any medications the patient used from the time of informed consent up to the day before first study treatment administration. Prior medications can be discontinued before first treatment administration or can be ongoing during the treatment phase.
- Concomitant medications are defined as any treatments received by the patient concomitantly with the study treatment, specifically from the first day of study treatment administration to the last study visit. Concomitant medications do not include medications started during the post-treatment period.
- Post-treatment medications are those medications administered to the patient during the time period starting from 1 days after the last study visit, and ending when the patient terminates the study.

4.4. Patient Disposition

Patient disposition includes the description of patient status at major milestone decisions in the study, as well as the patient analysis populations.

For patient study status, the following milestone categories are defined below. For all categories of patients, percentages will be calculated using the number of enrolled patients as the denominator, with two exceptions. Specifically, the two exceptions are for the screened and non-enrolled categories, which will not have associated percentages shown.

- Enrolled patients: met the inclusion criteria regarding the target indication and signed the informed consent form (ICF)
- Enrolled but not treated patients
- Enrolled and treated patients
- Patients complete 192 weeks of open-label treatment period (at least 190 weeks of exposure and visit W192 performed)
- Patients completed the study treatment period (i.e. as collected on the End of Open-Label Treatment eCRF)
- Patients who did not complete the study treatment period and patient's decision for treatment period discontinuation (as per the End of Open-Label Treatment eCRF)
- Patients who discontinued study treatment by main reason for permanent treatment discontinuation (as per the End of Open-label Treatment eCRF)
- Patients completed the study (i.e. as collected on the Study Completion eCRF)
- Patients who early terminated the study (as per the Study Completion eCRF)
- Patients who early terminated the study by main reason for early termination (as per the Study Completion eCRF)
- Status at last study contact
- Subject's visit impact due to COVID-19
- Study/Treatment discontinuation due to COVID-19

As defined in Section 3 of this document, the patient analysis populations are:

- Safety Population (SAF)

4.5. Study Treatment Exposure and Compliance Variables

Study treatment exposure variables are listed below with associated definitions:

- Patient duration of study treatment exposure in weeks defined as: (last study treatment administration date +14 – first study treatment administration date)/7, regardless of intermittent discontinuations.

- The following categories will be used for treatment exposure intervals: ≥1 day and <4 weeks, ≥4 weeks and <8 weeks, ≥8 weeks and <12 weeks, ≥12 weeks and <16 weeks, ≥16 weeks and <20 weeks, ≥20 weeks and <24 weeks, ≥24 weeks and <28 weeks, ≥28 weeks and <32 weeks, ≥32 weeks and <36 weeks, ≥36 weeks and <40 weeks, ≥40 weeks and <44 weeks, ≥44 weeks and <48 weeks, ……., ≥188 weeks and <192 weeks, ≥192 weeks.

- The total number of study treatment injections by patient.

In addition, for patients previously exposed to PRALUENT, the combined duration of treatment will be calculated as:

- (Date of the last study medication dose in the neurocognitive function study (R727-CL-1532) – date of the first study medication dose in the neurocognitive function study (R727-CL-1532) + 14) + (Date of the last study medication dose in R727-CL-1609 [current study] – date of the first study medication dose in R727-CL-1609 [current study] + 14).

Compliance will be assessed using the following variables with associated definitions:

- For each patient, the mean injection frequency for study treatment injections will be defined as the average number of days between 2 consecutive injections, that is: (last injection date – first injection date) / (number of injections - 1) for patients receiving at least 2 injections.

All important and minor protocol deviations randomization and drug-dispensing irregularities, as well as other deviations, will be collected and reviewed on an ongoing basis throughout the study as described in the Protocol Deviation Plan (PDP). Both monitoring-collected and programmatically derived deviations are listed and defined in the PDP.

4.6. Primary and Secondary Endpoints

4.6.1. Primary Endpoint

The primary endpoint in the study is the incidence of AEs after first administration of study drug through the last dose of study drug plus 2 weeks.

The following AEs will be described:

- AEs/serious adverse events (SAEs)
- AEs leading to treatment discontinuation
- Adverse events of special interest (AESI)

4.6.2. Secondary Endpoints

The secondary endpoints of the study are:

- Calculated LDL-C values and percent changes from baseline over time
- Values and percent changes from baseline in other lipids and other lipoproteins, including total cholesterol (Total-C), non-high-density lipoprotein cholesterol (non HDL-C), HDL-C, and triglycerides (TGs) over time
- Values and percent changes from baseline in gonadal hormones and gonadotropins over time: for female patients - estradiol, follicle-stimulating hormone (FSH) and luteinizing hormone (LH); for male patients - testosterone, FSH and LH;

4.7. Safety Variables

Patient safety will be assessed through the collection of reported adverse events (AEs), clinical laboratory data, and vital signs. Unless otherwise noted, the baseline value is defined as the last available value before the first dose study treatment.

4.7.1. Adverse Events Variables

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

- The PRE-TREATMENT period: defined as the time from the signed informed consent up to the first study treatment injection.
- The treatment-emergent adverse event (TEAE) period: defined as the time from the first dose of study drug to the last study visit.
- The POST-TREATMENT period: defined as starting the day after the end of the TEAE periods up to the patient's end of study.

4.7.1.1. Adverse Events and Serious Adverse Events

Adverse events (including serious adverse events (SAE), AEs causing permanent treatment discontinuation, deaths, and AEs of special interest) are recorded from the time of signed

informed consent until the end of study. All AEs diagnosed by the Investigator will be reported and described.

All AEs will be dictionary coded by "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 in effect at the time of database lock for the analysis.

Adverse Event Observation Period

- Pre-treatment AEs are AEs that developed or worsened or became serious during the pre-treatment period.
- Treatment-emergent adverse events (TEAEs) 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.

4.7.1.2. Adverse Events of Special Interest

Adverse events of special interest (AESI) are AEs (serious or non-serious) required to be monitored, documented, and managed in a pre-specified manner as 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 an e-CRF specific tick box on the AE page;
- General allergic events will be tabulated. Events will be selected using standardized MedDRA query (SMQ) "hypersensitivity" (broad and narrow) excluding the preferred terms linked to local injection site reactions (i.e. preferred terms containing "injection site" or "infusion site")
- ALT ≥3 ULN in the case baseline ALT < ULN or ALT ≥2 times the baseline value in the case baseline ALT ≥ ULN, selected using laboratory data. Baseline to be considered is the baseline of the present OLE study.
- Neurologic events selected using SMQs "demyelination" (broad and narrow), "peripheral neuropathy" (broad and narrow), and "Guillain-Barre syndrome" (broad and narrow) excluding the following preferred terms: "acute respiratory distress syndrome", "asthenia", "respiratory arrest" and "respiratory failure" and including selected PTs from SMQ "optic nerve disorders" (see Appendix 10.3, Table 3 for the list of terms)

- Symptomatic overdose with investigational medicine product, selected using HLT "Overdose" and the tick box "Symptomatic Overdose" in the e-CRF AE page.

- Pregnancy of female patient/subject (including male subject's partner), selected using appropriate MedDRA codes (PT "Pregnancy").

- Neurocognitive events:

  – Selected using a company MedDRA query (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 (FDA CMQ) (see Appendix 10.3, Table 4 for the list of terms)

- Cataract using HLT "Cataract conditions"

- New onset of diabetes (NOD) will be assessed in patients without diabetes at baseline (defined as patients without diabetes at baseline and during the study in the neurocognitive function study (R727-CL-1532)): The definition of new onset of diabetes (NOD) will be the following:

  – Type 1 or type 2 diabetes TEAE (grouping of Medical Dictionary for Regulatory Activities [MedDRA®] terms in Appendix 10.7 Table 7)

  and/or

  – At least 2 values of HbA1c ≥6.5% during the TEAE period

    NOTE: For patients with only a single measurement available during the TEAE period, a single value ≥6.5% will be considered and qualify the patient as NOD by default.

    For patients with several HbA1c measurements but only with the last one ≥6.5%, this single value ≥6.5% will be considered and qualify the patient as NOD by default

  and/or

  – At least 2 values of fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L)

    NOTE: For patients with only a single measurement available during the TEAE period, a single value ≥126 mg/dL (7.0 mmol/L) will NOT be considered and will NOT qualify the patient as NOD

For patients with several FPG measurements but only with the last one ≥126 mg/dL (7.0 mmol/L), this single value ≥ 126 mg/dL (7.0 mmol/L) will NOT be considered and will NOT qualify the patient as NOD

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

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

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

Neurocognitive Events of Special Interest

Neurocognitive events are defined in this study as AESI, specifically, neurocognitive AEs (serious or nonserious) required to be monitored, documented, and managed in a pre-specified manner as described in this protocol. The neurocognitive events will be adjudicated by the neurocognitive events review committee which is composed of experts in the field of cognition, independent from the sponsor and the investigators. This committee will be responsible for defining, validating, and classifying AEs of interest possibly related to cognition impairment. A charter and an operational manual will specify the procedures and criteria used for review of these events.

The committee will adjudicate whether a neurocognitive event identified by investigator or the CMQs is indeed a neurocognitive event (Yes/No).

The committee will also adjudicate whether possible etiology of the neurocognitive event is identified.

- Yes: means that there is a clear alternative explanation for the neurocognitive event.
- No: means that there is no clear alternative explanation for the neurocognitive event, and it might be study related.

4.7.1.3. Events Causing Death

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

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

4.7.2. Clinical Laboratory Safety Variables

Clinical laboratory tests will consist of blood analyses (including hematology and clinical chemistry) and urinalysis. Clinical laboratory values will be converted and analyzed in international units, including associated normal ranges provided by the central laboratory. International units will be used in all listings and tables. Clinical laboratory values in conventional (US) units will also be available in the database, with associated normal ranges (analyses can be provided upon request). Both actual test values and "change from baseline" values (defined as the post-baseline value minus the baseline value) will be used in the result summaries. Potentially clinically significant abnormalities (PCSA) ranges will be applied to the laboratory test values as applicable (see Appendix 10.2 for PCSA definitions).

Unless otherwise specified below, blood samples for clinical laboratories will be collected at the protocol scheduled visits, and visits will be assigned to the Analysis Windows (See Appendix 10.1). The laboratory parameters (excluding those considered as efficacy parameters) will be classified as follows:

- Hematology:
  - Red blood cells and platelets: hemoglobin, hematocrit, erythrocytes count, platelets count, reticulocyte count, ery. mean corpuscular Hemoglobin (MCH), ery. mean corpuscular HGB concentration (MCHC), ery. mean corpuscular volume (MCV)
  - White blood cells: white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils
- Clinical chemistry:
  - Metabolism: glucose, total protein, albumin, creatine phosphokinase
  - Electrolytes: sodium, potassium, chloride, calcium, phosphorus, bicarbonate
  - Renal function: creatinine, creatinine clearance, blood urea nitrogen (BUN), uric acid
  - Liver function: alanine Aminotransferase (ALT), aspartate aminotransferases (AST), alkaline phosphatase (ALP), GGT, bilirubin, LDH
- Hepatitis screen: anti-hepatitis-C antibody and hepatitis B surface antigen collected at day 1 and week 192.

4.7.3. Vital Sign Variables

Vital signs parameters will include height (cm), weight (kg), heart rate (bpm), systolic and diastolic blood pressure (mmHg) after resting at least five minutes. Both actual test values and "change from baseline" values (defined as the post-baseline value minus the baseline value) will be provided for protocol specified visits and visits will be assigned to the Analysis Windows (See Appendix 10.1). Potentially clinically significant Abnormalities (PCSA) ranges will be applied to the vital sign parameter values as applicable (see Appendix 10.2 for PCSA definitions).

4.8. Other Variables

The other endpoints of the study will include:

- The percent change in hs-CRP from baseline to protocol specified visits. Hs-CRP values greater or equal to 10 mg/L will be excluded from analyses in a second approach, since these are suggestive of concurrent infection(1). PCSA (potentially clinically significant abnormalities) criteria for hs-CRP are listed in Appendix 10.2.

- The absolute change in HbA1c (%) from baseline to protocol specified visits. PCSA criteria for HbA1c are listed in Appendix 10.2.

- The proportion of patients with two consecutives results, separated by at least 21 days, of calculated LDL-C <25 mg/dL (<0.65 mmol/L) (and again for calculated LDL-C <15 mg/dL [< 0.39 mmol/L]) during the treatment period.

- For the patients with two consecutive results as described above, the time to the first calculated LDL-C <25 mg/dL (<0.65 mmol/L) (and again for calculated LDL-C <15 mg/dL [< 0.39 mmol/L]) during the treatment period.

Protocol schedule visits will be assigned to the Analysis Windows (See Appendix 10.1).

4.9. Genomics Variables

Plans for analysis of genomics data will be provided in a separate SAP.

5. STATISTICAL METHODS

There will be no formal testing for safety variables. For the secondary efficacy endpoints, no formal statistical hypothesis will be tested.

Study data will be summarized descriptively for the following patient groups:

- The placebo treatment group (as-treated) in the neurocognitive function study (R727-CL-1532);
- The Praluent treatment group (as-treated) in the neurocognitive function study (R727-CL-1532);
- Overall: All patients in the safety population;

5.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively for the safety population. Parameters described in Section 4.1 will be summarized for the safety population.

The baseline value is generally defined as the baseline value in the neurocognitive function study (R727-CL-1532), i.e., the last available value before the first dose of double-blind study treatment in that study.

Continuous data will be summarized using the number of patients with data, mean, SD, median, minimum and maximum for each patient group. First quartile (Q1) and third quartile (Q3) will be also provided for baseline lipid parameters, HbA1c and hs-CRP. Categorical and ordinal data will be summarized using the number and percentage of patients in each patient group.

As applicable, other safety baseline data is presented collectively in the descriptive statistics summary tables containing respective post-baseline data.

5.2. Medical History and Disease Characteristics

Medical history and disease characteristics will be descriptively summarized. The medical history was not collected in this study. The medical history data from the neurocognitive function study (R727-CL-1532) will be used.

All reported patient's medical history and surgical history will be presented by primary SOC and HLT. The tables will be sorted by SOC internationally agreed order and decreasing patient frequency of HLT based on the overall incidence in the study. In addition, all medical

history of specific interest, as described in Section 4.2, will be summarized by patient incidence and percentage.

For the patients with primary CVD prevention status (see definition in Section 4.2), the number (and percentage) of patients with the following comorbidities/risk factors will be tabulated:

- Diabetes mellitus with target organ damage (renal damage (microalbuminuria, or macroalbuminuria, moderate CKD) and/or retinopathy (pre-proliferative or proliferative diabetic retinopathy and/or laser treatment for diabetic retinopathy)),
- Diabetes mellitus with 2 or more risk factors (see Section 4.2),
- Family History of premature CHD
- Hypertension,
- Moderate CKD
- Current smoker
- At least 2 of the above comorbidities/risk factors

In addition, smoking status will be summarized in patients with primary CVD prevention status.

For the patients with a secondary prevention status, the CVD history will be described using the number (%) of patients with:

- History of CHD (see Section 4.2)
- History of ischemic stroke
- History of PAD with severity criteria
  - Intermittent claudication and ankle brachial index ≤ 0.90
  - Peripheral revascularization procedure (angioplasty, stenting) for PAD
  - Thrombolysis for PAD
  - Peripheral revascularization surgery (arterial bypass) for PAD
  - Critical limb ischemia

Additionally:

- The number (%) of patients with a secondary prevention status with 1 or more associated comorbidity among hypertension, diabetes mellitus, and/or moderate CKD will be summarized.

- The number (%) of patients with history of CHD and 1 or more associated comorbidity among hypertension, diabetes mellitus, moderate CKD and/or other CVD (ischemic stroke, PAD) will be summarized.

For patient disease characteristics, as described in Section 4.2, continuous data will be summarized using the number of patients with data, mean, SD, median, minimum and maximum for the study and for each of the strata. Categorical and ordinal data will be summarized using the number and percentage of patients in the study.

5.3. Prior and Concomitant Medications

All prior medications, dictionary coded by WHO-DD, will be descriptively summarized for patients in the safety population. Summaries will present patient counts (and percentages) for all prior medications, by decreasing frequency of the overall incidence of ATC followed by therapeutic class. In case of equal frequency across anatomic or therapeutic categories, alphabetical order will be used. Patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication, but may be counted several times for the same medication.

All concomitant medications during the treatment period, dictionary coded by WHO-DD, will be descriptively summarized for patients in the safety population. Summaries will present patient counts (and percentages) for the concomitant medication groups described in Section 4.3 for all concomitant medications (including statin, non-statin LMT, CV), by decreasing frequency of the PRALUENT group incidence of ATC followed by therapeutic class. In case of equal frequency across anatomic or therapeutic categories, alphabetical order will be used. Patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication, hence may be counted several times for the same medication. Additionally, concomitant medications pre-specified as statin, non-statin LMT, and CV will be summarized by patient counts (and percentages) by therapeutic class or e-CRF pre-specified categories as appropriate and standardized medication name.

Post-treatment medications will be summarized as described above for all medications.

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

- atorvastatin 40 to 80 mg daily or rosuvastatin 20 to 40 mg daily or;

- atorvastatin below 40 mg daily or rosuvastatin below 20 mg daily or simvastatin at any daily dose, or other statins

- LMT other than statin only,

- no LMT.

The LMTs intensity at baseline is defined as:

- patients treated at enrollment with atorvastatin 40 to 80 mg daily or rosuvastatin 20 to 40 mg daily (high intensity statin),
- patients treated at enrollment with atorvastatin below 40 mg daily or rosuvastatin below 20 mg daily or simvastatin at any daily dose (low intensity statin), or other statins;
- non-statin LMT only,
- no LMT.

5.4. Patient Disposition

Patient disposition includes the description of patient status at major milestone decisions in the study, as well as the patient analysis populations.

Patient study status will be summarized for the study. Summaries will provide the frequency (and percentage as applicable) of patients that met the criteria for the variables described in Section 4.4. Exception listings will be generated for any subject treated but not enrolled, enrolled but not treated.

Patient analysis populations will be summarized, depicting frequencies (and percentages) of patients that met the criteria for each population described in Section 3.

5.5. Extent of Study Treatment Exposure and Compliance

The extent of study treatment exposure and study compliance parameters for the treatment period described in Section 4.5 will be assessed and summarized for patients in the safety population.

5.5.1. Exposure to Investigational Product

Study treatment exposure for the treatment period will be descriptively summarized for the treatment duration and total number of injections as described in Section 4.5. Treatment duration will be summarized using the number of patients with data, mean, SD, median, minimum and maximum. Categorized 4-week intervals of treatment duration will be summarized descriptively by counts and percentages.

The incidence of premature study treatment discontinuation (irrespective of the reason) and premature treatment discontinuation due to AEs will be presented graphically in the safety population using the Kaplan-Meier method.

5.5.2. Measurement of Compliance

Study treatment compliance parameters will be descriptively summarized using the number of patients with data, mean, SD, median, minimum and maximum for the variables listed in Section 4.5. According to protocol, cases of overdose are reported in the AE e-CRF pages and will be described in the AE analysis.

Both monitored and derived protocol deviations will be summarized for important deviations (counts of deviations), patients (incurring a deviation by count and percentage), and by type of important deviation (patient count and percentage). A patient listing of all important and minor protocol deviations will be provided.

5.6. Analyses of Efficacy Variables

For statistics where international and conventional units do not impact the results (e.g. percent changes from baseline, rates of patients below a threshold), derivations will be calculated and summaries will be run using conventional units. For other statistics (e.g. values at baseline and over time, absolute changes from baseline), derivations will be presented in both international and conventional units.

5.6.1. Analyses of Efficacy Variables

All lipid and special lipid measurements obtained from the central laboratory will be used to provide a value for the efficacy variables, if appropriate. The baseline value will be defined as the last available value before the first dose of double-blind study treatment in the neurocognitive function study (R727-CL-1532).

The efficacy variables will be explored through descriptive statistics at each scheduled visit, including the assessment prior to the first dose of the open-label study administration. The descriptive summaries will be performed in the Safety Analysis Set (for on-treatment analysis). Formal statistical testing is not planned.

Continuous variables will be summarized using the number of patients with data, mean, SD, median, first quartile (Q1) and third quartile (Q3), minimum and maximum.

Categorical variables (including the binary outcome variables) will be described by patient frequency of occurrence.

Descriptive statistics for calculated LDL-C will also be provided for patients with or without any study medication modification, separately.

Protocol schedule visits will be assigned to the Analysis Windows (See Appendix 10.1).

5.6.2. Sub-group Analyses

The subgroup analyses will be performed for LDL-C.

The following subgroups of interest will be evaluated, assuming there are enough patients in each subgroup level to perform the evaluation.

- The age group (<65, ≥65),
- Gender (Female, Male),
- BMI (<30 kg/m^2, ≥30 kg/m^2),
- Statins with versus without other LMT at baseline ,

5.6.3. Adjustment for Multiple Comparisons

Adjustments to the alpha level for the purposes of multiple testing are not applicable for this safety study.

5.7. Analysis of Safety Data

The summary of safety results will be presented on the safety population (Section 3.1). No formal inferential testing will be performed. Summaries will be descriptive in nature. All summaries of safety results described below will be presented for each period respectively, unless otherwise noted.

General common rules

All safety analyses will be performed, unless otherwise specified, using the following common rules:

- Safety data in patients who do not belong to the safety population (i.e., exposed but not enrolled) will be listed separately.
- The baseline value will be defined as the last available value before the first dose of double-blind study treatment in the neurocognitive function study (R727-CL-1532).
- 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 January 2009 [Appendix 10.3]). Considering that the threshold defined in the PCSA list for monocytes and basophils can be below the ULN, the following PCSA criterion will be used for the PCSA analysis of monocytes and basophils:
  - PCSA criterion for monocytes: >0.7 Giga/L or >ULN (if ULN ≥0.7 Giga/L).
  - PCSA criterion for basophils: >0.1 Giga/L or >ULN (if ULN ≥0.1 Giga/L).

- PCSA criteria will determine which patients had at least 1 PCSA during the TEAE period, taking into account all evaluations 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 Appendix 10.1, Table 1 in order to provide an assessment for week 8 to week 96 time points.

- For quantitative safety parameters including central laboratory measurements and vital sign scores, descriptive statistics will be used to summarize results and change from baseline values by visit, the last on-treatment value and the worst on-treatment value. The last on-treatment value is defined as the last post-baseline value collected during the respective treatment period (as defined in Section 4.7.1). The worst on-treatment value is defined post-baseline as the nadir and/or the peak value collected during the respective treatment period, according to the direction (minimum or maximum) of the abnormality as defined in the PCSA list.

- Analyses performed according to diabetes status will be done considering diabetic patients as patients with either type 1 or type 2 diabetes in the medical history e-CRF page (regardless of the ongoing status) in the neurocognitive function study (R727-CL-1532).

5.7.1. Analysis of Adverse Events

In general, the primary focus of AE reporting will be on TEAEs. Pre-treatment and post-treatment AEs will be provided separately.

If an AE date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the AE as pre-treatment, treatment-emergent, or post-treatment. The algorithm for imputing date/time of onset will be conservative and will classify an AE as treatment-emergent unless there is definitive information to determine pre-treatment or post-treatment status. Details on classification of AEs with missing or partial onset dates are provided in Section 6.4.

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

The table of all TEAEs presented by SOC and PT will be sorted by the internationally agreed SOC order and decreasing frequency of PTs within SOCs (in the PRALUENT group). This 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
- Number (%) of patients experiencing common TEAE(s) presented by primary SOC, HLT and PT (HLT incidence ≥ 5 % in the total patient group), sorted by SOC internationally agreed order and by alphabetic order for the other levels (HLT and PT);
- All TEAEs by primary SOC and PT, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC (in the PRALUENT group).
- All TEAEs regardless of relationship in one column and, in the same table a second column with TEAEs related to alirocumab according to investigator's opinion by primary SOC, HLGT, HLT and PT;
- All TEAEs by maximal severity (i.e., mild, moderate or severe), presented by primary SOC and PT, sorted as 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 study treatment to the first occurrence of selected TEAEs as well as incidence

rates at 48, 96, 144, and 192 weeks of exposure. Patients without any event will be censored at the end of the TEAE period. Selected TEAEs could be AESIs (e.g neurocognitive events), or TEAE related to any clinically significant signal that needs further characterization;

- The frequency of selected AEs by SOC and PT over time during the treatment period (number of patients experiencing AE and percentage by patient-months) will be provided, when appropriate, by time intervals defined as: ≤48 weeks, >48 to ≤96 weeks, >96 to ≤144 weeks, >144 to ≤192 weeks, using the PROC LIFETEST with the actuarial method. Only the first event will be counted.

Analysis of all treatment emergent serious adverse event(s)

- All serious TEAEs by primary SOC, HLGT, HLT, and PT and by SOC/PT; Patient listings of serious TEAEs will be provided for the report appendix.

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

- The event rate per patient-year will be provided for all serious TEAEs by SOC and PT.

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

- All TEAEs leading to permanent treatment discontinuation, by primary SOC, HLGT, HLT, and PT and by SOC/PT; Patient listings of TEAEs leading to permanent treatment discontinuation will be provided for the report appendix.

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

- All grouping of TEAEs including adverse events of special interest, as listed in Section 4.7.1.2, 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 PRALUENT group).

- Neurocognitive events adjudicated by the neurocognitive events review committee will also be summarized by primary SOC and PT. They will also be summarized according to the adjudication of possible etiology of the neurocognitive events (Yes/No) (Section 4.7.1.2).

- All TEAEs within diabetes grouping will be analyzed overall and according to the diabetic status at baseline.

The following variables will also be tabulated for the local injection site reactions TEAEs:

- Intensity of the event (mild, moderate, severe);
- Number of events divided by the number of study treatment injections received;
- Time from first study treatment injection to first injection site reaction;
- Description of the highest intensity of each symptom recorded in the specific e-CRF page with table and bar chart.

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

Post-treatment adverse events

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

Subgroup of patients with two consecutive LDL-C <25 mg/dL (<0.65 mmol/L)

If applicable, similar summaries of TEAEs as those described above will be provided on the safety subgroup population of patients with two consecutive results of LDL-C <25 mg/dL (as defined in Section 4.8) in both patient groups. Only TEAEs for which it will be confirmed or unclear that they occurred, worsened or became serious on the day or after the day the first level of LDL-C <25 mg/dL was observed will be considered in this summary.

In addition, the neurocognitive event rate in patients with 2 consecutive results separated by at least 21 days for calculated LDL-C <25 mg/dL, and calculated LDL-C <15 mg/dL, will be assessed.

5.7.1.1. Patient Deaths

The following summaries of deaths will be generated.

- Number (%) of patients who died by study period (TEAE and post-treatment);
- Deaths in enrolled but not treated patients;
- TEAEs leading to death (death as an outcome on the AE CRF page, as reported by the Investigator) by (at least) SOC (sorted by internationally agreed order), and PT (sorted by decreasing frequency, showing the number (n) and percentage (%) of patients) for the safety population.

5.7.2. Analysis of Clinical Laboratory Variables

Clinical laboratory parameter actual values (quantitative) and change from baseline values will be descriptively summarized at baseline and each post-baseline visit (collected up to the day of last dose of study treatment +21 days) by at least patient number, mean, median, Q1, Q3, SD, minimum and maximum for each patient group. Additionally, laboratory parameter measures for last on-treatment values and worst on-treatment values will be summarized in a similar manner. Clinical laboratory parameters mean changes from baseline, with the corresponding SE, can be plotted at each visit, in the case results warrant further investigation. These parameters will be presented by the biological functions defined in Section 4.7.2. For glucose, only fasting samples will be included in the summaries.

Individual patient laboratory parameter measurements will be additionally evaluated by PCSA criteria, specifically identifying patients with at least one post-baseline measurement that meets the PCSA criteria within the TEAE period. The following additional project specific PCSA criteria will also be evaluated during the TEAE period:

- Patients with a hemoglobin decrease from baseline ≥ 15 g/L.
- Patients meeting the ALT increase defined in Section 4.7.1.2.
- Glucose (quantitative summary and PCSA) will also be analyzed, overall and according to the diabetic status at baseline.

Patients meeting the PCSA criteria at least once will be summarized by patient count (and percent) for a post-baseline PCSA measurement while accounting for the baseline PCSA status (PSCA normal/missing; PCSA abnormal), for each patient group. For the appendix, this laboratory parameter PCSA table will be reproduced with patients meeting the PCSA criteria at least once during the TEAE period regardless of baseline PCSA status. These laboratory parameters will be presented by the biological functions defined in Section 4.7.2. Patient listings of laboratory measurements that meet PCSA criteria will be provided for the report appendix. For those laboratory parameters that don't have an associated PCSA criteria, similar summary tables can be provided based on measurements outside the central laboratory normal ranges, if applicable.

Drug-induced liver injury

The liver function tests, namely AST, ALT, ALP, and total bilirubin, are used to assess possible drug-induced liver toxicity. The proportion of patients with PCSA values or ALT increase as defined as AESI (see Section 4.7.1.2) during TEAE period by baseline status will be displayed for each parameter.

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

line corresponding to 3 x ULN for ALT and a horizontal line corresponding to 2 x ULN for total bilirubin.

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

The incidence of liver-related TEAEs will be summarized. The selection of PTs will be based on SMQ Hepatic disorder (see Section 4.7.1.2).

5.7.3. Analysis of Vital Sign Variables

The vital sign actual values and change from baseline values obtained while sitting will be descriptively summarized at baseline and each post-baseline visit (collected up to the day of last dose of study treatment +21 days) by at least patient number, mean, median, Q1, Q3, SD, minimum and maximum for each patient group. Additionally, vital sign measures for last on-treatment value and worst on-treatment value will be summarized in a similar manner. Vital sign mean changes from baseline, with the corresponding SE, can be plotted at each visit, in the case results warrant further investigation.

Individual patient vital sign measurements (regardless of sitting position) will be additionally evaluated by PCSA criteria, specifically identifying patients with at least one post-baseline measurement that meets the PCSA criteria within the TEAE period. Patients meeting the PCSA criteria at least once will be summarized by patient count (and percent) and patient group. Patient listings of vial sign measurements that meet PCSA criteria will be provided for the report appendix.

5.8. Analysis of Other Variables

The summary of other variables will be presented on the safety population. No formal inferential testing will be performed for either period. Summaries will be descriptive in nature.

All measurements, scheduled or unscheduled, fasting or not fasting, will be assigned to analysis windows in order to provide an assessment for week 8 to week 96 time points.

Hs-CRP and HbA1cparameters (Section 4.8) will be summarized for the number of patients with data, mean, SD, median, minimum, and maximum (for hs-CRP, Q1 and Q3 will be also provided) by analysis visit during the treatment period. For HbA1c, summaries will also be provided according to diabetes mellitus status at baseline. The time profile will be plotted for HbA1c showing the means and the corresponding SEs, while medians (with Q1-Q3) will be plotted for hs-CRP. Applying the PCSA criteria to these variables at any time during the TEAE period, the number of patients (and percentages) meeting the criteria will be summarized.

The gonadal hormone parameters (Section 4.6.2) will be summarized for the number of patients with data, mean, SD, median, minimum, and maximum by analysis visit during the treatment period. For FSH and LH, the summaries will be performed for all patients, female patients, and male patients. Estradiol will be summarized for female patients only, and testosterone will be summarized for male patients only. Summary tables will also be provided for gonadal hormone parameters based on measurements outside the central laboratory normal ranges, if applicable. When appropriate, for female patients the gonadal-gonadotrophin in menopausal and non-menopausal women will be summarized separately.

In order to minimize confounding factors with menopause or exogenous estrogens, the summaries of estradiol, FSH, and LH for female patients will be repeated by excluding patients who were receiving hormone replacement therapy, were ≥50 years, or had FSH levels ≥25 IU/L at baseline.

For male patients, the summaries of testosterone, FSH, and LH will be repeated by excluding patients who were receiving testosterone supplementation or had LH levels ≥15 IU/L at baseline.

Binary endpoints defined in Section 4.8 will be described through patient counts and percentages. Kaplan-Meier curves will be provided for the variables assessing time to first occurrence of an event (i.e., calculated LDL-C related outcome). Patients not meeting the event will be censored at the end of the treatment period. For the analysis of the time to the first of the two consecutive LDL-C events, patients without post-baseline LDL-C result or with only one post-baseline LDL-C result will not be included in the analysis.

5.9. Analysis of Genomics Variables

Plans for the analysis of genomics data will be provided in a separate SAP.

6. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

6.1. Definition of Baseline for Efficacy and Safety Variables

Unless otherwise specified, the baseline value is generally defined as the baseline value in the neurocognitive function study (R727-CL-1532), i.e., the last available value before the first dose of double-blind study treatment in that study.

In addition to the OLE study database, some data will be recovered from the neurocognitive function study (R727-CL-1532) database

6.2. General Data Handling Conventions

In general, 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. In the case the day is missing, the day will be put equal to 1st if the month and year of diagnosis equals the month and year of informed consent; otherwise it will be put equal to the 15th of the month.

Date of last dose of study treatment

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

Estimated GFR will be derived using the Modification of the Diet in Renal Disease (MDRD) equation:

$186.3 \times (\text{creatinine in } \mu\text{mol/L} / 88.4)^{-1.154} \times (\text{age in years})^{-0.203}$ (x 0.742 if female, x 1.21 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 (i.e., LLOQ/2) will be used for quantitative analyses. For data above the upper limit of quantification (ULOQ) / limit of linearity, the upper limit value (i.e., ULOQ) will be used for quantitative analyses.

6.3. General Missing Data Conventions

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 study treatment administration or time of assessment at week 0 visit is missing

If the time of the first study treatment administration or the time of assessment at week 0 visit is missing, then the baseline value is defined as the last available value obtained before or on the day of the first study treatment administration.

Handling of computation of treatment duration and compliance if study treatment first or end of treatment date is missing

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

Handling of safety and efficacy analysis periods and survival analysis if end of study treatment date is missing

If the last injection date is missing, then this date is imputed to the earliest between:

- the last day of the month and year, when applicable or else the 31st of December of the year,
- the date of the end of treatment visit (week 96 visit for completer, early end of treatment visit for patients who prematurely discontinued the study treatment),
- the date of the last contact

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

Handling of medication missing/partial dates

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

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

Missing or partial AE dates and times will be imputed so that if the partial AE date/time information does not indicate that the AE started prior to treatment or after the TEAE period, the AE will be classified as treatment-emergent. These data imputations are for categorization

purpose only and will not be used in listings. No imputation is planned for date/time of AE resolution.

Handling of adverse events when date and time of first study treatment administration is missing

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

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

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

Handling of potentially clinically significant abnormalities

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

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

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

6.4. Visit Windows for Time Points

Visit windows will be programmatically imposed on those efficacy and safety measures repeatedly collected over the course of the study. These visit windows are derived from the number of days in study, specifically assigning day ranges to mimic the study assessment schedule provided in the protocol. Data analyzed by time point (including efficacy, laboratory safety data, vital signs, physical examinations) will be summarized using the analysis windows given in Appendix 10.1. These analysis windows will be applicable for all analyses, and they are defined to provide more homogeneous data for time point-specific analyses. 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.

6.5. Unscheduled Assessments

For efficacy, safety laboratory data, vital signs, physical examinations, and ADA, 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 values and PCSA.

6.6. Pooling of Centers for Statistical Analyses

Not Applicable.

6.7. Statistical Technical Issues

Not Applicable.

7. TIMING OF STATISTICAL ANALYSES

There are no interim analyses planned. The statistical analysis will be conducted at the end of the study and will consist of the final analysis of primary and secondary endpoints and final safety analysis.

8. SOFTWARE

All analyses will be generated using SAS Version 9.4 or higher.

9. REFERENCES

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10. APPENDIX

10.1. Windows for Analysis Time Points

Below are the definitions for the visit windows programmatically imposed on measures repeatedly collected over the course of the study. These visit windows reflect the study schedule of assessments as described in the protocol. The visit windows are constructed using ranges applied to the number of days in study (study days) when the measure is collected. Day 1 is defined as the first date of double-blind study treatment administration, and is labeled as baseline for most variables. Since the protocol specifies that measurements be collected before study treatment is administered on a given day, it is appropriate that baseline include Day 1.

Table 1: Analysis Windows Definition

Time point	Targeted study day	Analysis window in study days
Week 8	57	29 to 70
Week 12	85	71 to 126
Week 24	169	127 to 252
Week 48	337	253 to 420
Week 72	505	421 to 588
Week 96	673	589 to 756
Week 120	841	757 to 924
Week 144	1009	925 to 1092
Week 168	1177	1093 to 1260
Week 192	1345	1261 to 1428

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

10.2. Criteria for Potential Clinical Significant Abnormalities (PCSA)

Parameter	PCSA	Comments
Clinical Chemistry		
ALT	By distribution analysis :	Enzymes activities must be expressed in ULN, not in IU/L.
	>3 ULN	Concept paper on DILI – FDA draft Guidance Oct 2007.
	>5 ULN	Internal DILI WG Oct 2008.
	>10 ULN	Categories are cumulative.
	>20 ULN	First row is mandatory. Rows following one mentioning zero can be deleted.
AST	By distribution analysis :	Enzymes activities must be expressed in ULN, not in IU/L.
	>3 ULN	Concept paper on DILI – FDA draft Guidance Oct 2007.
	>5 ULN	Internal DILI WG Oct 2008.
	>10 ULN	Categories are cumulative.
	>20 ULN	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	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative.
	>2 ULN	
		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	FDA Feb 2005.
	>10 ULN	Am J Cardiol April 2006.
		Categories are cumulative.
		First row is mandatory. Rows following one mentioning zero can be deleted.

Parameter	PCSA	Comments
Creatinine	≥150 µmol/L (Adults) ≥30% change from baseline ≥100% change from baseline	Benichou C., 1994.
CLcr (mL/min) (Estimated creatinine clearance based on the Cokcroft-Gault equation)	≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	Use is optional. 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 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	Use is optional. FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
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.
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.

Parameter	PCSA	Comments
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.

Parameter	PCSA	Comments
Urinalysis		
pH	≤4.6	
	≥8	
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm	To be applied for all positions (including missing) except STANDING.
	≥120 bpm and increase from baseline≥20 bpm	
SBP	≤95 mmHg and decrease from baseline ≥20mmHg	To be applied for all positions (including missing) except STANDING.
	≥160 mmHg and increase from baseline ≥20 mmHg	
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
	≥110 mmHg and increase from baseline ≥10 mmHg	
Orthostatic Hypotension		
Orthostatic SDB		
Orthostatic DBP	≤-20 mmHg	
	≤-10 mmHg	
Weight	≥5% increase from baseline	FDA Feb 2007.
	≥5% decrease from baseline	
ECG		Ref.: CPMP 1997 guideline.
HR	≤50 bpm and decrease from baseline ≥20 bpm	
	≥120 bpm and increase from baseline ≥20 bpm	
PR	≥220 ms and increase from baseline ≥20 ms	
QRS	≥120 ms	

Parameter	PCSA	Comments
QTc	Absolute values (ms)	To be applied to any kind of QT correction formula.
Borderline		
Prolonged*	Borderline: 431-450 ms (Male); 451-470 ms (Female)	
Additional		
	Prolonged: >450 ms (Male); >470 ms (Female)	*QTc prolonged and ΔQTc>60 ms are the PCSA to be identified in individual subjects/patients listings.
	≥500 ms	
	Increase from baseline	
	Borderline: Increase from baseline 30-60 ms	
	Prolonged: Increase from baseline >60 ms	

10.3. List of MedDRA terms for CMQs

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

MedDRA Term Label
Benign neoplasm of optic nerve
Optic atrophy
Optic discs blurred
Optic nerve disorder
Optic nerve injury
Optic nerve neoplasm
Optic nerve operation
Optic neuropathy
Papillitis
Pseudopapilloedema
Subacute myelo-opticoneuropathy
Toxic optic neuropathy
Visual evoked potentials abnormal
Amaurosis fugax
Blindness
Blindness unilateral
Colour blindness acquired
Colour vision tests abnormal
Cranial nerve injury
Delayed myelination
Fundoscopy abnormal
Hemianopia
Hemianopia heteronymous
Hemianopia homonymous
Loss of visual contrast sensitivity
Neuro-ophthalmological test abnormal
Night blindness
Ophthalmological examination abnormal
Optic pathway injury
Optical coherence tomography abnormal
Quadrantanopia
Visual acuity reduced
Visual acuity reduced transiently
Visual acuity tests abnormal
Visual field defect
Visual field tests abnormal
Visual impairment
Visual pathway disorder

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

MedDRA level	MedDRA Term Label
PTCD	Amnesia
PTCD	Amnestic disorder
PTCD	Anterograde Amnesia
PTCD	Neuropsychiatric symptoms
PTCD	Change in sustained attention
LLTCD	Cognitive Deterioration
PTCD	Cognitive Disorder
LLTCD	Confusion
LLTCD	Confusion Aggravated
PTCD	Confusional State
PTCD	Delirium
PTCD	Dementia
PTCD	Dementia Alzheimer's type
LLTCD	Dementia Nos
LLTCD	Dementia Nos Aggravated
LLTCD	Dementia of the Alzheimer's type NOS
PTCD	Dementia with Lewy Bodies
PTCD	Disorientation
PTCD	Disturbance in attention
PTCD	Executive dysfunction
PTCD	Frontotemporal Dementia
LLTCD	Global Amnesia
PTCD	Illogical Thinking
PTCD	Impaired reasoning
PTCD	Incoherent
PTCD	Judgement impaired
PTCD	Memory Impairment
PTCD	Mental Impairment
LLTCD	Mental Impairment Nos
LLTCD	Mental State Abnormal Aggravated
PTCD	Mental Status Changes
PTCD	Mini Mental Status Examination Abnormal
PTCD	Presenile Dementia
PTCD	Retrograde Amnesia
PTCD	Senile Dementia
LLTCD	Senile Dementia Nos
LLTCD	Short-term Memory Loss
PTCD	Thinking Abnormal
LLTCD	Thinking Slowed
PTCD	Transient Global Amnesia
PTCD	Vascular Dementia

Table 4: CMQ "Type 1 or Type 2 diabetes"

MedDRA Term Label	Preferred Term Code
Diabetes mellitus	10012601
Diabetes mellitus inadequate control	10012607
Insulin resistant diabetes	10022491
Diabetes mellitus malnutrition-related	10050197
Diabetes mellitus management	10051599
Insulin-requiring type 2 diabetes mellitus	10053247
Type 1 diabetes mellitus	10067584
Type 2 diabetes mellitus	10067585
Fulminant type 1 diabetes mellitus	10072628

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