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Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effect of Praluent on Neurocognitive Function in Patients with Heterozygous Familial Hypercholesterolemia or with Non-Familial Hypercholesterolemia at High and Very High Cardiovascular Risk

Compound:	Praluent
Clinical Phase:	4
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AMENDMENT HISTORY

Amendment 5

The main purpose of this amendment is to correct that optional laboratory evaluations are mandatory. Other minor edits and corrections were also made.

The table below outlines changes made in this amendment and indicates sections that were changed.

Change	**Section Changed**
Corrected that certain laboratory evaluations should be performed at the end of study visit even in the absence of clinically relevant abnormal values in these parameters at previous visits	Table 1 Schedule of Events Footnote 10
Minor edits and corrections • Clarified that medication history to be collected is limited to medication history related to lipid-modifying therapy • Clarified definition of non-high density lipoprotein • Specified that research samples should be serum and plasma • Specified that adverse events of special interest (AESI) should be reported • Completed sentence	Section 6.1 Demographic and Baseline Characteristics Section 7.6.1 Procedures Performed only at the Screening/Baseline Visit Section 6.2.3 Secondary Efficacy Endpoints Table 1 Schedule of Events Section 7.6.7.1 Use and Storage of Research Samples Section 7.6.4.5 Reporting Adverse Events of Special Interest Appendix 4 Drugs on the Anticholinergic Burden Scale, Note #7

Amendment 4

The following table outlines the changes made to the protocol and the affected sections:

Change	Section Changed
Added coronary calcium scan as a clarification of possible diagnostic methods to document history of coronary heart disease	Section 4.2.1 Inclusion Criteria (#2av)
Revised exclusion criteria to enhance enrollment (#5), to provide a definition for "as needed" (pro re nata [PRN]) use (#6), to provide comprehensive list of exclusionary medications (#6), to clarify "hyperthyroidism/or hypothyroidism" (#8), and to remove history of serious allergic reactions (such as anaphylaxis) as this is not included in the approved drug labeling (#11)	Section 4.2.2 Exclusion Criteria (#5, #6, #8, #11)
Clarified procedures to follow if emergency unblinding is required	Section 5.5.2 Emergency Unblinding
Added collection of menstrual cycle data in the study to facilitate meaningful analysis of reproductive hormone data	Table 1 Schedule of Events (row added; new footnote #6 added)
Clarified the visits (days on which blood samples are not collected) when study drug may be administered prior to study assessments to provide more flexibility in drug administration.	Table 1 Schedule of Events (footnote #7)
Added collection of a laboratory sample for hepatitis B surface antigen and hepatitis C antibody at the end-of-study visit	Table 1 Schedule of Events Section 7.6.4.3 Laboratory Testing
Removed the requirement that patients be identified by their initials on case report forms (CRFs) and other documents submitted to the sponsor to preserve patient confidentiality	Section 13.3 Patient Confidentiality and Data Protection
Removed gabapentin from the list of exclusionary medications since use of gabapentin won't impact interpretation of study endpoints	Appendix 3 Mood Stabilizers, Antipsychotics, and Medications to Treat Dementia
Provided a more comprehensive list of medications for calculating the anticholinergic burden (ACB)	Appendix 4 Drugs on the Anticholinergic Burden Scale
Made minor editorial changes	Table 1 Schedule of Events

Amendment 3

The main purpose of this amendment is to incorporate the following changes requested during the regulatory review via the Voluntary Harmonization Procedure (VHP).

- To add a history of serious allergic reactions and severe hepatic impairment as exclusion criteria.
- To provide the list of highly effective contraception methods in accordance with recommendations of the Clinical Trial Facilitation Group (CTFG).
- To describe the procedure to be followed if emergency unblinding of a patient by the investigator is required during the study.
- To indicate that any patient with 2 consecutive LDL-C levels that are increased >25% compared to the randomization visit LDL-C level may receive rescue treatment if no reason for LDL-C levels above the threshold value can be determined.
- To add mild cognitive impairment and dementia as reasons for potential permanent discontinuation of study drug.
- To define what constitutes the end of the study.

Amendment 2

The overall purpose of this amendment is to address inconsistencies, provide clarifications and correct errors as follows:

- A EudraCT number belonging to a different study was erroneously used in the original protocol. The EudraCT number was corrected and replaced in this amendment.
- To clarify that the last study drug administration is week 94 and not week 96.
- To revise the total number of site locations from up to 600 to up to 300.
- To add study milestones.
- To add the proportion of patients reaching LDL-C <50 (1.29 mmol/L) mg/dL as a secondary efficacy endpoint because it is the criterion for dose adjustment.
- To clarify gonadal hormone levels for female and male patients.
- To add GDS-S and MoCA to the Schedule of Events table.
- To add that limited clinical data are available on the impact of very low circulating LDL on neurocognitive function.
- To allow study drug administration prior to performing study assessments at visit 4.
- To allow unscheduled neurocognitive testing during visits when a neurocognitive AE is reported and the CANTAB test is not planned or in the case of early treatment discontinuation.
- To modify reasons for permanent discontinuation of study drug.
- To add new onset of diabetes as an AE of interest.

- To revise the list of AE causality evaluation factors for the "not related" category.
- To more precisely define Neurocognitive Events of Special Interest.
- To add electronic systems used to process and/or collect data.
- To clarify that the sponsor may not implement a change in the design or operation of the protocol/ICF without a heath authority and/or IRB/EC approved amendment.
- To make editorial changes corrections, and clarifications.

Amendment 1

The purpose of this amendment is incorporate changes made based on feedback received from the FDA and to address inconsistencies in the original version.

CLINICAL STUDY PROTOCOL SYNOPSIS

TITLE	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effect of Praluent on Neurocognitive Function in Patients with Heterozygous Familial Hypercholesterolemia or with Non-Familial Hypercholesterolemia at High and Very High Cardiovascular Risk
SITE LOCATIONS	Multinational, up to 300 sites
Principal Investigator	Multicenter
OBJECTIVES	The primary objective of the study is to evaluate neurocognitive function with use of Praluent after 96 weeks of treatment versus placebo. The secondary objectives are: • To evaluate the effect of Praluent in comparison with placebo on lipoproteins • To evaluate the safety and tolerability of Praluent
STUDY DESIGN	This is a randomized, double-blind, placebo controlled trial to evaluate neurocognitive function in patients with heterozygous familial hypercholesterolemia (heFH), or in non-familial hypercholesterolemia (FH) patients, at high or very high cardiovascular risk. Patients will be randomized in a 1:1 ratio to receive either placebo or 75 mg Praluent every 2 weeks (Q2W). Randomization will be stratified by age (<65 or ≥65) and by statin use (no statin, low lipophilicity of the concomitant statin, or high lipophilicity of the concomitant statin). The study consists of the following 2 periods: • A screening period of up to 3 weeks. The patient or caregiver will be trained to self-inject/inject using a dose of placebo during the screening period or at the first visit of the double-blind treatment period. • A double-blind treatment period of 96 weeks. On day 1 (baseline), after completion of study assessments and after collection of blood samples, and as soon as possible after the patient is randomized into the study, the first dose of study drug will be administered. The patient will be monitored at the clinical site for 30 minutes after the first dose. Subsequent doses of study drug must be administered Q2W. The last dose of study drug will be administered at week 94. Patients' neurocognitive function will be assessed every 6 months. The dose of study drug will be increased (using a blinded process) at the week 12 visit in patients whose low-density lipoprotein (LDL) cholesterol (LDL-C) levels are ≥50 mg/dL (1.3 mmol/L) at week 8. Those patients who are randomized to Praluent will receive Praluent 150 mg Q2W at week 12 and until end of study. All patients randomized to placebo will continue to receive placebo. Lipid results will be blinded for specimens obtained after randomization. No attempts should be made by the investigator or patient to have the patient's lipid values evaluated independently from the time of randomization until the last study visit. Patients should be on a on a stable regimen of lipid-modifying therapy (LMT; including a maximally-tolerated dose of statin, unless statin-intolerant) for 28 days prior to screening, as well as on a stable diet. Patients will be asked to maintain both their statin dose and diet from screening to the end of the study.

POPULATION	
Sample Size	Approximately 2170 patients are planned to be randomized: placebo, 1085; Praluent 75 mg Q2W/up-titrate 150 mg Q2W, 1085.
Target Population	The study population consists of patients with heFH or non-FH patients at high or very high cardiovascular risk. High or very high cardiovascular risk patients include patients with coronary heart disease (CHD), non-CHD cardiovascular disease (CVD), and other risk factors. Patients must have had a history of CHD without adequate control of their hypercholesterolemia with LDL-C ≥70 mg/dL, or all other patients with LDL-C ≥100 mg/dL, and be on a maximally-tolerated dose of statin (unless they are statin-intolerant).
TREATMENTS	
Study Drug	Praluent
Dose/Route/Schedule	75 mg /subcutaneous (SC)/Q2W for 94 weeks* *If LDL-C is ≥50 mg/dL (1.3 mmol/L) at week 8, Praluent dose will be increased to 150 mg Q2W at week 12
Placebo	Placebo matching Praluent
Dose/Route/Schedule:	SC/Q2W for 94 weeks
ENDPOINTS	
Primary	The primary outcome measure is the change in Cambridge Neuropsychological Test Automated Battery (CANTAB) cognitive domain Spatial Working Memory (SWM) strategy score from baseline to week 96.
Secondary Endpoints	Exploratory neurocognitive outcome measures to further assess neurocognitive function in the CANTAB domains are provided below for each patient: • Paired Associates Learning (PAL) at week 96 defined as both a PAL z-score change from baseline and PAL raw score change from baseline, following the definitions and rules provided for the primary neurocognitive endpoint • Reaction Time (RTI) at week 96 defined as both a RTI z-score change from baseline and RTI raw score change from baseline, following the definitions and rules provided for the primary neurocognitive endpoint • SWM between-errors score at week 96 defined as both a SWM between-errors z-score change from baseline and SWM between-errors raw score change from baseline, following the definitions and rules provided for the primary neurocognitive endpoint • Global Composite score at week 96 change from baseline is defined as (the average of the following 4 measures at week 96: SWM strategy z-score, PAL z-score, RTI z-score, and the SWM between-errors z-score) minus the average of the same 4 z-score measures at baseline Secondary efficacy endpoints are: • The percent change in calculated LDL-C, apolipoprotein (Apo) B, non-high-density lipoprotein cholesterol (non-HDL-C), and total cholesterol (Total-C) from baseline to weeks 12, 24, 48, 72, and 96 • The percent change in lipoprotein a [Lp(a)], HDL-C, triglyceride (TG), and Apo A-1 from baseline to weeks 12, 24, 48, 72, and 96 • The proportion of patients reaching LDL-C <70 mg/dL (1.81 mmol/L) at weeks 12, 24, 48, 72 and 96. • The proportion of patients reaching LDL-C <50 mg/dL (1.29 mmol/L) at weeks 12, 24, 48, 72, and 96
Other Endpoints	• Anti-drug antibody status (positive/negative) and titers assessed at the end of the study.

	• Gonadal hormone levels (for female patients - estradiol, follicle-stimulating hormone (FSH) and luteinizing hormone (LH); for male patients - testosterone, FSH and LH)
PROCEDURES AND ASSESSMENTS	The CANTAB will include the following 3 tests which will take approximately 25 minutes to complete: SWM, PAL and RTI. In addition, efficacy of Praluent will be assessed by clinical laboratory evaluation of lipid levels. Overall safety will be assessed by monitoring/evaluation of treatment-emergent adverse events (TEAEs), physical examinations, blood pressure and heart rate, and clinical safety laboratory tests at prespecified time points. Blood samples will be collected for determination of anti-drug antibody levels at predetermined time points. Research samples and samples for exploratory biomarker analysis will be collected.
STATISTICAL PLAN	The primary neurocognitive analysis is a statistical evaluation of the noninferiority of the Praluent 75 mg Q2W/up-titrate 150 mg Q2W dose regimen to placebo for the primary endpoint of change in SWM strategy z-score from baseline to week 96 in the primary safety population. The 2-sided 95% confidence interval (CI) for the mean treatment difference at week 96 will be determined using an appropriate contrast statement in a mixed-effect model with repeated measures (MMRM). The upper CI limit will be compared to the noninferiority margin which is defined as 0.2 and the noninferiority will be declared if the upper CI limit is below the noninferiority margin. To further understand the effects of Praluent on cognitive function and support the primary neurocognitive analysis, the 3 domain endpoints (specifically PAL, RTI, and SWM between-error scores) and the Global Composite score will also be evaluated for noninferiority at week 96 in the primary safety population. These 4 measures will not be evaluated for superiority. For secondary efficacy endpoints of lipids, descriptive summaries and analyses will be performed in the intent-to-treat (ITT) population (for ITT analysis) and the modified intent-to-treat (mITT) population (for on-treatment analysis). P-values for the testing of study treatment effect will be provided for descriptive purposes only (nominal p-values). The general safety analysis will be based on the safety analysis population (safety analysis set [SAF]). The safety variables include reported TEAEs and other safety information (ie, clinical laboratory evaluations, vital signs). The summary of safety results will be presented by the 2 treatment groups (placebo, and Praluent 75 mg Q2W/up-titrate 150 mg Q2W). No formal inferential testing will be performed. Summaries will be descriptive in nature.
STUDY DURATION	Each patient is planned to participate in the study for approximately 99 weeks (3 weeks of screening and 96 weeks of treatment). As committed to FDA, the study is expected to complete August, 2020, and a final study report will be submitted December, 2020.

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LIST OF ABBREVIATIONS AND DEFINITIONS 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
EDC	Electronic data capture
eCRF	Electronic case report form
eGFR	Estimated Glomerular Filtration Rate
FH	Familial hypercholesterolemia
FSH	Follicle-stimulating hormone
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
LH	Luteinizing hormone
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
SAF	Safety analysis set
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. INTRODUCTION AND RATIONALE

Praluent® is a human monoclonal antibody that binds proprotein convertase subtilisin/kexin type 9 (PCSK9) to inhibit its function. All relevant information concerning the compound is available in the latest version of the Investigator's Brochure. Praluent was approved in the US on July 24, 2015 for use, in addition to diet and maximally tolerated statin therapy, in adult patients with heterozygous familial hypercholesterolemia (heFH) or patients with clinical atherosclerotic cardiovascular disease (CVD) such as heart attacks or strokes, who require additional lowering of low-density lipoprotein (LDL) cholesterol (LDL-C). Praluent was approved in the EU on 23 September 2015 for use in adults with primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidemia, as an adjunct to diet in combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin, or alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant or for whom a statin is contraindicated.

Praluent is also referred to as alirocumab, REGN727 or SAR236553. In the context of the R727-CL-1532 clinical study protocol, it will be referred to as Praluent.

1.1. Introduction

This is a randomized, double-blind, placebo controlled trial to evaluate neurocognitive function in patients with heFH, or in non-familial hypercholesterolemia (FH) patients, at high or very high cardiovascular risk. To objectively evaluate neurocognitive function, the Cambridge Neuropsychological Test Automated Battery (CANTAB) will be employed. In addition, this study will evaluate the effect of Praluent on LDL-C, various lipid sub-fractions, and overall safety.

Studies (trials and observational) have linked midlife and late-life cardiovascular risk factors to cognitive function (Joas 2012, Mielke 2010, Reijmer 2012). A recent epidemiological study has also shown that cumulative exposure to cardiovascular risk factors from early to middle adulthood, especially above guideline-recommended targets, was associated with worse cognition in midlife (Yaffe 2014). This was a prospective study of 3381 adults (age, 18 to 30 years at baseline) with 25 years of follow-up. Assessment of cognitive function was performed at year 25 (2010 to 2011) with the Digit Symbol Substitution Test, Stroop Test, and Rey Auditory Verbal Learning Test analyzed with standardized z scores. The primary predictor was 25-year cumulative exposure estimated by areas under the curve for resting systolic and diastolic blood pressures, fasting blood glucose, and total cholesterol (Total-C). Higher cumulative systolic and diastolic blood pressures and fasting blood glucose were consistently associated with worse cognition on all 3 tests. These associations were significant, primarily for exposures above recommended guidelines; cognitive test z scores were between 0.06 and 0.30 points less, on average, for each 1-standard deviation increase in risk factor area under the curve after adjustment for age, race, sex, and education ($p<0.05$ for all). Fewer significant associations were observed for cholesterol.

Although accumulating data from observational studies suggest that cardiovascular risk factors may be modifiable risk factors for cognitive impairment (Kivipelto 2001, Whitmer 2005), randomized controlled trials targeting the treatment of these conditions, including hypertension, dyslipidemia, and diabetes mellitus have reported mixed results (Shepardson 2011, Staessen 2011, Morris 2012).

Additionally, in 2012, the Food and Drug Administration expanded its advice on statin risks to include memory loss or confusion. Review of published data on statins does not suggest an adverse effect of statins on cognition, but the strength of available evidence is limited, particularly regarding high dose statins (Richardson 2013). In addition, highly lipophilic statins with specific pharmacokinetic properties (atorvastatin, simvastatin) appear to confer a significantly greater risk of adverse cognitive effects compared to other lipophilic statins and those with hydrophilic solubility properties (Sahebzamani 2014).

The brain synthesizes or re-uses up to 95% of its cholesterol requirements (Pfrieger 2011), thus, limiting the potential biological impact of low-circulating LDL-C on central nervous system function. Moreover, LDL particles have not been reported to cross the blood-brain barrier. Consequently, low levels of circulating LDL-C are unlikely to affect central nervous system cholesterol metabolism and function. Moreover, monoclonal antibodies, including Praluent, would not cross the blood brain barrier and are unlikely to have direct effects on the brain. However, limited clinical data are available on the impact of very low circulating LDL on neurocognitive function.

Neurocognitive events were reported overall at a low incidence in the phase 3 Praluent development program. Analysis of neurocognitive events using a predetermined set of adverse event (AE) terms from both the placebo- and ezetimibe-controlled pools did not reveal an imbalance for any particular event in double-blind studies up to 18 months of treatment with Praluent.

Cambridge Neuropsychological Test Automated Battery Assessment

The proposed neurocognitive test battery (CANTAB) targets key cognitive domains commonly affected by pharmacological manipulation, including psychomotor processing speed, visual episodic memory, working memory, and executive function. The CANTAB has been widely used as a tool for assessment of patterns of cognitive function in a wide variety of neurological and psychiatric disorders such as dementia, schizophrenia, depression, and Parkinson's Disease (De Jager 2005, Bartok 2005, Weiland-Friedler 2004, Foltynie 2003). These tests have been employed extensively in clinical trials and have been shown to be sensitive to pharmacological manipulation in healthy individuals, both in compounds inducing cognitive deficits (Rusted 1988, Jäkälä 1999, Harmer 2001, Ryan 2006), and those showing procognitive effects (Elliott 1997, Greig 2005, Randall 2005, Attwood 2007).

All tests in the battery are nonverbal and culturally neutral and suitable for use in nonliterate or multicultural populations. This also facilitates the use of the battery in multinational trials as data will be valid regardless of cultural background. The CANTAB is self-administered using a computer and touch sensitive monitor, which allows immediate feedback. Parallel modes and automatic stimuli randomization ensure participants can be re-tested over time for longitudinal studies. Inter-rater variance is greatly reduced with standardized test delivery and CANTAB tests also have translational utility, meaning that data can be compared directly to preclinical findings. CANTAB Connect Research software has been validated for use on all iPad Air devices and is fully Good Clinical Practice (GCP)-compliant, meeting regulations for computerized systems used in clinical research and 21 CFR Part 11.

The proposed CANTAB includes the following 3 tests which will take approximately 25 minutes to complete: Spatial Working Memory (SWM), Paired Associates Learning (PAL), and Reaction Time (RTI).

Spatial Working Memory

Spatial Working Memory requires retention and manipulation of visuospatial information, and assesses the ability of the participant to retain spatial information and manipulate it in working memory. This is a self-ordered task that has notable executive function demands, and measures strategy use as well as errors. These are reported as 2 separate end points: between search errors, reflecting the cognitive domain of working memory; and a score reflecting the use of a consistent search strategy, reflecting the cognitive domain of executive function. A number of colored boxes are presented on the screen, and the computer hides a token in these boxes one at a time. The participant is instructed to touch the boxes in turn to search for the token that has been hidden. When a token is found it should be placed in a home area on the right side of the screen. The participant then searches for more tokens until the same number of tokens as the number of colored boxes has been found. The key task instruction is that the computer will never hide a token in the same colored box twice in the same problem. As the test progresses, so it becomes more difficult. Spatial Working Memory performance is impaired by damage to the prefrontal cortex, especially the dorsolateral prefrontal cortex. Similarly, in neuroimaging studies in healthy volunteers, SWM performance is associated with activations in the dorsolateral and mid ventrolateral prefrontal cortex.

Paired Associates Learning

Paired Associates Learning assesses visual memory and new learning, and is a sensitive tool for accurate assessment of episodic memory. Boxes are displayed on the screen and open in turn to reveal a number of patterns. Participants are instructed to try to remember the location in which each pattern was shown. After all the boxes have been opened, each pattern is then shown in the center of the screen in a randomized order, and the participant touches the box in which the pattern was located. If an error is made, all the patterns are re-presented to remind the participant of their locations. As the test progresses so the stages become more difficult, the number of patterns to be remembered will increase up to a maximum of 8 patterns. For participants who fail to complete all levels, an adjusted total is calculated that allows for errors predicted in the stages that were not attempted. Successful performance of the PAL test is dependent on functional integrity of the temporal lobe, particularly the entorhinal cortex.

Reaction Time

Reaction Time provides assays of motor and mental response speeds, as well as measures of movement time, RTI, and response accuracy. In this 5-choice RTI task the participant holds down a button at the bottom of the screen until a yellow spot appears in 1 of 5 circles at the top of the screen. They must then release the button and touch inside the circle where the yellow spot appeared as quickly as they can. Practice trials are included to familiarize participants with the task.

1.2. Rationale

1.2.1. Rationale for Study Design

The primary goal of this study is to evaluate neurocognitive function in heFH patients and non-FH patients at high or very high cardiovascular risk receiving Praluent compared with placebo after 96 weeks of treatment. The 96-week treatment duration is considered sufficient to evaluate the effect of Praluent on neurocognitive function.

1.2.2. Rationale for Dose Selection

This study will use the 75 mg Praluent every 2 weeks (Q2W) regimen, the recommended starting dose for Praluent in the US (or usual starting dose in EU), with an increase to 150 mg Q2W at week 12 (using a blinded process) if LDL-C is ≥50 mg/dL (1.3 mmol/L) at week 8. This is the titration threshold being used in ODYSSEY OUTCOMES, an ongoing study assessing the effect of Praluent on major cardiovascular events. It is supported by findings from post-hoc analyses of the PROVE-IT, TNT and JUPITER trials, aiming to achieve an LDL-C level within the 'physiologic ideal' zone.

2. STUDY OBJECTIVES

The primary objective of the study is to evaluate neurocognitive function with use of Praluent after 96 weeks of treatment versus placebo.

The secondary objectives are:

- To evaluate the effect of Praluent in comparison with placebo on lipoproteins
- To evaluate the safety and tolerability of Praluent

3. STUDY DESIGN

3.1. Study Description and Duration

This is a randomized, double-blind, placebo controlled trial to evaluate neurocognitive function in patients with heFH, or in non-FH patients, at high or very high cardiovascular risk.

Patients will be randomized in a 1:1 ratio to receive either placebo or 75 mg Praluent Q2W. Randomization will be stratified by age (<65 or ≥65) and by statin use (no statin, low lipophilicity of the concomitant statin, or high lipophilicity of the concomitant statin).

The study consists of the following 2 periods, which are shown schematically in Figure 1.

- A screening period of up to 3 weeks.

  The patient or caregiver will be trained to self-inject/inject using a dose of placebo during the screening period or at the first visit of the double-blind treatment period.

- A double-blind treatment period of 96 weeks.

  On day 1 (baseline), after completion of study assessments and after collection of blood samples, and as soon as possible after the patient is randomized into the study, the first dose of study drug will be administered. The patient will be monitored at the clinical site for 30 minutes after the first dose. Subsequent doses of study drug must be administered Q2W. The last dose of study drug will be administered at week 94.

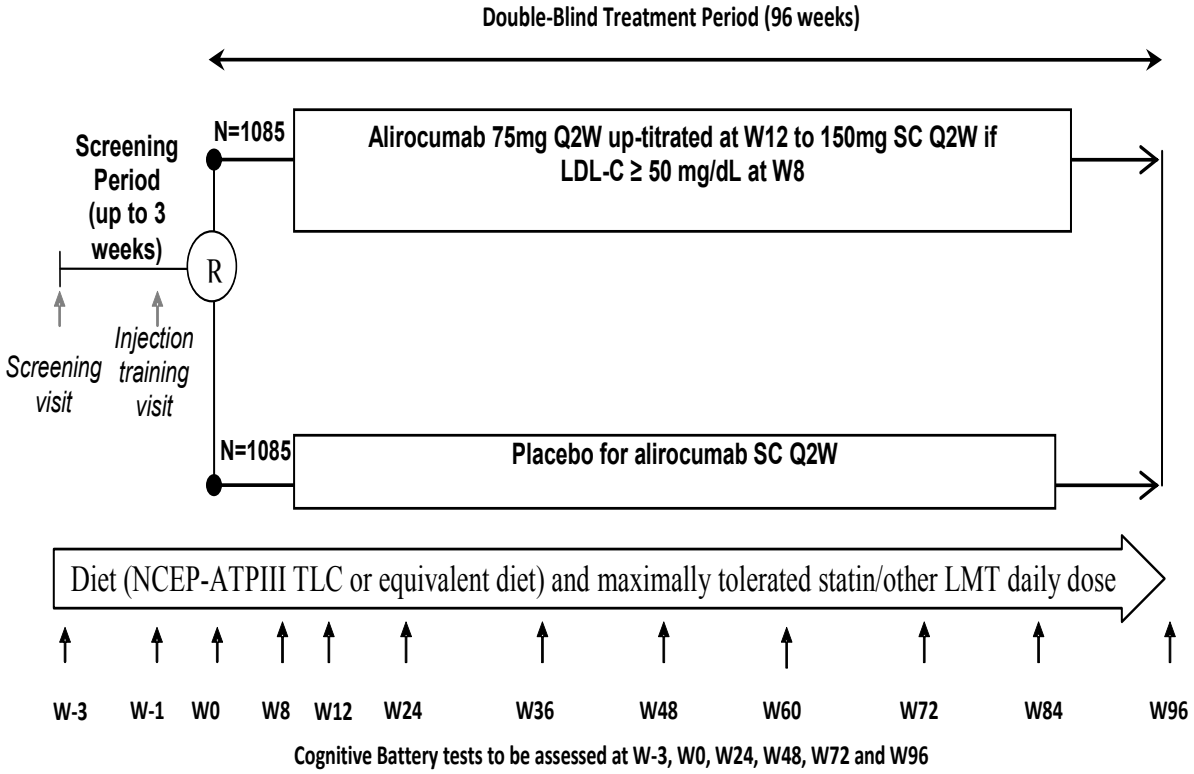
  Patients' neurocognitive function will be assessed every 6 months.

  The dose of study drug will be increased (using a blinded process) at the week 12 visit in patients whose LDL-C levels are ≥50 mg/dL (1.3 mmol/L) at week 8. Those patients who are randomized to Praluent will receive Praluent 150 mg Q2W at week 12 and until end of study. All patients randomized to placebo will continue to receive placebo.

  Lipid results will be blinded for specimens obtained after randomization. No attempts should be made by the investigator or patient to have the patient's lipid values evaluated independently from the time of randomization until the last study visit.

  Patients should be on a stable regimen of lipid-modifying therapy (LMT) (including a maximally-tolerated dose of statin, unless statin-intolerant) for 28 days prior to screening, as well as on a stable diet. Patients will be asked to maintain both their statin dose and diet from screening to the end of the study.

Figure 1: Study Flow Diagram



3.2. Planned Interim Analysis

No interim analysis is planned.

3.3. Study Committees

3.3.1. Neurocognitive Events Review Committee

The neurocognitive events review committee 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 (in a blinded fashion) 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.

4. SELECTION OF PATIENTS

4.1. Number of Patients Planned

Approximately 2170 patients are planned. The patients will be randomized as follows, stratified by age (<65 or ≥65) and by statin use (no statin, or low lipophilicity of the concomitant statin, or high lipophilicity of the concomitant statin):

- Placebo: 1085 patients
- Praluent 75 mg Q2W/up-titrate 150 mg Q2W: 1085 patients

This will be a multinational study. The planned number of sites is up to 300.

4.2. Study Population

The study population consists of patients with heFH or non-FH patients at high or very high cardiovascular risk. Patients must have had a history of CHD without adequate control of their hypercholesterolemia with LDL-C ≥70 mg/dL, or all other patients with LDL-C ≥100 mg/dL, and be on a maximally-tolerated dose of statin (unless they are statin-intolerant).

4.2.1. Inclusion Criteria

A patient must meet the following criteria to be eligible for inclusion in the study:

1. Men and women ≥ age 40 and ≤ age 85
2. Patients with heFH (see Appendix 1 and Appendix 2 for diagnosis criteria) or non-FH patients at high or very high cardiovascular risk

   High and very high cardiovascular risk patients include patients with coronary heart disease (CHD), non-CHD CVD, and other risk factors. Definitions for CHD, non-CHD CVD, and other risk factors:

   a. A documented history of CHD (includes 1 or more of the following):

      i. Acute myocardial infarction

      ii. Silent myocardial infarction

      iii. Unstable angina

      iv. Coronary revascularization procedure (eg, percutaneous coronary intervention or coronary artery bypass graft surgery)

      v. Clinically significant CHD diagnosed by invasive or non-invasive testing (eg, coronary angiography, stress test using treadmill, stress echocardiography, coronary calcium scan, or nuclear imaging).

   b. Non-CHD CVD (includes 1 or more of the following criteria):

      vi. Documented previous ischemic stroke with a focal ischemic neurological deficit that persisted more than 24 hours, considered as being of atherothrombotic origin. Computed tomography (CT) or magnetic resonance

imaging (MRI) must have been performed to rule out hemorrhage and non-ischemic neurological disease.

vii. Peripheral arterial disease

viii. Abdominal aortic aneurysm

ix. Atherosclerotic renal artery stenosis

x. Carotid artery disease (transient ischemic attacks or >50% obstruction of a carotid artery)

c. Other risk factors

xi. Documented moderate chronic kidney disease as defined by 30≤ Estimated Glomerular Filtration Rate (eGFR) <60 mL/min/1.73 m2 for 3 months or more, including the screening visit

xii. Type 1 or type 2 diabetes mellitus

xiii. A calculated 10-year fatal CVD risk SCORE ≥5% (ESC/EAS Guidelines for the management of dyslipidemias, Perk 2012)

* For CVD risk categories, see Appendix 5.

3. Patients with history of CHD not having adequate control of their hypercholesterolemia with LDL-C ≥70 mg/dL, or all other patients with LDL-C ≥100 mg/dL
4. Patients have been on a maximally-tolerated dose of statin for at least 28 days prior to the screening visit (all statins are allowed), unless they are statin-intolerant. Statin intolerance is defined as the inability to tolerate at least 2 statins: 1 statin at the lowest daily starting dose (defined as rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg, or pitavastatin 2 mg), AND another statin at any dose, due to skeletal muscle-related symptoms, other than those due to strain or trauma, such as pain, aches, weakness, or cramping that began or increased during statin therapy and stopped when statin therapy was discontinued. For these patients, the maximally-tolerated dose of statin is defined as 0 mg.
5. Patients must have successfully completed the Motor Screening Task
6. Patients must be willing and able to comply with clinic visits and study-related procedures.
7. Patients must provide signed informed consent.

4.2.2. Exclusion Criteria

1. Patients with known Alzheimer's disease or other dementia, schizophrenia, bipolar disorder, severe depression (≥11 score of the Geriatric Depression Scale short form [GDS-S; Appendix 8]), cognitive impairment (<26 score of the Montreal Cognitive Assessment [MoCA]; Appendix 9]), or patients with a sleep disorder requiring daily pharmacological treatment
2. Patients >85 year old
3. Patient with a hemorrhagic stroke within last 5 years

4. Patients with planned major surgery or carotid stenting
5. Patients who have previously participated in a clinical trial involving a PCSK9 antibody, or had any exposure to a PCSK9 antibody

   Note: If patients had previously participated in a clinical trial involving a PCSK9 antibody, and it was subsequently determined that they had been in a placebo group, then this exclusion criterion does not apply.
6. Patients treated with medications listed in Appendix 3, and/or with medications adding up to an anticholinergic burden (ACB) of 3 and above (see Appendix 4) within 3 months prior to the screening visit

   Note: Medications listed in Appendix 4 used "as needed"/pro re nata (PRN), ≤2 times per week should not be included in calculating the ACB score.
7. Patients with a history of substance abuse (alcohol or drug) or substance dependence meeting the DSM-IV criteria within 12 months prior to the screening visit (American Psychiatric Association 2000)
8. Signs and symptoms of hyperthyroidism or hypothyroidism (thyroid replacement therapy is permitted, if stable for 12 weeks prior to screening and patient is documented to be euthyroid)
9. History of a myocardial infarction, unstable angina leading to hospitalization, coronary artery bypass graft surgery, percutaneous coronary intervention, uncontrolled cardiac arrhythmia, carotid surgery or stenting, stroke, transient ischemic attack, or carotid revascularization within 3 months prior to the screening visit, or endovascular procedure or surgical intervention for peripheral vascular disease within 3 months prior to the screening visit
10. eGFR <30 mL/min/1.73 m^2 according to 4-variable Modification of Diet in Renal Disease Study equation (calculated by a central lab).
11. Any condition or situation, including other significant mental or neurological disorders that, in the investigator's opinion, may confound the study results, or may interfere significantly with the patient's participation in the study.
12. Pregnant or breastfeeding women
13. Women of childbearing potential* who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 6 months after the last dose. Highly effective contraceptive measures include stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal ligation; vasectomized partner; and or sexual abstinence**.

   *Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of childbearing potential. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

**Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

14. A positive human immunodeficiency virus (HIV) test
15. Patients with severe hepatic impairment (Child-Pugh Class C)

4.3. Replacement of Patients

Patients prematurely discontinued from the study will not be replaced.

5. STUDY TREATMENTS

The study treatment is 1 subcutaneous (SC) injection Q2W of 1 mL, as follows:

- Placebo group: 1 injection of placebo Q2W
- Praluent 75 mg Q2W/up-titrate 150 mg Q2W: 1 injection of 75 mg Q2W Praluent with an increase to 1 injection of 150 mg Q2W at week 12 (using a blinded process) if LDL-C is ≥50 mg/dL (1.3 mmol/L) at week 8

The injections will be provided in prefilled pens and will be administered SC into the abdomen, thigh, or outer area of the upper arm.

The patient or caregiver will use placebo for injection training at the clinical site (see Section 5.1). On day 1 (baseline), after completion of study assessments and after collection of blood samples, and as soon as possible after the patient is randomized into the study, the first dose of double-blind study drug will be administered in the clinic. The patient will be monitored at the clinical site for 30 minutes after the first dose. Subsequent doses of study drug must be administered Q2W.

Doses of study drug should be administered at approximately the same time of day (based upon patient preference) throughout the study. It is acceptable for dosing to fall within a window of ±3 days.

In the event an injection is delayed by more than 7 days or completely missed, the patient should return to the original schedule of study drug dosing without administering additional injections. If the delay is less than or equal to 7 days from the missed date, the patient should administer the delayed injection and then resume the original dosing schedule.

Site personnel will provide the patient/caregiver with detailed instructions for transport, storage, preparation, and administration of study drug.

5.1. Injection Training

After study eligibility is confirmed, the patient or caregiver will be trained to self-inject/inject using placebo at visit 2. Injection training can be done at visit 3 (as an alternative to or in addition to visit 2) using placebo. All patients and caregivers who will inject study drug must be trained by the study staff.

Investigators will have the option of providing a second placebo dose to patients who require additional injection training before randomization. The patient and/or investigator may elect to inject the additional dose of placebo at home or at the study site.

5.2. Investigational and Reference Treatments

Sterile Praluent drug product is supplied at a concentration of 75 mg/mL or 150 mg/mL in histidine, pH 6.0, polysorbate 20, and sucrose in a prefilled pen.

Placebo matching Praluent is supplied in the same formulation as Praluent, without the addition of protein, in a prefilled pen.

In case of disruption of supply of prefilled pens, patients will be switched to the use of prefilled syringes of placebo, 75 mg and 150 mg, with 1 injection of 1 mL for each of these doses. Should

disruption occur, site staff will train all patients/caregivers on the correct administration using the prefilled syringe.

5.3. Background Treatment

Patients should be on their maximally tolerated dose of statin as defined in inclusion criterion 4 (Section 4.2.1). The statin dose should remain stable throughout the entire study, from screening to the end of study visit. If a patient is not taking the maximally allowed dose (per the label for that region or country), or if the patient is statin intolerant, a justification should be provided in the electronic case report form (e-CRF).

Background treatment with LMTs is allowed for all patients (those who are using concomitant statins and for those who are not). The background LMT dose should remain stable throughout the entire study, from screening to the end of study visit.

5.4. Dose Modification

In patients whose LDL-C levels are ≥50 mg/dL (1.3 mmol/L) at week 8 (visit 4), the dose will be increased in a double-blind manner beginning at week 12 (visit 5), as follows:

- Placebo group: no change; placebo Q2W
- Praluent 75 mg Q2W group: 150 mg Praluent Q2W

To maintain the blind, the sites and the sponsor's operational team will be blinded to LDL-C results and to dose modification.

5.5. Method of Treatment Assignment

The randomized list of treatment kit numbers will be generated centrally. An interactive voice response system (IVRS) and/or interactive web response system (IWRS) will be used in this study. Study drug will be packaged in accordance with this list.

Patients will be randomly assigned to receive placebo or Praluent 75 mg Q2W in a 1:1 ratio stratified by age (<65 or ≥65) and by statin use (no statin, low lipophilicity of the concomitant statin, or high lipophilicity of the concomitant statin).

Depending on each site's preference, the centralized treatment allocation system can be accessed by the IVRS or the IWRS. The treatment kit numbers will be allocated using the centralized treatment allocation system at the randomization visit, at weeks specified in Table 1 as re-supply visits, and at unscheduled visits, if needed. The treatment kit allocated at week 12 for patients randomized to the Praluent treatment groups will be based on their week 8 LDL-C level (see Section 5.4).

5.5.1. Blinding

Study patients, the principal investigators, and study site personnel will remain blinded to all randomization assignments throughout the double-blind portion of the study. The Regeneron Study Director, Medical Monitor, Study Monitor, and any other Regeneron and contract research organization (CRO) personnel who are in regular contact with the study site will remain blinded to all patient randomization assignments.

Lipid results from blood samples collected after the randomization visit will not be communicated to the sites, and the sponsor's operational team will not have access to these laboratory results until after the final database lock.

Sites and the sponsor's operational team will be blinded to changes in treatment dose in the event a patient meets a criterion for a change in dose.

Blinded study drug kits coded with a medication numbering system will be used. In order to maintain the blind, lists linking these codes with product lot numbers will not be accessible to individuals involved in study conduct.

Anti-drug antibody (ADA) results will not be communicated to the sites, and the sponsor's operational team will not have access to results associated with patient identification until after the final database lock.

Information on unblinding is provided in Section 5.5.2.

5.5.2. Emergency Unblinding

Unblinding of treatment assignment for a patient may be necessary due to a medical emergency or any other significant medical event (eg, pregnancy).

- If unblinding is required:
  - Only the investigator will make the decision to unblind the treatment assignment.
  - Only the affected patient will be unblinded.
  - The designated study pharmacist(s)/designee at the study site will provide the treatment assignment to the investigator. If there is no study pharmacist, the investigator for the site will unblind the patient.
  - The investigator must notify Regeneron and/or designee before unblinding the patient, whenever possible.

5.6. Treatment Logistics and Accountability

5.6.1. Packaging, Labeling, and Storage

A medication numbering system will be used in labeling blinded investigational study drug provided in individual prefilled pens. Lists linking medication numbers with product lot numbers will be maintained by the groups (or companies) responsible for study drug packaging. In order to maintain the blind, the lists will not be accessible to individuals involved in study conduct.

Training kits containing 1 placebo prefilled pen will be provided to the sites for patient/caregiver injection training that will be performed before randomization at the injection training visit or at the baseline visit. A second placebo prefilled pen can be used before randomization if the patient/caregiver requires additional injection training.

Study drug will be refrigerated at the site at a temperature of 2ºC to 8ºC. Storage temperature will be logged. Detailed storage instructions are provided in the study manual.

5.6.2. Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2ºC to 8ºC to the investigator or designee as needed during the study. At specified time points during the study (ie, interim site monitoring visits), at the site close-out visit, and after drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be returned to the sponsor or designee according to directions provided in the study manual.

Study drug will be dispensed to each patient and transported to the patient's home. Study drug will be stored, prepared, and administered by the patient/caregiver according to instructions provided to each patient/caregiver.

5.6.3. Treatment Accountability and Compliance

All accountability and compliance records must be made available for inspection by the sponsor and regulatory agency inspectors. Photocopies must be provided to the sponsor at the conclusion of the study.

Patients will complete a dosing log to document compliance with study drug administration. Measures taken to ensure and document study drug accountability and compliance are as follows:

- The investigator or designee will obtain via IVRS/IWRS the treatment kit number(s) and will dispense the treatment kit(s) to the patient.
- Accountability is to be verified during study drug kit re-supply visits only. The used and unused kit(s) should be brought to these visits for accountability purposes.
- All kits, including used and unused kits, are to be returned by the patient at the designated visit. An unused kit contains all of the unused prefilled pens. A used kit is one from which the patient has removed 1 or more prefilled pens. A used prefilled pen is one that has been removed from the kit with the intention of administration, including those injections that have been partially or fully injected. The patient should discard all used prefilled pens into the sharps container and never put used prefilled pens back into the used kit.
- All sharps containers should be returned to the site by the patient.
- The investigator/study coordinator will enter data in the appropriate e-CRF pages, according to data recorded in the treatment log form.
- The monitor will check the data consistency among e-CRF pages, treatment log form and returned unused prefilled pens of a corresponding kit.

All treatments kits will be retrieved by the sponsor. A detailed treatment log of the returned study drug will be established with the investigator or designee and countersigned by the investigator and the monitoring team.

5.7. Concomitant Medications

Concomitant medications should be kept to a minimum during the study. If considered necessary for the patient's welfare and unlikely to interfere with study drug, concomitant medications (other than those that are prohibited during the study) may be given at the discretion of the investigator, at a stable dose when possible.

Any treatment administered from the time of informed consent to the end of the study will be considered concomitant medication. This includes medications that were started before the study, and are ongoing during the study.

5.7.1. Allowed Concomitant Medications

Lipid-modifying therapies, nutraceuticals, and over-the-counter therapies that may affect lipids are allowed only if they have been used at a stable dose and regimen for at least 4 weeks before the screening visit and during the screening period. The dose and regimen must remain stable during the double-blind treatment period (see Section 5.7.3).

5.7.2. Prohibited Medications

Commercially-available PCSK9 antibodies are prohibited from the initial screening visit until the end of the study visit.

Sleep-aid medications are prohibited the night before the baseline visit, or the week 24, week 48, week 72, or week 96 visits. If the patient used such medication, the visit should be rescheduled as soon as possible.

5.7.3. Rescue Treatment for LDL-C Increase >25%

An LDL-C increase >25% compared with the randomization visit LDL-C on 2 consecutive occasions (Section 7.6.3.1) will generate an alert that the patient may require rescue therapy. The investigator should determine whether a reasonable explanation exists for insufficient LDL-C control (such as an alternative medical cause like corticosteroid use, etc.), and in particular should ensure that

- Compliance with diet is appropriate
- Compliance with background LMT is appropriate and ongoing
- Study treatment is given as planned

If any of the above factors can reasonably explain the insufficient LDL-C control, the investigator should stress the absolute need to be compliant with all treatments and, if necessary, organize a specific interview with a qualified nutrition professional and stress the absolute need to be compliant with diet, and perform a blinded LDL-C assessment within 1 to 2 months prior to initiating rescue treatment.

Rescue treatment may be initiated as outlined in Appendix 10, in the event that no reason for LDL-C above the threshold value can be found.

6. STUDY VARIABLES

6.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, gender, weight, height, etc.), disease characteristics including prior medication history related to LMT, and medical history.

6.2. Primary and Secondary Endpoints

6.2.1. Primary Neurocognitive Endpoint

The primary outcome measure is the change in CANTAB cognitive domain SWM strategy score from baseline to week 96. Two definitions will be provided for this endpoint, specifically:

- SWM strategy z-score change from baseline is defined for each patient as: week 96 SWM strategy z-score minus the patient's baseline SWM strategy z-score. The change from baseline SWM strategy z-score is used for the primary analysis evaluation of noninferiority. A lower score denotes better SWM function (ie, less impairment).
  - A patient's SWM strategy z-score at week 96 is defined as: (week 96 SWM strategy raw score minus the SWM strategy mean baseline score) divided by the SWM strategy baseline standard deviation. The SWM strategy mean baseline score and the SWM strategy baseline standard deviation are calculated using patients in both treatment groups (ie, Praluent and placebo).
  - The SWM strategy z-score at baseline is defined for each patient in the same manner as the calculation for the SWM strategy z-score at week 96, replacing the patient's week 96 raw score with the patient's baseline raw score.
- SWM strategy raw score change from baseline is defined for each patient as: week 96 SWM strategy raw score minus the patient's SWM strategy baseline score. The SWM strategy raw score change from baseline is provided descriptively for clinical interpretation of function at week 96. Lower change from baseline raw scores reflect better SWM performance (ie, less impairment).

The baseline SWM strategy score is the last score obtained before the first dose of study treatment. The SWM Strategy score at week 96 is the score obtained within the week 96 analysis window and during the treatment-emergent adverse event (TEAE) period. The TEAE period is defined as the time from the first double-blind study treatment injection up to 70 days after the last double-blind study treatment injection. The analysis window used to allocate a time point to a measurement will be defined in the statistical analysis plan (SAP).

6.2.2. Exploratory Neurocognitive Endpoints

Exploratory neurocognitive outcome measures to further assess neurocognitive function in the CANTAB domains are provided below for each patient:

- PAL at week 96 defined as both a PAL z-score change from baseline and PAL raw score change from baseline, following the definitions and rules provided for the primary neurocognitive endpoint
- RTI at week 96 defined as both a RTI z-score change from baseline and RTI raw score change from baseline, following the definitions and rules provided for the primary neurocognitive endpoint
- SWM between-errors score at week 96 defined as both an SWM between-errors z-score change from baseline and SWM between-errors raw score change from baseline, following the definitions and rules provided for the primary neurocognitive endpoint

- Global Composite score at week 96 change from baseline is defined as (the average of the following 4 measures at week 96: SWM strategy z-score, PAL z-score, RTI z-score, and the SWM between-errors z-score) minus the average of the same 4 z-score measures at baseline

Standard outcome measures to assess general safety include overall AEs, SAEs (includes patient death), AEs causing discontinuation, adverse events of special interests (AESI), review of neurocognitive AEs, vital signs and laboratory values.

6.2.3. Secondary Efficacy Endpoints

The secondary efficacy endpoints are provided below. For those efficacy endpoints described as percent change from baseline at a given visit, the definition is: 100 multiplied (post-baseline visit measurement – baseline measurement) divided by the baseline measurement.

The baseline measurements are the last values obtained before the first dose of study treatment.

The secondary efficacy endpoint at a given visit is the measurement obtained within the analysis window of the visit and during the main efficacy period. The main efficacy period is defined as the time from the first double-blind study treatment injection up to the upper limit of the week 96 analysis window.

All secondary efficacy endpoints (scheduled or unscheduled) may be used to provide a value for the efficacy endpoint, if appropriate, according to above definition. The analysis window used to allocate a time point to a measurement will be defined in the SAP:

- The percent change in calculated LDL-C, apolipoprotein (Apo) B, non-high-density lipoprotein cholesterol (non-HDL-C), and Total-C from baseline to weeks 12, 24, 48, 72, and 96
- The percent change in lipoprotein a [Lp(a)], HDL-C, triglyceride (TG), and Apo A-1 from baseline to weeks 12, 24, 48, 72, and 96
- The proportion of patients reaching LDL-C <70 mg/dL (1.81 mmol/L) at weeks 12, 24, 48, 72 and 96
- The proportion of patients reaching LDL-C <50 mg/dL (1.29 mmol/L) at weeks 12, 24, 48, 72, and 96

6.2.4. Other Endpoints

- Anti-drug antibody status (positive/negative) and titers assessed at the end of the study
- Gonadal hormone levels (for female patients - estradiol, follicle-stimulating hormone (FSH) and luteinizing hormone (LH); for male patients - testosterone, FSH and LH)

7. STUDY SCHEDULE OF EVENTS AND VISIT DESCRIPTIONS

7.1. Schedule of Events

Study assessments and procedures are presented by study period and visit in Table 1.

Table 1: Schedule of Events

	Screening Period		Double-Blind Treatment Period (DBTP)									EOS
			Baseline									
	Visit 1	**Visit 2[1]**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**
Day	d-21 to d-8	d-7	d1	d57	d85	d169	d253	d337	d421	d505	d589	d673
Visit Window (days)		+/-7d	0	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-7d
Week	**W-3**	**W-1[1]**	**W0[1]**	**W8**	**W12**	**W24**	**W36**	**W48**	**W60**	**W72**	**W84**	**W96**
Screening/Baseline:												
Study informed consent	X											
Inclusion/exclusion	X		X									
Medical/surgical history	X											
Medication history	X											
Demographics	X											
Measured height	X											
Randomization			X									
IVRS/IWRS contact	X	X	X	X	X	X	X	X	X	X	X	X
GDS-S and MoCA	X											
Motor Screening Task	X											
HIV testing	X											
Treatment:												
Injection training		X[2]	X[2]									
Administer study drug			X[3]	X	X	X	X	X	X	X	X	
Study drug kit dispensation[4]			X		X	X	X	X	X	X	X	
Kit return					X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Diet:												
Review of diet[5]	X	X	X	X	X	X	X	X	X	X	X	X
Safety Assessments:[7]												
Blood pressure and pulse rate	X	X	X	X	X	X	X	X	X	X	X	X
Body weight	X		X			X		X		X		X
Physical exam	X											X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Neurocognitive Battery[8]	X		X			X		X		X		X

	Screening Period		Double-Blind Treatment Period (DBTP)									EOS
			Baseline									
	Visit 1	**Visit 2[1]**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**
Day	d-21 to d-8	d-7	d1	d57	d85	d169	d253	d337	d421	d505	d589	d673
Visit Window (days)		+/-7d	0	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-3d	+/-7d
Week	**W-3**	**W-1[1]**	**W0[1]**	**W8**	**W12**	**W24**	**W36**	**W48**	**W60**	**W72**	**W84**	**W96**
Menstrual Cycle:												
Collection of menstrual cycle data[6]	X		X			X		X		X		X
Laboratory Testing:[7]												
Lipid panel[9]	X		X	X	X	X		X		X		X
Hematology	X		X			X		X		X		X
Chemistry	X		X			X		X		X		X
Gonadal hormones[10]	X		X			X		X		X		X
Creatine phosphokinase (CPK)	X		X			X		X		X		X
Liver panel	X		X			X		X		X		X
Hepatitis B surface antigen	X											X
Hepatitis C antibody	X											X
Pregnancy test (WOCBP)	S		U		U	U	U	U	U	U	U	U
Urinalysis[11]	X		X			X		X		X		X
HbA1c	X					X		X		X		X
TSH	X											
hs-CRP			X			X		X		X		X
ADA sample			X					X				X
Research samples (serum and plasma)			X			X		X				X
[redacted]			X									

ADA = anti-drug antibody, CPK = creatine phosphokinase, EOS = end of study, F/U = follow-up, HbA1c = hemoglobin A1c, hs-CRP = high-sensitivity C-reactive protein, S = serum, TSH = thyroid-stimulating hormone, U = urine, WOCBP = women of childbearing potential

1. Visit 2 is optional.
2. Injection training will be performed with the patient and/or caregiver at visit 2, at visit 3, or at visits 2 and 3 using placebo. Refer to Section 5.1 for additional information on injection training.
3. The patient or caregiver will administer the first dose of double-blind study drug in the clinic on day 1. The patient will be monitored for 30 minutes after the first dose. Subsequent doses of study drug must be administered Q2W. Study drug will be administered at home between week 84 and week 94. The last dose of study drug will be administered at home at week 94. Patients will come into the clinic for the last study visit at week 96.
4. Injection supplies and the dosing log will be provided to the patient.
5. See Appendix 6 for diet.
6. Menstrual cycle data will be collected for women of childbearing potential who are not on hormonal contraceptives.

7. On days when a clinic visit coincides with a dosing day (visits 3, and 8), blood samples (including ADA samples) will be collected after study assessments are performed and before the dose of study drug is administered. At visits 4, 5, 6, 7, 9, 10, and 11, study drug may be administered prior to study assessments.
8. If a neurocognitive AE is reported during the visits when the test is not planned or in case of early treatment discontinuation, an unscheduled neurocognitive battery test will be performed.
9. Samples will be tested for Total-C, calculated LDL-C, HDL-C, TG, and non-HDL-C, Apo B, Apo A-1, Apo B/Apo A-1 ratio, and Lp(a).
10. For female patients – estradiol, follicle-stimulating hormone (FSH) and luteinizing hormone (LH); for male patients – testosterone, FSH and LH.
11. Dipstick and, if abnormal, microscopy.

[redacted]

7.2. Study Visit Descriptions

For all visits after the randomization visit, if the visit 1 date is changed, then the next visit should take place according to the original study schedule.

Alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding blood sampling are discouraged.

7.2.1. Unscheduled Visits

All attempts should be made to keep patients on the study schedule. Unscheduled visits may be necessary to repeat testing or for a proper follow-up.

7.3. Handling of Study Drug Discontinuation and Patient Withdrawal from the Study

7.3.1. Study Drug Discontinuation

Study drug should be continued whenever possible. In the event study drug dosing is stopped, it should be determined if the stop can be made temporarily. Permanent discontinuation should be a last resort. In any case, the patient should remain in the study as long as possible.

Patients who prematurely discontinue study drug should remain in the study and undergo all study visits and procedures, with the exception of dosing with study drug. At the time of study drug discontinuation, the patient should have, as soon as possible, an unscheduled visit with the assessments that are normally done at the end of study (EOS) visit (this should take place within 5 days of discontinuation of study drug, if possible), and then resume the original study schedule until end of study.

Assessment of patients who do not consent to remain in the study after discontinuation of study drug should be managed according to Section 7.4.1.

7.3.1.1. Reasons for Temporary Discontinuation of Study Drug

Temporary discontinuation of study drug may be considered by the investigator because of suspected AEs, including allergic events related to the dose of study drug. Reinitiating study drug dosing will be done under close and appropriate clinical and/or laboratory monitoring.

Temporary discontinuation of study drug is defined as 1 or more scheduled injections that are not administered to the patient as decided by the investigator.

7.3.1.2. Reasons for Permanent Discontinuation of Study Drug

Patients should permanently discontinue study drug for the following reasons:

- Pregnancy, intention for pregnancy, or no longer with effective contraceptive method of birth control (females enrolled in this study, only)
- Acute injection reaction of clinical concern
- SAE (or non-serious but severe in intensity) of hypersensitivity reaction considered related to study drug

- At patient request
- If, in the investigator's opinion a patient's cognition deteriorates to the degree of Mild Cognitive Impairment (MCI), or dementia, the investigator will seek diagnostic confirmation from the required specialist per local practice. If diagnosis is confirmed, study drug may be discontinued
- If, in the investigator's opinion, continuation of study drug dosing would be detrimental to the patient's well being
- Intercurrent condition that requires discontinuation of study drug
- At the specific request of the sponsor
- Patient receives double-blind treatment before randomization

The IVRS/IWRS should be notified when a patient prematurely discontinues study treatment.

Note: Patients who discontinue study treatment should be encouraged to continue to participate in the study and, at a minimum, return for the primary endpoint assessment at week 96.

7.4. Patient Withdrawal from the Study

A patient has the right to withdraw from the study at any time, for any reason, and without repercussion.

The investigator and sponsor have the right to withdraw a patient from the study in the event of an intercurrent illness, AE, treatment failure, protocol violation, and for administrative or other reasons. An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

7.4.1. Early Termination from the Study

If for any reason the patient refuses to continue the study, the patient should undergo an unscheduled visit with assessments normally planned at the end of study visit (it should take place within 5 days of treatment discontinuation, if possible). The patient should be followed until recovery or stabilization of any AE. An end of study visit can take place with assessments as specified in the end of study visit after the premature discontinuation of study drug (see Table 1).

The investigator should make the best effort to contact any patient (eg, contacting patient's family or private physician, reviewing available registries or health care database) who fails to return to the site and to determine health status, including vital status at a minimum. Attempts to contact such patients must be documented in the patient's records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter).

7.5. Replacement of Patients

Patients who are prematurely discontinued from the study will not be replaced.

7.6. Study Procedures

7.6.1. Procedures Performed only at the Screening/Baseline Visit

Medical/surgical history, medication history related to lipid-modifying therapy, demographics, height, hepatitis B surface antigen and hepatitis C antibody testing, HIV testing, serum pregnancy testing, GDS-S and MoCA, and the Motor Screening Task will be performed for the purpose of determining study eligibility or characterizing the baseline population.

7.6.2. Neurocognitive Assessment Battery Procedures

7.6.2.1. CANTAB

The CANTAB will be performed at time point according to Table 1 and includes the following 3 tests, which will take approximately 25 minutes to complete: SWM, PAL, and RTI. Training will be done at screening. Additional details will be provided in the study manual.

7.6.3. Efficacy Procedures

All laboratory samples will be collected before the dose of study drug is administered.

Alcohol consumption within 48 hours or intense physical exercise within 24 hours preceding blood sampling is discouraged.

Total cholesterol, HDL-C, TG, Apo B, Apo A-1, and Lp(a) will be directly measured by the central laboratory. Low-density lipoprotein cholesterol will be calculated using the Friedewald formula. If TG values exceed 400 mg/dL (4.52 mmol/L), or if calculated LDL-C values are below 15 mg/dL, then the central lab will reflexively measure LDL-C using the beta quantification method. Non-HDL-C will be calculated by subtracting HDL-C from the Total-C. The Apo B/Apo A-1 ratio will be calculated.

Detailed procedures of sample preparation, storage, and shipment are provided in the laboratory manual.

7.6.3.1. Lipid Panel

Blood samples for the lipid panel (Total-C, TG, HDL-C, non-HDL-C, calculated LDL-C, Apo B, Apo A-1, Apo B/Apo A-1 ratio, and Lp(a)) will be collected at time points according to Table 1.

Lipid results from blood samples obtained after the randomization visit will not be communicated to the investigators. Sites will be notified if the following occurs: LDL-C increase >25% compared with the randomization visit LDL-C value in 2 consecutive LDL-C assessments. The patient should be managed according to Section 5.7.3.

7.6.4. Safety Procedures

7.6.4.1. Blood Pressure and Heart Rate

Blood pressure and heart rate will be assessed at time points according to Table 1.

Note: in case of high blood pressure values at screening, the investigator is responsible for the optimization of the patient's treatment to achieve blood pressure targets as defined by local

guidelines or the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (Chobanian 2003).

7.6.4.2. Physical Examination

A thorough and complete physical examination, including height and weight, will be performed at the first screening visit (visit 1). Additional physical exams will be performed at other time points according to Table 1. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.

Body Weight and Height

Body weight should be obtained at time points according to Table 1, with the patient wearing undergarments or very light clothing and no shoes, and with an empty bladder. The same scale should be used throughout the study.

The use of calibrated balance scales is recommended, if possible. Self-reported weights are not acceptable; patients must not read the scales themselves.

Height should be measured at screening; self-reported heights are not acceptable.

7.6.4.3. Laboratory Testing

All laboratory samples (including ADA samples) will be collected after assessments are performed and before a dose of study drug is administered at visits that correspond with a dosing day. At visit 4, study drug may be administered prior to study assessments.

Samples for laboratory testing will be collected at time points according to Table 1 and analyzed by a central laboratory during the study. Detailed instructions for blood sample collection are in the laboratory manual provided to study sites. Specific tests are listed below.

Blood Chemistry

Sodium	Total protein
Potassium	Creatinine
Chloride	Blood urea nitrogen
Bicarbonate	Lactate dehydrogenase (LDH)
Calcium	Phosphorus
Glucose	Uric acid
Albumin	Gamma-glutamyl transpeptidase

Hematology

Hemoglobin	Differential:
Hematocrit	Neutrophils
Red blood cells (RBCs)	Lymphocytes
White blood cells (WBCs)	Monocytes
Platelet count	Basophils
Reticulocyte count	Eosinophils
RBC distribution width	

Urinalysis

Color	Glucose	RBCs
Clarity	Blood	Hyaline and other casts
pH	Bilirubin	Bacteria
Specific gravity	Leukocyte esterase	Epithelial cells
Ketones	Nitrite	Crystals
Protein	WBCs	Yeast

Other Laboratory Tests

Pregnancy testing (serum or urine) will be performed at time points according to Table 1.

Samples for the liver panel (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin), hepatitis C antibody, hepatitis B surface antigen, hemoglobin A1c (HbA1c), creatine phosphokinase (CPK), thyroid-stimulating hormone (TSH), high-sensitivity C-reactive protein (hs-CRP), and gonadal hormones (for female patients - estradiol, follicle-stimulating hormone [FSH] and luteinizing hormone [LH]; for male patients – testosterone, FSH and LH) will be collected at time points according to Table 1.

Abnormal Laboratory Values and Laboratory Adverse Events

- All laboratory values must be reviewed by the investigator or authorized designee.
- Significantly abnormal tests must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study medication or its administration, the medical monitor must be consulted.
- The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values as AEs are provided in Section 8.2.4.

7.6.4.4. Adverse Event Information Collection

The investigator (or designee) will record all AEs that occur during the study from the time the informed consent is signed through the last study visit. Information on follow-up for AEs is provided in Section 8.2.5. Abnormalities in laboratory results, vital signs, or electrocardiograms (ECGs) are to be recorded as AEs, as outlined in Section 8.2.4.

The definition of an AE and SAE, and information on the determination of severity and relationship to treatment are provided in Section 8.

7.6.4.5. Reporting Adverse Events of Special Interest

The sponsor should be notified within 24 hours after the site learns about the following AEs of interest (the reporting function of the e-CRF should be used to report the event):

- Increase in ALT: ALT ≥3 x ULN (if baseline ALT <ULN), or ALT ≥2 times the baseline value (if baseline ALT ≥ ULN)
- Allergic events and/or local injection site reactions that are allergic in nature and that require consultation with another physician for further evaluation
- Pregnancy
- Symptomatic overdose with investigational medicinal product
- Neurologic events that require additional examinations/procedures and/or referral to a specialist
- Neurocognitive events

- Cataracts
- New onset of diabetes

7.6.5. Anti-Drug Antibody Procedures

Samples for ADA assessments will be collected in the clinic after all visit assessments have been completed, at time points listed in Table 1. At visits that take place on dosing days, all samples for ADA assessments will be collected before a dose of study drug is administered. Detailed procedures of sample preparation, storage, and shipment are provided in the laboratory manual.

To maintain the blind of the study, ADA samples will be collected from all patients, including those who received only placebo.

The Regeneron Sample Analysis group will analyze the ADA samples.

7.6.6. Other Assessments

7.6.6.1. Review of Diet

Patients will be following a diet equivalent to the Nation Cholesterol Education Program-Adult Treatment Panel (NCEP-ATP III TLC) diet at the screening visit and will be asked to continue the dietary plan until the last study visit. Patients will be queried about compliance with the dietary plan during the double-blind treatment period, at time points according to Table 1.

Details are provided in the study reference manual and in Appendix 6.

7.6.6.2. Collection of Menstrual Cycle Data

Menstrual cycle data will be collected for women of childbearing potential who are not on hormonal contraceptives at time points according to Table 1.

[redacted]

8. SAFETY DEFINITIONS, REPORTING, AND MONITORING

8.1. Definitions

8.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease, which is temporally associated with the use of a study drug, whether or not considered related to the study drug.

An AE also includes any worsening (ie, any clinically significant change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the study drug.

8.1.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger).
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or **prolongation of existing hospitalization**. In-patient hospitalization is defined as admission to a hospital or an emergency room for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician.

- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is an **important medical event** - Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent 1 of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

8.2. Recording and Reporting Adverse Events

All SAEs, regardless of assessment of causal relationship to study drug must be reported to the sponsor (or designee) as follows:

- Telephone the sponsor (or designee) at the contact information provided in the SAE completion guidelines, within 24 hours of learning of the event
- Complete the SAE form utilizing the AE e-CRF in the electronic data capture (EDC) system and submit within 24 hours of learning of the event

The sponsor (or designee) will provide the investigators with blank SAE forms, which are to be completed in the event that access to the EDC system is not available. Once the EDC system is available, the SAE information must be entered within 24 hours of the system availability. Information not available at the time of the initial report must be documented in the EDC within 24 hours of receipt of the new information. Substantiating data such as relevant hospital or medical records and diagnostic test reports may also be requested.

The investigator must promptly report to the Institutional Review Board (IRB)/Ethics Committee (EC) all unanticipated problems involving risks to patients. This includes death from any cause and all SAEs related to the use of the study drug. It is recommended that all SAEs be reported to the IRB/EC, regardless of assessed causality.

In the event the investigator is informed of an SAE after the patient completes the study, the following will apply:

- SAE with an onset within 30 days of the end of study/early termination visit - the SAE will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome until the event is considered chronic and/or stable.
- SAE with an onset day greater than 30 days from the end of study/early termination visit - only fatal SAEs and those deemed by the investigator to be drug-related SAEs will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome of a drug-related SAE until the event is considered chronic and/or stable.

8.2.1. Deaths

Any AE that results in death is considered an SAE. Deaths that occur from the time the patient signs the ICF until 70 days after dosing must be reported to the appropriate IRB/EC and to Regeneron Pharmacovigilance and Risk Management (or designee) within 24 hours of learning of the death. The reporting procedures detailed in Section 8.2 should be followed.

Any available autopsy reports and relevant medical reports must be sent to the sponsor (or designee) as soon as possible.

8.2.2. Pregnancy and Other Events that Require Accelerated Reporting

The following events also require reporting to the sponsor (or designee) within 24 hours of learning of the event:

Overdose: An overdose (accidental or intentional) is an event suspected by the investigator or spontaneously notified by the patient (not based on systematic injection counts), and defined as at least twice of the intended dose within the intended therapeutic interval; to be reported using the corresponding screens in the e-CRF using the term "symptomatic OVERDOSE (accidental [or intentional])." The patient should be monitored and appropriate symptomatic treatment instituted.

and/or,

Accidental or intentional administration of the study drug at a frequency higher than that allowed by the study protocol, if associated with an AE.

Pregnancy: Although it is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee) by telephone within 24 hours, any pregnancy occurring in a female patient or partner of a male patient (if permitted by the female partner and by local regulatory policies), during the study or within 70 days following the last dose of study drug. Study drug will be discontinued in female study participants who become pregnant, per Section 7.3.1.2. The sponsor will provide the investigator with a Pregnancy Tracking Form that is to be completed by the study site on a monthly basis and faxed to the sponsor (or designee). The investigator will follow the pregnancy until delivery, or longer. If the pregnancy continues to term (delivery), the health of the infant must also be reported to the sponsor (or designee).

Information on AEs of interest that requires accelerated reporting is provided in Section 7.6.4.5.

Whenever possible and practical, a blood sample to potentially measure plasma drug levels should be obtained upon the development of any SAE or unusual AE that is judged related to study treatment.

8.2.3. Reporting Adverse Events Leading to Withdrawal from the Study

All AEs that lead to a patient's withdrawal from the study must be reported to the sponsor's medical monitor within 30 days. All SAEs leading to a patient's withdrawal from the study must be reported as outlined in Section 8.2.

8.2.4. Abnormal Laboratory, Vital Signs, or Electrocardiogram Results

The criteria for determining whether an abnormal objective test finding should be reported as an AE include:

- the test result is associated with accompanying symptoms, and/or
- the test result requires additional diagnostic testing or medical/surgical intervention, and/or
- the test result leads to a change in dosing (outside of protocol-stipulated dose adjustments), discontinuation from the study/study drug, significant additional concomitant drug treatment, or other therapy

Contact the medical monitor in the event the investigator feels that an abnormal test finding should be reported as an AE, although it does not meet any of the above criteria.

Repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

Evaluation of severity of laboratory abnormalities will be assessed according to the scale outlined in Section 8.3.1.

8.2.5. Follow-up

Adverse event information will be collected until the end of study visit, or the early termination visit if the patient withdraws consent.

The investigator must make every effort to obtain follow-up information on the outcome of any SAE until the event is considered chronic and/or stable.

8.3. Evaluation of Severity and Causality

8.3.1. Evaluation of Severity

8.3.1.1. Adverse Events (Excluding Local Injection Site Reactions)

The severity of each AE (excluding local injection site reactions, see Section 8.3.1.2) will be graded by the investigator using a 3-point scale (mild, moderate, or severe) and reported in detail as indicated on the e-CRF and/or SAE form, as appropriate.

- **Mild:** Does not interfere in a significant manner with the patient's normal functioning level. It may be an annoyance. Prescription drugs are not ordinarily needed for relief of symptoms, but may be given because of personality of the patient.
- **Moderate:** Produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment. Treatment for symptom may be needed.
- **Severe:** Produces significant impairment of functioning or incapacitation and is a definite hazard to the patient's health. Treatment for symptom may be given and/or patient hospitalized.

If a laboratory value is considered an AE, its severity should be based on the degree of physiological impairment the value indicates.

8.3.1.2. Local Injection Site Reactions

The severity of local injection site reactions will be graded by the investigator using a 4-point scale (mild, moderate, severe, or very severe) adapted from the toxicity grading scale table from the Food and Drug Administration Draft Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials dated April 2005. Local injection site reactions will be reported in detail as indicated on the e-CRF and/or SAE form, as appropriate.

The complete severity grading scale for assessing local injection site reactions is provided in Appendix 7.

8.3.2. Evaluation of Causality

The relationship of AEs to study drug is a clinical decision that will be made based on all available information, by the investigator, who will answer the following question:

Is there a reasonable possibility that the AE was caused by the study drug?

The possible answers are:

Not Related: There is no reasonable possibility that the event may have been caused by the study drug

Related: There is a reasonable possibility that the event may have been caused by the study drug (ie, a causal relationship cannot reasonably be ruled out)

The investigator will provide a comment on the SAE reporting form to explain the basis of the causality assessment for SAEs.

8.3.2.1. Causality Evaluation Factors

Factors to consider when determining the relationship of an AE to study drug are included below.

Not Related:

- Existence of a clear alternative explanation or nonplausibility (eg, the patient is struck by an automobile when there is no indication that the drug caused disorientation, or cancer diagnosed a few days after first drug administration)
- Due to external causes such as other treatment(s) being administered
- Due to the patient's disease state or clinical condition
- Does not follow a reasonable temporal sequence following the time of administration of the dose of study drug
- Does not reappear or worsen when dosing with study drug is resumed (ie, negative re-challenge)

Related:

- Could not be explained by other treatment(s) being administered
- Could not be explained by the patient's disease state or clinical condition
- Follows a reasonable temporal sequence following the time of administration of the dose of study drug
- Resolves or improves after discontinuation of study drug
- Reappears or worsens when dosing with study drug is resumed (ie, positive re-challenge)
- Known to be a response to the study drug based upon preclinical data or prior clinical data
- Known to be strongly associated with drug exposure (eg, angioedema, Stevens-Johnson Syndrome)

8.4. Investigator Alert Notification

Regeneron (or designee) will inform all investigators participating in this clinical trial, as well as in any other clinical trial using the same investigational drug, of any SAE that meets the relevant requirements for expedited reporting (an AE that is serious, is unexpected based on the Investigator's Brochure, and has a reasonable suspected causal relationship to the study drug).

9. STATISTICAL PLAN

9.1. Statistical Hypothesis

Let μ_0 and μ_1 be the population means of the change in SWM strategy z-score from baseline to week 96 under placebo and Praluent, respectively. For the primary and exploratory neurocognitive variables, the following null and alternative hypotheses will be assessed for noninferiority:

$$H_0 : \mu_1 - \mu_0 \geq NI\ margin$$
$$versus$$
$$H_1 : \mu_1 - \mu_0 < NI\ margin$$

Age (dichotomized by <65 or ≥65) and by statin use (no statin, low lipophilicity of the concomitant statin, or high lipophilicity of the concomitant statin) will be the 2 stratification factors for patient randomization, and will be accounted for in the statistical modeling for neurocognitive function assessment.

9.2. Determination of Sample Size

To demonstrate the noninferiority of the Praluent 75 mg Q2W/up-titrate 150mg Q2W dose regimen relative to placebo for the primary endpoint of mean change in SWM strategy z-score from baseline to week 96, the sample size for this study is calculated to be 1085 patients per treatment group. This sample size is based on the noninferiority margin of 0.2 for the primary outcome measure. Specifically, a worsening in the SWM strategy z-score of 0 to 0.2 at the group

level (small effect size) would not be considered clinically meaningful. Whereas a worsening of 0.3 to 0.5 (or greater), a small-to-medium effect size, might be considered clinically relevant, indicating increased cognitive impairment (Roiser 2015). Therefore, a noninferiority margin of 0.2 on the SWM strategy z-score change from baseline is a conservative estimate of the largest clinically meaningless mean difference between Praluent and placebo treatment groups. Additionally, the assumed mean difference between the treatment groups is 0 and the standard deviation is 1.0 (the standard deviation is obtained from the Cambridge Cognition internal normative data). To achieve 95% power using a 2-sided 95% confidence interval (CI) approach (2-sided alpha=0.05), the sample size is calculated to require 651 patients per treatment group. Assuming dropout rate of 20% in the first year and 25% in the second year, the sample size is increased to 1085 patients per treatment group.

The nQuery Advisor 7.0 was used for the sample size calculations.

9.3. Analysis Sets

9.3.1. Safety Analysis Sets

9.3.1.1. Safety Population

The safety population will be defined as all patients randomized and exposed to at least 1 dose of study drug, regardless of the amount of treatment administered. Patients will be analyzed according to the treatment received (placebo or Praluent 75 mg Q2W/up-titrate 150 mg Q2W).

9.3.1.2. Primary Safety Population

The primary safety population used to analyze the neurocognitive endpoints will be defined as patients from the safety population who had an assessment of the SWM strategy score at baseline, and at least 1 score measured during the TEAE period. The TEAE period is defined as the first double-blind treatment dose to last dose of double-blind treatment + 70 days (10 weeks). Patients will be analyzed according to the treatment actually received.

In addition:

- Randomized patients for whom it is unclear whether they took the study drug will be included in the safety population as randomized.
- For patients receiving study drug from more than 1 treatment group during the trial, the treatment group allocation for as-treated analysis will be Praluent.

9.3.2. Efficacy Analysis Set

9.3.2.1. Intent-to-Treat

The intent-to-treat (ITT) population is defined as all randomized patients who had an evaluable secondary efficacy endpoint. The endpoint is evaluable when the following 2 conditions are met:

- Availability of at least 1 measurement value for calculated LDL-C before first dose of study drug (ie, baseline)

- Availability of at least 1 measurement value for calculated LDL-C within 1 of the analysis windows during the main efficacy period; the main efficacy period is defined as the time from the first double-blind study treatment injection up to the upper limit of the week 96 analysis window

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

9.3.2.2. Modified Intent-to-Treat

The modified intent-to-treat (mITT) population (also known as the full analysis set) is defined as the all randomized population who took at least 1 dose or part of a dose of study drug and have an evaluable secondary efficacy endpoint. The endpoint is considered as evaluable when both of the following conditions are met:

- Availability of at least 1 measurement value for calculated LDL-C before first dose of study drug (ie, baseline)
- Availability of at least 1 calculated LDL-C value during the efficacy treatment period and within 1 of the analysis windows up to week 96; the efficacy treatment period is defined as the time from the first double-blind study drug injection up to 21 days after the last double-blind study drug injection

Patients in the mITT population will be analyzed according to the treatment group allocated by randomization.

9.3.3. Other Analysis Set

The anti-drug antibody analysis will be performed on all treated patients (safety population) with a blood sample at week 0 (baseline) and at least 1 evaluable blood sample for anti-alirocumab antibodies after the first dose of study drug.

9.4. Patient Disposition

Screened patients are defined as any patient who originally met the inclusion criteria and signed the informed consent.

Randomized patients consist of all screened patients, with a double-blind treatment kit number allocated and recorded in the IVRS/IWRS database, regardless of whether the treatment kit was used or not. Patients treated without being randomized or treated with a double-blind treatment kit before the randomization will not be considered as randomized and will not be included in any analysis population. The safety experience of patients treated and not randomized will be reported separately.

For any patient randomized more than once, safety data from the first randomization will be included in the safety population, with safety data associated with the later randomization reported separately. Since this is expected to be a rare event, inclusion of efficacy data from patient randomized more than once in the efficacy population will be decided on a case-by-case basis prior to the unblinding of treatment assignments and will be documented in the clinical study report.

9.5. Statistical Methods

9.5.1. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively for the 2 treatment groups in the safety population. Continuous variables will be summarized with mean, Q1, median, Q3, standard deviation, minimum, and maximum. Categorical variables will be summarized with frequency and percentage.

9.5.2. Safety and Efficacy Analyses

9.5.2.1. Primary Neurocognitive Analysis

The primary neurocognitive analysis is a statistical evaluation of the noninferiority of the Praluent 75 mg Q2W/up-titrate 150 mg Q2W dose regimen to placebo for the primary endpoint of change in SWM strategy z-score from baseline to week 96 in the primary safety population. The 2-sided 95% CI for the mean treatment difference at week 96 will be determined using an appropriate contrast statement in a mixed-effect model with repeated measures (MMRM). The upper CI limit will be compared to the noninferiority margin which is defined as 0.2 and the noninferiority will be declared if the upper CI limit is below the noninferiority margin.

In the case noninferiority is achieved for the primary neurocognitive function endpoint comparison, superiority of the primary neurocognitive function endpoint will be assessed using the same upper CI limit calculated for the primary comparison. Specifically, the upper CI limit will be compared to zero and superiority will be declared if the upper CI limit is below zero. A statistical multiplicity adjustment is not needed, since this process of noninferiority achievement followed by superiority assessment using the same 95% upper CI limit on the primary endpoint corresponds to a simple closed test procedure (EMA/CPMP/EWP/482/99 – 27July 2000).

The MMRM model will include the fixed categorical effects of treatment group (placebo, Praluent), both randomization strata (as per IVRS/IWRS), time point (weeks 24, 48, 72, and 96), treatment-by-time point interaction, and strata-by-time point interaction, as well as the continuous covariate of baseline SWM strategy raw score value and baseline value-by-time point interaction. Post-baseline assessments within a patient's TEAE period will be included in the analysis and missing data are accounted for by the MMRM model. Model assumptions for normality will be explored prior to the analysis testing.

This model will be run using Statistical Analysis Software (SAS) mixed procedure with an unstructured correlation matrix to model the within-patient errors. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Denominator degrees of freedom will be estimated using Satterthwaite's approximation. This model will provide baseline adjusted least-squares means estimates at week 96 for both treatment groups with their corresponding standard errors.

To support the clinical interpretation of the primary neurocognitive analysis, the SWM strategy raw score change from baseline to week 96 in the primary safety population will also be descriptively provided using the MMRM analysis method described above (at least includes least squares mean and 95% CI).

Robustness of this statistical method will be assessed via sensitivity analyses detailed in the SAP, including different methodologies for missing data (multiple imputation and potentially pattern mixture modeling).

9.5.2.2. Exploratory Neurocognitive Analyses

To further understand the effects of Praluent on cognitive function and support the primary neurocognitive analysis, the 3 domain endpoints (specifically PAL, RTI, and SWM between-error scores) and the Global Composite score will also be evaluated for noninferiority at week 96 in the primary safety population. These 4 measures will not be evaluated for superiority. The analysis method (MMRM) and noninferiority evaluation approach (evaluation of the 95% CI for the mean treatment difference at week 96) described for the primary neurocognitive analysis will also be used for the 3 domain's z-scores change from baseline and the Global Composite score change from baseline. To support the clinical interpretation of the 3 domains, the raw score change from baseline to week 96 in the primary safety population will also be descriptively provided using the MMRM analysis method.

The 4 domain endpoint scores (including the primary neurocognitive endpoint) and the Global Composite scores will be descriptively summarized by time point, and the details will be provided in the SAP.

9.5.2.3. Secondary Efficacy Analyses

For secondary efficacy endpoints of lipids (defined in Section 6.2.3), descriptive summaries and analyses will be performed in the ITT population (for ITT analysis) and the mITT population (for on-treatment analysis). P-values for the testing of study treatment effect will be provided for descriptive purposes only (nominal p-values).

For descriptive summaries, percent change from baseline in calculated LDL-C, Total-C, HDL-C, TG, non-HDL-C, Apo B, Apo A-1, and Lp(a) will be provided at each time point for each treatment group. All measurements, scheduled or unscheduled, will be assigned to analysis windows defined in the SAP in order to provide an assessment for these time points. Laboratory assessments other than the ones provided by the central laboratory will be excluded. The time profile of each parameter will be plotted by treatment group with the corresponding standard errors. For TG and Lp(a), summary statistics will include Q1 and Q3.

Multiple types of measurements are planned to be analyzed during the trial, specifically continuous measurements expected to have a normal distribution (eg, percent change in calculated LDL-C), continuous measurements expected to have a non-normal distribution (eg, TG), and binary measurements (eg, proportion of patients reaching LDL-C <70 mg/dL).

I. Continuous Endpoints Anticipated to have a Normal Distribution

Continuous secondary efficacy variables, defined in Section 6.2.3, anticipated to have a normal distribution (ie, lipids other than TG and Lp(a)) will be analyzed in the analysis populations using the same MMRM method as described for the primary neurocognitive endpoint. Specifically, the model will contain fixed categorical effects of treatment group, both randomization strata, planned time points up to week 96 (specific time points are weeks 8, 12, 24, 48, 72, and 96), strata-by-time point interaction and treatment-by-time point interaction, as well as, the continuous fixed covariates of corresponding baseline value and baseline value-by-time point interaction.

II. Continuous Endpoints Anticipated to have a Non-Normal Distribution

Continuous secondary efficacy endpoints, defined in Section 6.2.3, anticipated to have a non-normal distribution (ie, TG and Lp(a)) will be analyzed in the analysis populations using a robust regression model (ie, ROBUSTREG SAS procedure with M-estimation option) with treatment group and randomization strata as main effect and corresponding baseline value(s) as the covariate. Missing values will be addressed using a multiple imputation approach, which will be described in the SAP. The variables in the multiple imputation model will at least include the same variables as used in the robust regression model. The treatment group combined means will be provided with respective standard error estimates. The combined mean difference between the treatment groups will be provided with the standard error, 95% CI, and p-value.

III. Binary Endpoints

Binary secondary efficacy endpoints, defined in Section 6.2.3, will be analyzed in the analysis populations using stratified logistic regression (using the strata option of the SAS logistic procedure) with treatment group and randomization strata as main effect and corresponding baseline value(s) as the covariate. Missing values will be addressed using a multiple imputation approach which will be described in the SAP. The variables in the multiple imputation model will at least include the same variables used in the logistic regression model. Treatment effects will be compared and the combined odds ratio estimate between the treatment groups, with their corresponding 95% CIs and p-value, will be provided.

In the data dependent case that the logistic regression method is not applicable (eg, the response rate is zero in 1 treatment group and thus the maximum likelihood estimate may not exist), the last observation carried forward (LOCF) approach would be used for handling of missing values and an exact conditional logistic regression would be performed to compare treatment effects. The LOCF imputation method will consist of using the last value obtained up to the applicable time point window (weeks 12, 24, 48, 72, and 96 as applicable) to impute the missing week value.

9.5.2.4. Multiplicity Considerations

Adjustments to the alpha level for the purposes of multiple testing are not applicable for this safety study. The exploratory neurocognitive and secondary efficacy lipid endpoints are supportive of the primary analysis and not hypothesis-testing. Any statistical testing is for descriptive purposes only (ie, any p-values provided are nominal).

9.5.2.5. General Safety Analyses

The general safety analysis will be based on the safety analysis population (SAF). The summary of safety results will be presented by the 2 treatment groups (placebo and Praluent 75 mg Q2W/up-titrate 150 mg Q2W). No formal inferential testing will be performed. Summaries will be descriptive in nature.

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

- The baseline value is defined as the last available value before the first dose of study treatment.

9.5.2.6. Adverse Events

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®). The verbatim text, the preferred term (PT), and the system organ class (SOC) will be provided in patient listings.

Definitions

For safety variables, the following observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before the first dose of study treatment.
- The TEAE period is defined as the time from the first dose of study treatment to the last dose of study treatment + 70 days (10 weeks) (residual effect of treatment is expected until 10 weeks after the last dose of study drug).
- The post-treatment observation period is defined as the time from the day after the end of the TEAE period up to the last study visit.

Pretreatment AEs are defined as those that developed, worsened, or became serious during the pretreatment period.

Treatment-emergent adverse events are defined as those that developed, worsened, or became serious during the TEAE period.

Post-treatment AEs are defined as those that developed, worsened, or became serious during the post-treatment period.

Analysis

Adverse event incidence tables will be presented by (at least) SOCs sorted by internationally agreed order, and PTs sorted by decreasing frequency in the Praluent group. The number (n) and percentage (%) of patients experiencing an AE will be shown. The high level group term and high level term can be added in alphabetical order, as applicable. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. Data conventions for missing or partial AE dates will be addressed in the SAP. The denominator for computation of percentages is the safety population within each treatment group.

Adverse event incidence tables will be provided by treatment group for all types of TEAEs: all TEAEs, all TEAEs of interest (defined with a PT or a prespecified grouping), TEAE by severity, all treatment-emergent SAEs, and all TEAEs leading to permanent treatment discontinuation.

If any clinically significant signal is detected and further characterization is needed or for AEs of clinical interest, selected TEAEs will be analyzed using a time-to-event approach (Kaplan-Meier methodology) to account for the differential exposure time in all patients. Time from the first dose of study drug to the first occurrence of the event will be calculated (only the first event will be counted). Patients without any event will be censored at the end of the TEAE period. Kaplan-Meier curves will be provided.

Death

The following death summaries will be generated:

- Number (%) of patients who died by study period (TEAE and post-study) summarized on the safety population by treatment received
- Death in nonrandomized patients or randomized and not treated patients
- TEAE leading to death (death as an outcome on the AE e-CRF page as reported by the investigator) by (at least) SOCs sorted by internationally agreed order, and PTs sorted by decreasing frequency in the Praluent group, showing the number (n) and percentage (%) of patients

Drug-Induced Liver Injury

Liver function tests, namely ALT, AST, alkaline phosphatase, and total bilirubin, are used to assess possible drug-induced liver toxicity. The proportion of patients with potentially clinically significant abnormal values (PCSAs) at any post-baseline visit by baseline status will be displayed by treatment group for each parameter. A graph of distribution of peak values of ALT versus peak values of total bilirubin will also be presented (note that the ALT and total bilirubin values are presented on a logarithmic scale). The graph will be divided into 4 quadrants with a vertical line corresponding to 3 x upper limit of normal (ULN) for ALT and a horizontal line corresponding to 2 x ULN for total bilirubin.

The incidence of liver-related AEs will be summarized by treatment group. The selection of PTs will be based on a standardized MedDRA query hepatic disorder. Time to liver-related treatment discontinuation and time to liver death may also be provided based on the hepatic disorder standardized MedDRA query.

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 prespecified manner as described in this protocol. The number and percentage of patients experiencing a neurocognitive event will be summarized for each treatment group by SOC and PT. Time-to-event analyses could also be performed (if relevant, based on the number of events). In addition, the neurocognitive event rate in patients with 2 consecutive results separated by at least 21 days, and with only 1 such event for calculated LDL-C <25 mg/dL, and calculated LDL-C <15 mg/dL, will be assessed.

9.5.2.7. Laboratory Data and Vital Signs

The following definitions will be applied to laboratory parameters and vital signs:

- The baseline value is defined as the last available value before first dose of study treatment.
- 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 and vital signs.
- The PCSA criteria will determine which patients had at least 1 PCSA during the TEAE period, taking into account all evaluations performed during the TEAE period,

including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the PCSA percentage.

- Treatment period: the treatment period used for quantitative analysis (laboratory results and vital signs) is defined as the time from first dose of study treatment to the last dose of study treatment + 21 days.

Summary statistics (including mean, median, Q1, Q3, standard error, minimum and maximum) of all laboratory variables and all vital sign parameters (raw data and changes from baseline) will be calculated for each visit, last and worst value assessed during the treatment period, and presented by treatment group. For selected parameters, mean changes from baseline with the corresponding standing error will be plotted over time (at same time points) in each treatment group.

The incidence of PCSAs at any time during the TEAE period (on-treatment PCSAs) will be summarized by treatment group, whatever the baseline level and/or according to the following baseline categories:

- Normal/missing
- Abnormal according to PCSA criteria

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

Hepatitis C Test

The number and percentage of patients with an observed seroconversion for hepatitis C test will be provided by treatment group.

9.5.2.8. Treatment Exposure

The duration of treatment exposure will be calculated for each treatment group. The following measures of exposure will be summarized:

- Duration of Praluent exposure in weeks, defined as (last study treatment dosing date +14 minus first study treatment dosing date)/7, regardless of unplanned intermittent discontinuations
- The total number of injections by patient

Treatment exposure duration, measured in weeks, will be summarized by at least mean, median, standard deviation, and minimum/maximum. The categorical data of maximum number of injections will be summarized by patient counts and percentages.

The number (n) and percentage (%) of patients with an up-titration (a change in dose) in the Praluent group will be provided for the overall safety population.

9.5.2.9. Treatment Compliance

Study treatment compliance will be assessed by treatment group using the following parameter:

- The injection frequency will be defined for each patient as the average number of days between 2 injections, that is: (last dose date minus first dose date)/(number of injections minus 1)

These parameters will be summarized descriptively (N, mean, standard deviation, median, minimum and maximum).

9.5.2.10. Analysis of Other Endpoints

All analyses for other endpoints will be performed on the safety population. The baseline value is defined as the last available value before first dose of study drug.

Exploratory variables, such as those defined in Section 6.2.4, will be summarized by time points using number of available data, mean, standard deviation, median, minimum, and maximum for each treatment group.

The antibody status (positive/negative) and antibody titers will be summarized by treatment group and visit using descriptive statistics. If appropriate, correlations between antibody titers, safety and/or efficacy endpoints will be provided by graphical methods.

The number and percentage of 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 provided by treatment group.

Further details will be provided in the SAP.

10. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

10.1. Data Management

A data management plan specifying all relevant aspects of data processing for the study (including data validation, cleaning, correcting, and releasing) will be maintained and stored at Regeneron.

A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, AEs, applicable baseline findings, medication, and medical history/surgical history) will be done using internationally recognized and accepted dictionaries.

The e-CRF data for this study will be collected with an EDC tool.

10.2. Electronic Systems

Electronic systems used to process and/or collect data in this study will include the following:

- IVRS/IWRS system – randomization, study drug supply
- EDC system – data capture
- SAS – statistical review, analysis, and reporting
- AWARE, Business Objects XI – pharmacovigilance activities

- Central laboratory – data capture
- Cambridge Cognition – data capture

11. STUDY MONITORING

11.1. Monitoring of Study Sites

The study monitor and/or designee (eg, CRO monitor) will visit each site prior to enrollment of the first patient, and periodically during the study. In accordance with ICH guidelines, the monitor will compare the e-CRF entries with the appropriate source documents. Additional review may include, but is not limited to, patient ICFs, documentation of patient recruitment and follow-up, AEs, SAEs, and concomitant therapy; as well as records of study drug dispensing, compliance, and accountability. A copy of the drug dispensing log must be provided to the sponsor upon request.

11.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents).

The investigator must keep all source documents on file with the e-CRF (throughout this protocol, CRF refers to either a paper CRF or an electronic CRF). Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

11.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on e-CRFs by trained site personnel. An e-CRF must be completed for every patient enrolled in the study. After review of the clinical data for each patient, the investigator must provide an electronic signature. A copy of each e-CRF page is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

Corrections to the e-CRF will be entered in the e-CRF by the investigator or an authorized designee. All changes, including date and person performing the corrections, will be available via a system-generated audit trail. For corrections made via data queries, a reason for any alteration must be provided.

12. AUDITS AND INSPECTIONS

This study may be subject to a quality assurance audit or inspection by the sponsor or regulatory authorities. Should this occur, the investigator is responsible for:

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor's participation in the inspection

- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, e-CRFs, medical records, correspondence, ICFs, IRB/EC files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

In all instances, the confidentiality of the data must be respected.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

It is the responsibility of both the sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

13.2. Informed Consent

The principles of informed consent are described in ICH guidelines for GCP.

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB/EC. A copy of the IRB/EC -approved ICF and documentation of approval must be provided to the sponsor before study drug will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each patient prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the patient in a language that he/she can understand. The ICF should be signed and dated by the patient and by the investigator or authorized designee who reviewed the ICF with the patient.

- Patients who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Patients who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the patient’s study record, and a copy of the signed ICF must be given to the patient.

If new safety information results in significant changes in the risk/benefit assessment, the ICF must be reviewed and updated appropriately. All study patients must be informed of the new information and provide their written consent if they wish to continue in the study. The original signed revised ICF must be maintained in the patient's study record and a copy must be given to the patient.

13.3. Patient Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study patient will be maintained. Patients should be identified by a patient identification number, only, on e-CRFs or other documents submitted to the sponsor. Documents that will not be submitted to the sponsor (eg, signed ICF) must be kept in strict confidence.

The patient's and investigator's personal data, which may be included in the sponsor database, will be treated in compliance with all applicable laws and regulations. The sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

13.4. Institutional Review Board/Ethics Committee

An appropriately constituted IRB/EC, as described in ICH guidelines for GCP, must review and approve:

- The protocol, ICF, and any other materials to be provided to the patients (eg, advertising) before any patient may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/EC should be informed as soon as possible
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

In addition, the IRB/EC should be informed of any event likely to affect the safety of patients or the continued conduct of the clinical study.

A copy of the IRB/EC approval letter with a current list of the IRB/EC members and their functions must be received by the sponsor prior to shipment of drug supplies to the investigator. The approval letter should include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB/EC review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

14. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design or operation of the protocol or ICF without a health authority and/or IRB/EC-approved amendment.

15. END OF STUDY DEFINITION

The last patient last visit constitutes the end of study.

16. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE

16.1. Premature Termination of the Study

The sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the sponsor decide to terminate the study, the investigators will be notified in writing.

16.2. Close-out of a Site

The sponsor and the investigator have the right to close-out a site prematurely.

Investigator's Decision

The investigator must notify the sponsor of a desire to close-out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the sponsor. Both parties will arrange the close-out procedures after review and consultation.

Sponsor's Decision

The sponsor will notify the investigator(s) of a decision to close-out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study, but has not enrolled any patient within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of patients required for the study are enrolled earlier than expected

In all cases, the appropriate IRB/EC and Health Authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the patients' interests.

17. STUDY DOCUMENTATION

17.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the e-CRFs must be signed by the investigator. This certification form accompanies each set of e-CRFs. The signed form will be provided to the sponsor with the final set of e-CRFs for each patient.

17.2. Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of e-CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer if a longer period is required by relevant

regulatory authorities. The investigator must consult with the sponsor before discarding or destroying any essential study documents following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the sponsor and the relevant records will be transferred to a mutually agreed-upon destination.

18. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

19. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

20. PUBLICATION POLICY

The publication policy is provided as a separate agreement.

21. REFERENCES

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22. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effect of Praluent on Neurocognitive Function in Patients with Heterozygous Familial Hypercholesterolemia or with Non-Familial Hypercholesterolemia at High and Very High Cardiovascular Risk, and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council for Harmonisation Guideline for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved. I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the IRB/EC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

APPENDIX 1. SIMON BROOME REGISTER DIAGNOSTIC CRITERIA FOR HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

Definite familial hypercholesterolemia is defined as:

- Total-C >6.7 mmol/l (260 mg/dL) or LDL cholesterol above 4.0 mmol/l (155 mg/dL) in a child <16 years or Total-C >7.5 mmol/l (290 mg/dL) or LDL cholesterol above 4.9 mmol/l (190 mg/dL) in an adult. (Levels either pre-treatment or highest on treatment)

PLUS

- Tendon xanthomas in patient, or in 1st degree relative (parent, sibling, child), or in 2nd degree relative (grandparent, uncle, aunt)

OR

- DNA-based evidence of an LDL receptor mutation or familial defective Apo B-100

Possible familial hypercholesterolemia is defined as:

- Total-C >6.7 mmol/l (260 mg/dL) or LDL cholesterol above 4.0 mmol/l (155 mg/dL) in a child <16 years or Total-C >7.5 mmol/l (290 mg/dL) or LDL cholesterol above 4.9 mmol/l (190 mg/dL) in an adult. (Levels either pre-treatment or highest on treatment)

And at least one of the following:

- Family history of myocardial infarction below 50 years of age in 2nd degree relative or below 60 years of age in 1st degree relative.

Family history of raised cholesterols >7.5 mmol/l (290 mg/dL) in adult 1st or 2nd degree relative or >6.7 mmol/l (260 mg/dL) in child or sibling under 16 years of age.

APPENDIX 2. WHO CRITERIA (DUTCH LIPID NETWORK CLINICAL CRITERIA) FOR DIAGNOSIS OF HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

Diagnostic Scoring for Heterozygous Familial Hypercholesterolemia			
Family history			
a First degree relative with known premature (men <55 yrs, women <60 yrs) coronary and vascular disease.			1
b First degree relative with known LDL-cholesterol >95th percentile for age and sex.			
and/or			
a First degree relative with tendon xanthomata and/or arcus cornealis.			2
b Children below 18 yrs. with LDL-cholesterol >95th percentile for age and sex.			
Clinical history			
a Patient has premature (men <55 yrs, women <60 yrs) coronary artery disease			2
b Patient has premature (men <55 yrs, women <60 yrs) cerebral or peripheral vascular disease.			1
Physical examination			
a Tendon xanthomata			6
b Arcus cornealis below the age of 45 yrs.			4
Laboratory analysis			
		mmol/L	mg/dL	
a LDL-cholesterol		>8.5	>330	8
b LDL-cholesterol		6.5-8.4	250-329	5
c LDL-cholesterol		5.0-6.4	190-249	3
d LDL-cholesterol		4.0-4.9	155-189	1
(HDL-cholesterol and triglycerides are normal)				
DNA-analysis			
a Functional mutation low-density lipoprotein receptor gene present			8
Diagnosis of heFH is:			
Certain When		>8 points	
Probable When		6-8 points	
Possible When		3-5 points	

APPENDIX 3. MOOD STABILIZERS, ANTIPSYCHOTICS AND MEDICATIONS TO TREAT DEMENTIA

(Exclusionary medications, regardless of indication for use)

Mood Stabilizers	Antipsychotics	Dementia Treatment
Lithium	Risperidone	Donepezil
Valproic Acid	Olanzapine	Galantamine
Topiramate	Quetiapine	Rivastigmine
Lamotrigine	Clozapine	Memantine
Divalproex	Ziprasidone	
Valproate	Aripiprazole	
Oxcarbazine	Lurasidone	
Riluzole	Asenapine	
Carbamazepine	Pailperidone	
	Iloperidone	
	Haloperidol	
	Fluphenazine	
	Chlorpromazine	
	Perphenazine	
	Pimozide	
	Thiothixine	

APPENDIX 4. DRUGS ON THE ANTICHOLINERGIC BURDEN SCALE

(A total ACB scale score of three or more is considered exclusionary)

ACB Score 1 (mild)	ACB Score 2 (moderate)	ACB Score 3 (severe)
Alimemazine	Amantadine	Amitriptyline
Alprazolam	Belladonna alkaloids	Amoxapine
Alverine	Cyclobenzaprine	Atropine
Aripiprazole	Cyproheptadine	Benztropine
Asenapine	Loxapine	Brompheniramine
Atenolol	Meperidine	Carbinoxamine
Beclometasone dipropionate	Methotrimeprazine	Chlorpheniramine
Benzodiazepines	Molindone	Chlorpromazine
Bupropion hydrochloride	Nefopam	Clemastine
Captopril	Oxcarbazepine	Clomipramine
Cetirizine	Pethidine hydrochloride	Clozapine
Chlorthalidone		Darifenacin
Cimetidine hydrochloride		Desipramine
Clidinium		Dicyclomine
Clorazepate		Dimenhydrinate
Clonazepam		Diphenhydramine
Opiates		Doxepin
Colchicine		Fesoterodine
Desloratadine		Flavoxate
Dextropropoxyphene		Hydroxyzine
Digoxin		Hyoscyamine
Dipyridamole		Imipramine
Disopyramide phosphate		Meclizine
Fentanyl		Methocarbamol
Fluvoxamine		Nortriptyline
Furosemide		Olanzapine
Hydralazine		Orphenadrine
Hydrocortisone		Oxybutynin
Iloperidone		Paroxetine
Isosorbide preparations		Perphenazine
Levocetirizine		Procyclidine
Loperamide		Promazine
Loratidine		Promethazine
Metoprolol		Propentheline
Morphine		Propiverine
Nifedipine		Pyrilamine
Paliperidone		Quetiapine
Prednisone/Prednisolone		Scopolamine
Quinidine		Solifenacin
Ranitidine		Thioridazine (withdrawn)
Risperidone		Tolterodine
Sertraline		Trifluoperazine
Theophylline		Trihexyphenidyl
Timolol maleate		Trimipramine
Trazodone		Trospium
Triamterene		
Venlafaxine		
Warfarin		

Notes:

1. Certain medicines eg Risperidone (mild ACB), Quetiapine (severe ACB) and Olanzapine (severe ACB) were licensed after 1990 and therefore not prescribed to the original CFAS cohort.
2. Brand names may conceal generic drug names.
3. Some combination medicines contain anticholinergic drugs.
4. This list is indicative and some related medicines were taken by patients in the CFAS study; if appropriate these related medicines were given an ACB score based on the ACB of the related medicine in the Aging Health publication (see Reference 1 below).
5. Medications listed in Appendix 4 used "as needed"/pro re nata (PRN), ≤2 times per week should not be included in calculating the ACB score
6. All products that include metoprolol (eg, metoprolol succinate [Toprol XL] or metoprolol tartrate [Lopressor]) should be scored "1."
7. All opiate products (eg, oxycodone, hydrocodone, tramadol, etc) should be scored as "1."

References:

1. Boustani MA, Campbell NL, Munger S, Maidment I, Fox GC. Impact of anticholinergics on the aging brain: a review and practical application. Aging Health. 2008;4(3):311-20.
2. Campbell N, Boustani M, Limbil T, Ott C, et al. The cognitive impact of anticholinergics: a clinical review. Clinical Interventions in Aging. 2009;4(1):225-33

APPENDIX 5. DEFINITION OF CARDIOVASCULAR DISEASE RISK CATEGORIES

- **Very high CV risk** is defined as a history of documented CHD, ischemic stroke, transient ischemic attack, carotid artery occlusion >50% without symptoms, carotid endarterectomy or carotid artery stent procedure, peripheral arterial disease, abdominal aortic aneurysm, renal artery stenosis, renal artery stent procedure, type 1 or type 2 diabetes mellitus with target organ damage.

  A history of documented CHD includes 1 or more of the following:

  – Acute myocardial infarction

  – Silent myocardial infarction

  – Unstable angina

  – Coronary revascularization procedure (eg, percutaneous coronary intervention or coronary artery bypass graft surgery).

  – Clinically significant CHD diagnosed by invasive or non-invasive testing (such as coronary angiography, stress test using treadmill, stress echocardiography or nuclear imaging)

- **High CV risk** is defined as a calculated 10-year fatal CVD risk SCORE ≥5% (ESC/EAS 2012), moderate chronic kidney disease, type 1 or type 2 diabetes mellitus without target organ damage, or heFH.

- **Moderate CV risk** is defined as a calculated 10-year fatal CVD risk SCORE ≥1 and <5% (ESC/EAS 2012).

APPENDIX 6. SUMMARY OF TLC DIET FOR HIGH CHOLESTEROL

Total Fat	25% - 35% total calories*
Saturated fat*	< 7% total calories
Polyunsaturated fat	up to 10% total calories
Monounsaturated fat	up to 20% total calories
Carbohydrates†	50% - 60% total calories*
Protein	~15% total calories
Cholesterol	< 200 mg/day (5.172 mmol/day)
Plant Sterols	2g
Soluble Fiber such as psyllium	10g - 25g

* ATP III allows an increase of total fat to 35 percent of total calories and a reduction in carbohydrate to 50 percent for persons with the metabolic syndrome. Any increase in fat intake should be in the form of either polyunsaturated or monounsaturated fat. Trans-fatty acids are another LDL-raising fat that should be kept at a low intake.

† Carbohydrate should derive predominantly from foods rich in complex carbohydrates including grains—especially whole grains—fruits, and vegetables.

APPENDIX 7. ASSESSMENT OF LOCAL INJECTION SITE REACTIONS

Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Very Severe (Grade 4)
Pain	Does not interfere with activity	Interferes with activity or repeated use of non-narcotic pain reliever	Prevents daily activity or repeated use of narcotic pain reliever	Emergency Room (ER) visit or hospitalization
Tenderness	Mild pain to touch	Pain with movement	Significant pain at rest	ER visit or hospitalization
Erythema/ Redness*	2.5 – 5 cm	5.1 – 10 cm	>10 cm	Necrosis or exfoliative dermatitis
Swelling**	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis
Itching	Does not interfere with activity	Interferes with activity or repeated use of topical or systemic treatment	Prevents daily activity or leads to other significant dermatologic conditions (such as infection, scarring, etc.)	Emergency Room (ER) visit or hospitalization
Other (Please specify)***	No modification of daily activities and/or does not require symptomatic treatment.	Hinders normal daily activities and/or requires symptomatic treatment.	Prevents daily activities and requires symptomatic treatment.	Emergency Room (ER) visit or hospitalization

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

**Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

***Please specify the other signs or symptoms (for example, hematoma, discoloration, re-activation, etc.).

ADAPTED from the toxicity grading scale table from the FDA Draft Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials April 2005

APPENDIX 8. GERIATRIC DEPRESSION SCALE SHORT FORM

Geriatric Depression Scale (GDS)
Scoring Instructions

Instructions: Score 1 point for each bolded answer. A score of 5 or more suggests depression.

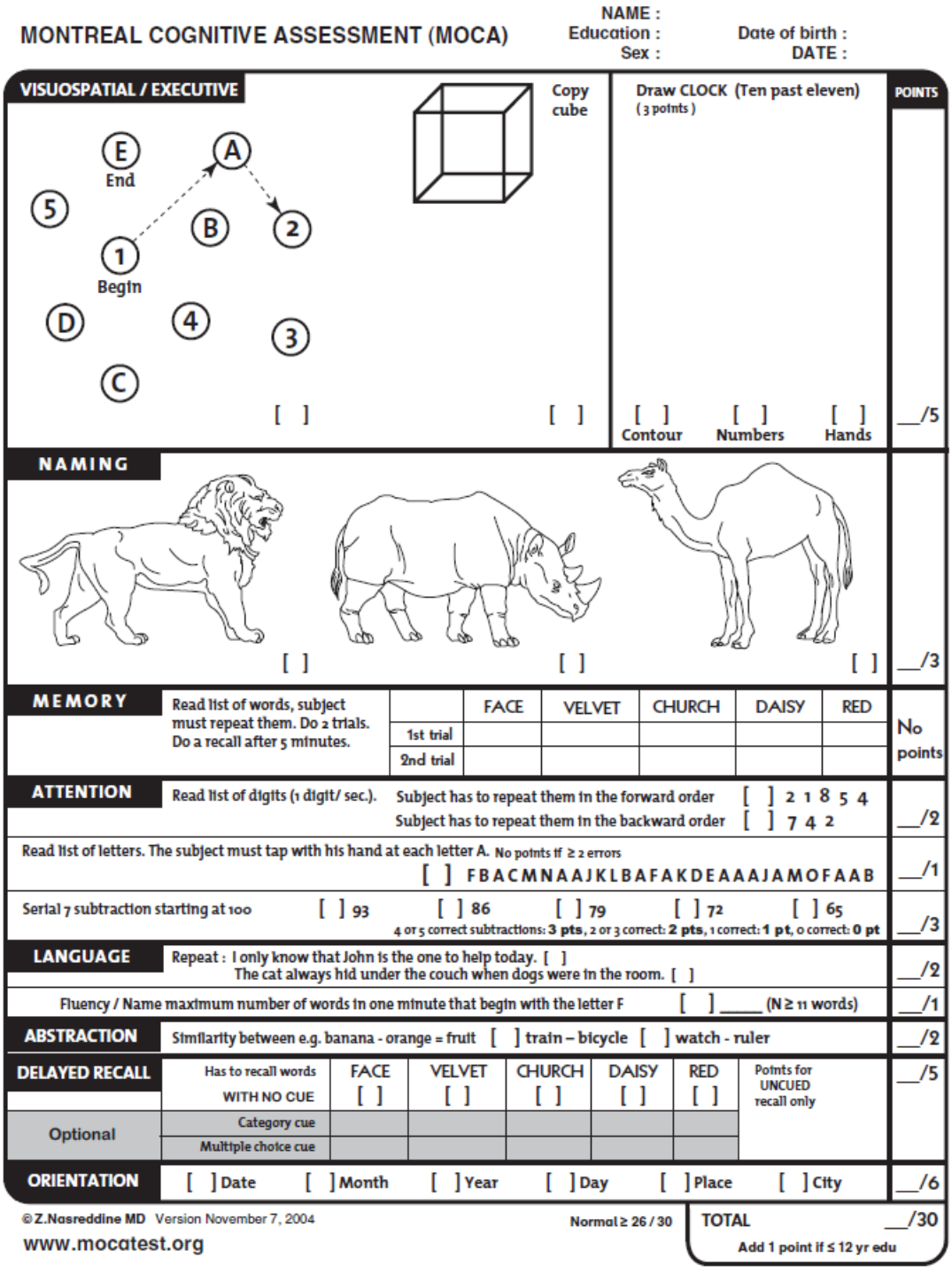
1.	Are you basically satisfied with your life?	yes	**no**
2.	Have you dropped many of your activities and interests?	yes	no
3.	Do you feel that your life is empty?	yes	no
4.	Do you often get bored?	yes	no
5.	Are you in good spirits most of the time?	yes	**no**
6.	Are you afraid that something bad is going to happen to you?	yes	no
7.	Do you feel happy most of the time?	yes	**no**
8.	Do you often feel helpless?	yes	no
9.	Do you prefer to stay at home, rather than going out and doing things?	yes	no
10.	Do you feel that you have more problems with memory than most?	yes	no
11.	Do you think it is wonderful to be alive now?	yes	**no**
12.	Do you feel worthless the way you are now?	yes	no
13.	Do you feel full of energy?	yes	**no**
14.	Do you feel that your situation is hopeless?	yes	no
15.	Do you think that most people are better off than you are?	yes	no

A score of ≥ 5 suggests depression ***Total Score*** _____

Ref. Yes average: The use of Rating Depression Series in the Elderly, in Poon (ed.): Clinical Memory Assessment of Older Adults, American Psychological Association, 1986

2 Tools may be copied without permission

APPENDIX 9. MONTREAL COGNITIVE ASSESSMENT



MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :
Education :
Sex :
Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE — POINTS

Copy cube [ ] [ ]

Draw CLOCK (Ten past eleven) (3 points) [ ] Contour [ ] Numbers [ ] Hands — __/5

NAMING [ ] [ ] [ ] — __/3

MEMORY Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2 — __/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B — __/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** — __/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ] — __/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] ____ (N ≥ 11 words) — __/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler — __/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City — __/6

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www.mocatest.org

Normal ≥ 26 / 30

TOTAL __/30
Add 1 point if ≤ 12 yr edu

APPENDIX 10. LDL-C RESCUE MEDICATION PRINCIPLES

If no reason for LDL-C above the threshold value can be found, or if appropriate action fails to decrease LDL-C below the threshold value, rescue medication may be introduced. The effectiveness of any such changes will be made based on lack of rescue threshold from blinded lipid testing at the next routinely scheduled lab draw.

Patients per protocol already receive a maximum tolerated dose of statin, so statin uptitration or switch will not be an option.

For further LDL-C lowering, the investigator may consider adding:

- A cholesterol absorption inhibitor (ezetimibe), or
- A bile acid-binding sequestrant (the resins cholestyramine and colestipol, or colesevelam, a nonabsorbable polymer)

The following lipid modifying agents may also be considered:

- Fenofibrate

  Note: Caution should be exercised when combining fibrates with other cholesterol lowering medications such as statins because of the risk of myopathy. When a fibrate is combined with a statin, fenofibrate is the fibrate of choice because it does not affect statin glucuronidation.

- Nicotinic acid (niacin)

  Note: Niacin raises blood glucose but has been shown to be effective in modifying lipid disorders in people with diabetes if glucose control is maintained.

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

(Medical/Study Director, Regulatory Representative, Clinical Study Team Lead, and Biostatistician)

To the best of my knowledge, this protocol accurately describes the conduct of the study.

Study Title: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effect of Praluent on Neurocognitive Function in Patients with Heterozygous Familial Hypercholesterolemia or with Non-Familial Hypercholesterolemia at High and Very High Cardiovascular Risk

Protocol Number: R727-CL-1532

Protocol Version: R727-CL-1532 Amendment 5

See appended electronic signature page

Sponsor's Responsible Medical/Study Director

See appended electronic signature page

Sponsor's Responsible Regulatory Representative

See appended electronic signature page

Sponsor's Responsible Clinical Study Team Lead

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Sponsor's Responsible Biostatistician

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Approval	[redacted]
Approval	[redacted]

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