AMENDED NON-INTERVENTIONAL POST AUTHORIZATION SAFETY STUDY (PASS) PROTOCOL 02

A drug utilization study (DUS) of alirocumab in Europe to assess the effectiveness of the dosing recommendation to avoid very low LDL-C levels

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COMPOUND: Praluent®/alirocumab

STUDY NUMBER: OBS14697

STUDY NAME: DUS

The Study is conducted by Sanofi/CRO hereinafter referred also as the "MAH/CRO delegated by the MAH".

Version Number:	1		
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PASS Information

Title	A drug utilization study (DUS) of alirocumab in Europe to assess the effectiveness of the dosing recommendation to avoid very low LDL-C levels
Protocol version identifier	Amended protocol 02 version 1
Date of last version of protocol	09-Jul-2020
EU PAS register number	EUPAS21314
Active substance	Alirocumab ATC code: C10AX14
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Product reference	EU/1/15/1031
Procedure number	EMEA/H/C/003882/MEA019
Marketing authorization holder(s)	Sanofi-aventis groupe 54, rue La Boétie 75008 Paris France
Joint PASS	No
Research question and objectives	The primary objective of this drug utilization study is to evaluate the effectiveness of the Praluent (brand name of alirocumab) dosing recommendations for the 3 dosage regimens approved to date, ie, 75 mg once every two weeks, 150 mg once every two weeks, and 300 mg once every 4 weeks (monthly) to avoid very low LDL-C levels. The secondary objective is to describe the pattern of Praluent utilization in real-world clinical practice with respect to the dosing recommendations in the labelling of the 3 dosage regimens approved to date, ie, 75 mg once every two weeks, 150 mg once every two weeks, and 300 mg once every 4 weeks (monthly) to avoid very low LDL-C levels.
Country(-ies) of study	European countries (this study consists of 3 waves, Germany, United Kingdom, Belgium, and Netherlands will participate in Wave 1; for Wave 2 and Wave 3, the following countries have been selected based on the extent of patient exposure estimated from EU sales data: Austria, Belgium, Germany, Italy, Netherlands, Spain, and United Kingdom in Wave 2; Austria, Belgium, Italy, Netherlands, Spain, and United Kingdom in Wave 3).
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1 TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS

AE:	adverse event
ASCVD:	atherosclerotic cardiovascular disease
CRO:	Contract Research Organization
CVD:	cardiovascular disease
DUS:	drug utilization study
e-CRF:	electronic case report form
EDC:	electronic data capture
EMA:	European Medicines Agency
EMR:	electronic medical record
ENCePP:	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
GVP:	good pharmacovigilance practices
ICF:	informed consent form
INN:	international nonproprietary name
IRB/IEC:	Institutional Review Board/Independent Ethics Committee
LDL-C:	low-density lipoprotein cholesterol
LDLR:	low-density lipoprotein receptor
MAH:	Marketing Authorization Holder
PASS:	post-authorization safety study
PCSK9:	proprotein convertase subtilisin kexin type 9
PRAC:	Pharmacovigilance Risk Assessment Committee
Q1:	first quarter
Q2:	second quarter
Q3:	third quarter
QC:	quality control
RMP:	risk management plan
SAP:	statistical analysis plan
SmPC:	summary of product characteristics

3 RESPONSIBLE PARTIES

The execution of this protocol is the responsibility of the following parties:

- Marketing Authorization Holder (MAH),
- Contract Research Organization (CRO [CRO delegated by the MAH]).

4 ABSTRACT

***Title**:*

A drug utilization study (DUS) of alirocumab in Europe to assess the effectiveness of the dosing recommendation to avoid very low LDL-C levels

***Rationale and background**:*

- Low-density lipoprotein cholesterol levels in Praluent®-treated patients

In the context of evaluation of very low plasma low-density lipoprotein cholesterol (LDL-C) levels, 2 thresholds were set in the Praluent (brand name of alirocumab) clinical studies and assessed in the submission dossier:

- A 25 mg/dL (0.65 mmol/L) threshold based on the 2008 American College of Cardiology Foundation and American Diabetes Association consensus report (1) stating that: 1) the lower limit to safe and effective cholesterol lowering has not been established; 2) individuals with genetic mutations causing lifelong very low LDL-C levels appear not only to avoid cardiovascular disease (CVD) but also to be free of other abnormalities that might conceivably be linked to their very low plasma cholesterol levels, and 3) a plasma level of 25 mg/dL (0.65 mmol/L) for LDL-C was estimated to be sufficient to supply peripheral cholesterol needs, based on in vitro cell cultures (2).
- A 15 mg/dL (0.39 mmol/L) threshold was chosen arbitrarily.

In the global pool of Phase 2 and Phase 3 studies, a total of 1426 (42.7%) patients treated with Praluent (alirocumab) had at least 1 value of LDL-C<25 mg/dL (0.65 mmol/L), including 839 (25.2%) patients with 2 consecutive values of LDL-C<25 mg/dL separated by at least 21 days. The LDL-C <25 mg/dL (<0.65 mmol/L) levels mostly occurred in the LTS11717 (LONG-TERM) study, where all patients were initiated and maintained on the 150 mg Q2W dose, regardless of the baseline LDL-C value or the response to treatment. No particular safety concerns were observed in this subgroup of patients (3).

Nonetheless, due to limited data collected from patients with very low LDL-C (<25 mg/dL) exposed to Praluent for over 18 months, “Clinical impact of very low LDL-C for extended period of time” was considered as a missing information in the Praluent Risk Management Plan (RMP), as endorsed by CHMP opinion dated 23 September 2015. Following a Type II variation for Praluent submitted on 14 August 2019 to modify the EU RMP, the missing information “clinical impact of very low LDL-C for extended period of time” was removed from the RMP (4) in the CHMP opinion dated 16 January 2020. This DUS is still part of the RMP but is not related to the missing information “clinical impact of very low LDL-C for extended period of time”.

- Praluent dosing recommendation

  In the Summary of Product Characteristics (SmPC) of Praluent approved on 02 June 2020 (5), the following is stated about the method of administration of Praluent.

  "The usual starting dose for Praluent is 75 mg administered subcutaneously once every 2 weeks. Patients requiring larger LDL-C reduction (>60%) may be started on 150 mg once every 2 weeks, or 300 mg once every 4 weeks (monthly), administered subcutaneously.

  The dose of Praluent can be individualised based on patient characteristics such as baseline LDL-C level, goal of therapy, and response. Lipid levels can be assessed 4 to 8 weeks after treatment initiation or titration, and dose adjusted accordingly (up-titration or down-titration). If additional LDL-C reduction is needed in patients treated with 75 mg once every 2 weeks or 300 mg once every 4 weeks (monthly), the dosage may be adjusted to the maximum dosage of 150 mg once every 2 weeks."

- The European Medicines Agency's request

  In the RMP approved by the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC), dated 23 September 2015, a post-authorization safety study (PASS) was implemented as part of pharmacovigilance plan of the RMP for Praluent, in response to PRAC request.

At that time, only 2 dosage regimens, 75 mg once every two weeks and 150 mg once every two weeks, were approved in European Union; therefore, this drug utilization study was designed to assess, in Europe, the effectiveness of the dosing recommendation included in the labeling for these 2 approved dosages regimens to avoid very low LDL-C levels; however, a new dosage regimen of 300 mg once every 4 weeks (monthly) was approved in the European Union and the updated SmPC was approved on 14 November 2016 (6). Consequently, the study design was updated to reflect the administration of the new approved dosage regimen in a real-world setting.

***Research question and objectives**:*

The primary objective of this study is to assess the effectiveness of the Praluent (brand name of alirocumab) dosing recommendations for the 3 dosage regimens approved to date, ie, 75 mg once every two weeks, 150 mg once every two weeks, and 300 mg once every 4 weeks (monthly) to avoid very low LDL-C levels. The secondary objective is to describe the pattern of Praluent utilization in real-world clinical practice with respect to the dosing recommendations in the labelling of the 3 dosage regimens approved to date, ie, 75 mg once every two weeks, 150 mg once every two weeks, and 300 mg once every 4 weeks (monthly) to avoid very low LDL-C levels.

***Study design**:*

This is a non-interventional (with regard to the therapeutic strategy), retrospective cohort study in patients who were initiated with Praluent (brand name of alirocumab) 75 mg once every two weeks, 150 mg once every two weeks, or 300 mg once every 4 weeks (monthly). The clinical setting and data sources of the study will mirror real life management of those patients.

***Population**:*

1. Setting

This study is planned to be conducted in European countries, and consists of 3 waves: Germany, United Kingdom, Belgium, and Netherlands participated in Wave 1; for Wave 2 and Wave 3, the following countries have been selected based on the extent of patient exposure estimated from EU sales data: Austria, Belgium, Germany, Italy, Netherlands, Spain, and United Kingdom in Wave 2; Austria, Belgium, Italy, Netherlands, Spain, and United Kingdom in Wave 3.

The availability of essential data, in particular the LDL-C values that will allow the MAH to assess the objectives of the study, will be ensured during the physician selection. According to the feasibility assessment result, the vast majority of the responding sites in the selected countries collect LDL-C values.

2. Enrollment of physicians and patients

(1) Enrollment of physicians:

This study consists of 3 waves. In the first and second waves, a selected sample of 20 and 61 physicians of any specialty who have prescribed Praluent during the eligibility period was enrolled, respectively. In Wave 3, 36 to 63 physicians are expected to be selected. National prescriber databases containing health care professionals' information and their prescribing information will be used to identify physicians in each selected country. For each wave, a 3-step process will be followed: identification from prescription database(s), selection, and remote recruitment.

(2) Selection of patients

For each participating physician, up to 8 patients will be randomly enrolled (with appropriate consent) from a pool of all patients who have started Praluent in the eligibility period (please refer to Section 6). If there are 2 physicians from a practice/institution participating in the same wave of the study, the combined total number of patients selected from these 2 physicians will be limited to 10.

Variables:

Physicians' characteristics will be collected at the time of their recruitment.

Medical chart reviews will be conducted to retrospectively collect data in a 6-month observational period following the date of the first prescription of Praluent (index date) for each patient. Such data include: (1) patient characteristics, (2) prescriptions of Praluent and other lipid-lowering drugs in the observational period, and (3) LDL-C values (please refer to Section 11 for adverse event [AE] details).

Data Sources:

The data sources will consist of medical records (either electronic medical records [EMRs] or paper source files). Patients' data will be collected using an electronic case report form (e-CRF).

Study size:

According to the global pool of Phase 2 and Phase 3 studies, 42.7% of patients treated with Praluent (alirocumab) had at least 1 value of LDL-C <25 mg/dL, regardless of the dose of Praluent received and the baseline LDL–C level. Compared to what will be seen in actual clinical practice, this percentage is probably overestimated.

In the initial plan, a sample size of 400 patients per wave was estimated to provide sufficient levels of precision in estimating proportions of patients with very low LDL-C value (<25 mg/dL or <0.65 mmol/L) ranging from 1% to 90%. A sample size of 400 patients per wave was to ensure a reasonable measurement uncertainty (CI half-width) of 4.8% to the observed proportion of patients (95% CI = [38.0; 47.6]) with very low LDL-C level.

According to the feasibility results, the number of physicians might be limited in each country. The initial estimate was that a minimum of 100 physicians were needed to reach the recruitment goal of 400 patients per wave. It was anticipated that given the uncertainty of Praluent market penetration in each country, the number of sites might need to be adjusted in order to reach the target of 400 patients per wave.

In 2018, the MAH encountered challenges in Wave 1 recruitment that prevented it from reaching the target sample size in the anticipated timeframe. Despite the remediation actions taken by the MAH, the site enrollment projections demonstrated that the initial plan of recruiting 400 patients from 100-138 sites for Wave 1 could not be accomplished due to continued lower than expected positive site response rate, low Praluent prescriptions, and limited patient eligibility period of 4 months from March 2017 to June 2017 for the first Praluent prescription. Therefore, the MAH decreased the projected number of sites and patients enrolled in Wave 1 to 25 sites and 75 patients, as base case (or at the minimum), and 30 sites and 90 patients, as best case, assuming an average of 3 patients per site. The half-width of 95% CI for Wave 1 would then be 11.7% (95% CI = [31.3; 54.7]) for this Wave. For Wave 2 and Wave 3, minimum 90 sites and 400 patients were deemed feasible for enrollment at that time (Table 1).

Twenty sites enrolled 68 patients in Wave 1 and 61 sites enrolled 251 patients in Wave 2. Although the remediation actions as outlined in Amended protocol 01 (21 December 2018) (Annex 3) are being taken during Wave 3 enrollment, the target total sample size of 875-890 will not be reached at the end of the recruitment period of the Wave 3. Based on the current projection, the total number of sites enrolled in Wave 3 is expected to be ranging from 36 to 63 due to both recruitment challenges and the impact of Coronavirus disease 2019 (COVID-19) at the time of sites selection, and these sites are expected to enroll 135 to 255 patients. However, best efforts will be made to enroll as many eligible patients as possible not limiting to 255 in Wave 3. The total number of patients enrolled in this study is expected to range from approximately 454 to 574.

Table 1 - Study size

	Patients planned in 2018	Sites planned in 2018	Actual/projected Patients	Actual/projected sites
Wave 1	75-90	25-30	68	20
Wave 2	400	90	251[a]	61
Wave 3	400	90	135-255[b]	36-63
Total	875-890	205-210	Approximately 454-574	Approximately 117-144

a 251 patients will be included in the Wave 2 interim report. Additional 25 patients may be available in the final study report once queries are resolved, which may bring the total patient number in Wave 2 to 276.

b Best efforts will be made to enroll as many eligible patients as possible not limiting to 255 in Wave 3.

Data analysis:

Descriptive analyses will be conducted for each wave separately. In addition, analyses will be conducted using all the data obtained from all 3 waves. Point estimates of proportions and 95% confidence intervals will be calculated. For continuous outcome measures, means and standard deviations will be calculated.

The following descriptive analyses will be presented according to different parameters:

- Primary analyses:
  - Occurrence of very low LDL-C levels (both definitions of very low LDL-C <25 mg/dL [0.65 mmol/L] and <15 mg/dL [0.39 mmol/L] will be presented),
  - Evolution of LDL-C level after the occurrence of very low LDL-C level,
  - Change in treatment after the occurrence of very low LDL-C level.
- Secondary analyses:
  - The starting dose of Praluent,
  - The dosage regimen modification of Praluent,
  - Timing of LDL-C tests,
  - Discontinuation of Praluent: reasons will be described, if available,
  - Reason for Praluent prescription,
  - Adverse events.

Statistical tests will be performed at the 5% global significance level using 2-sided tests.

Study timelines:

Table 2 - Study timeline

Wave	Eligibility Period	Observational Period (6-Month Period After the Index Date for each patient)	Physician Recruitment, Regulatory[a] and Ethics Committees Submission, Patient Recruitment, and Data Abstraction
1	Mar 2017- Jun 2017	Mar 2017-Dec 2017	Q2 2018-Q1 2019
2	Jul 2017-Jun 2018	Jul 2017-Dec 2018	Q1 2019-Q1 2020
3	Jul 2018-Jun 2019	Jul 2018-Dec 2019	Q1 2020-Q1 2021

a If applicable.
Q1: first quarter; Q2: second quarter.

Milestones:

Interim reports:

Wave 1: in the third quarter (Q3) of 2019;

Wave 2: in Q3 2020;

Final report:

Wave 3: in Q3 2021.

Note: the final report will include the results of Wave 3 and the overall results.

5 AMENDMENTS AND UPDATES

DOCUMENT HISTORY

Number	Date	Section of study protocol	Amendment or update	Reason
Amended protocol 02 version 1 (electronic 1.0)	09-Jul-2020	PASS information, Section 4, Section 7.1, Section 9.2 and Section 9.5	Amendment	• To align the study protocol with the current approved Praluent RMP • To update the projected number of sites and patients enrolled in Wave 3 and total sample size of the study
Amended protocol 01 version 1 (electronic 1.0)	21-Dec-2018	PASS Information, Section 4 to Section 6, and Section 9	Amendment	• To decrease the projected number of sites and patients enrolled in Wave 1 • To modify the study design for Waves 2 and 3 to increase the likelihood of enrollment
Original Protocol version 1 (electronic 7.0)	08-Mar-2018	Not applicable	Not applicable	Not applicable

AMENDED PROTOCOL 02 (09-JUL-2020)

OVERALL RATIONALE FOR THE AMENDMENT

In the Praluent RMP approved by the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC), as endorsed by CHMP opinion dated 23 September 2015, the dosing recommendation was presented as a routine risk minimization measure for the missing information on the "Clinical impact of very low LDL-C for extended period of time". Following a Type II variation for Praluent submitted on 14 August 2019 to modify the EU RMP, the missing information "clinical impact of very low LDL-C for extended period of time" was removed from the RMP in the CHMP opinion dated 16 January 2020. This DUS is still part of the RMP but is not related to the missing information "clinical impact of very low LDL-C for extended period of time".

This amended protocol also aims to provide the actual sample sizes achieved for Waves 1 and 2 and the projected number of sites and patients to be enrolled in Wave 3.

The actual number of sites and patients enrolled in the study in the first two waves were:

- 20 sites and 68 patients in Wave 1.
- 61 sites and 251 patients in Wave 2.

Based on the current projection, the total number of sites enrolled in Wave 3 is expected to be ranging from 36 to 63 instead of the originally planned 90 sites due to both recruitment challenges and the impact of Coronavirus disease 2019 (COVID-19) at the time of site selection, and these sites are expected to enroll 135-255 patients in Wave 3 instead of the originally planned 400 patients from 90 sites and best efforts will be made to enroll as many eligible patients as possible not limiting to 255 in Wave 3. Therefore, the total number of patients enrolled in this study is expected to range from approximately 454 to 574 and the target total sample size of 875-890 will not be reached at the end of the recruitment period of the Wave 3.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 4 Abstract and Section 7.1 Background	Added: …as endorsed by CHMP opinion dated 23 September 2015. Following a Type II variation for Praluent submitted on 14 August 2019 to modify the EU RMP, the missing information "clinical impact of very low LDL-C for extended period of time" was removed from the RMP in the CHMP opinion dated 16 January 2020. This DUS is still part of the RMP but is not related to the missing information "clinical impact of very low LDL-C for extended period of time".	To align the study protocol with the current Praluent RMP
Section 4 Abstract, Section 9.2.4.1 Physician selection, and Section 9.5 Study size	Provided the actual sample sizes and sites achieved for Waves 1 and 2 and the projected number of sites and patients to be enrolled in Wave 3 and the total sample size of the study.	To update the projected number of sites and patients to be enrolled in Wave 3 due to both recruitment challenges and the impact of COVID-19 at the time of sites selection
PASS information, Section 4 Abstract and Section 9.2 Setting	Revised: for Wave 2 and Wave 3, the following countries have been selected based on the extent of patient exposure estimated from EU sales data: Austria, Belgium, Germany, Italy, Netherlands, Spain, and United Kingdom in Wave 2; Austria, Belgium, Italy, Netherlands, Spain, and United Kingdom in Wave 3.	To provide the actual country list included in the Wave 2 and Wave 3.
Section 7.1 Background	Updated the indications for Praluent in Europe	To reflect the current indications in Europe according to the latest version of SmPC dated 02 June 2020.
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

6 MILESTONES

Milestone	Planned date
Eligibility period	Wave 1: Mar 2017-Jun 2017
	Wave 2: Jul 2017-Jun 2018
	Wave 3: Jul 2018-Jun 2019
Observational period (6-month period after the index date for each patient)	Wave 1: Mar 2017-Dec 2017
	Wave 2: Jul 2017-Dec 2018
	Wave 3: Jul 2018-Dec 2019
Physician recruitment, regulatory[a] and ethics committees submission, patient recruitment and data abstraction	Wave 1: Q2 2018-Q1 2019
	Wave 2: Q1 2019-Q1 2020
	Wave 3: Q1 2020-Q1 2021
Interim reports	Wave 1: in Q3 2019
	Wave 2: in Q3 2020
Final report of study results[b]	Wave 3: in Q3 2021

a If applicable.

b The final report will include the results of Wave 3 and the overall results.

Q1: first quarter; Q2: second quarter; Q3: third quarter.

7 RATIONALE AND BACKGROUND

7.1 BACKGROUND

Praluent® (brand name of alirocumab) is a fully human monoclonal antibody that binds with high affinity to proprotein convertase subtilisin kexin type 9 (PCSK9) across several species. PCSK9 binds to low-density lipoprotein receptors (LDLRs) and promotes the internalization and removal of LDLR on hepatocytes.

By blocking PCSK9 binding to LDLR, Praluent increases the number of LDLR available to remove LDL-C from circulation. Hence, Praluent is an effective treatment to lower plasma LDL-C levels.

The European Commission granted a marketing authorization valid throughout the European Union for Praluent (brand name of alirocumab) on 23-Sep-2015.

According to the latest version SmPC dated 02 June 2020 (5), the current indications for Praluent in Europe are:

Primary hypercholesterolaemia and mixed dyslipidaemia

Praluent is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, 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.

Established atherosclerotic cardiovascular disease

Praluent is indicated in adults with established atherosclerotic cardiovascular disease to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors:

- in combination with the maximum tolerated dose of a statin with or without other lipid-lowering therapies or,
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

LDL-C levels in Praluent-treated patients:

In the context of evaluation of very low plasma LDL-C levels, two thresholds were set in the Praluent (alirocumab) clinical studies and assessed in the submission dossier:

- A 25 mg/dL (0.65 mmol/L) threshold based on the 2008 American College of Cardiology Foundation and American Diabetes Association consensus report (1) stating that: 1) the lower limit to safe and effective cholesterol lowering has not been established; 2) individuals with genetic mutations causing lifelong very low LDL-C levels appear to avoid CVD and are also free of abnormalities that might conceivably be linked to their very low plasma cholesterol levels, and 3) a plasma level of 25 mg/dL (0.65 mmol/L) for LDL-C was estimated to be sufficient to supply peripheral cholesterol needs, based on in vitro cell cultures (2).
- A 15 mg/dL (0.39 mmol/L) threshold was chosen arbitrarily.

In the global pool of Phase 2 and Phase 3 studies, a total of 1426 (42.7%) patients treated with Praluent (alirocumab) had at least 1 value of LDL-C<25 mg/dL (0.65 mmol/L), including 839 (25.2%) patients with 2 consecutive values of LDL-C<25 mg/dL separated by at least 21 days. The LDL-C <25 mg/dL (<0.65 mmol/L) levels mostly occurred in the LTS11717 (LONG-TERM) study, where all patients were initiated and maintained on the 150 mg Q2W dose, regardless of the baseline LDL-C value or the response to treatment. No particular safety concerns were observed in this subgroup of patients (3). Nonetheless, due to limited data collected from patients with very low LDL-C (<25 mg/dL) exposed to Praluent for over 18 months, "Clinical impact of very low LDL-C for extended period of time" was considered as a missing information in the Praluent RMP, as endorsed by CHMP opinion dated 23 September 2015. Following a Type II variation for Praluent submitted on 14 August 2019 to modify the EU RMP, the missing information "clinical impact of very low LDL-C for extended period of time" was removed from the RMP in the CHMP opinion dated 16 January 2020. This DUS is still part of the RMP but is not related to the missing information "clinical impact of very low LDL-C for extended period of time".

Praluent dosing recommendation:

Praluent is currently available as 75 and 150 mg/mL solution for injection, as 1 mL single-use pre-filled pen and 1 mL single-use pre-filled syringe.

The following dosing recommendations were stated in the Section 4.2 Posology and method of administration of the SmPC of Praluent latest approved on 02 June 2020 (5):

"The usual starting dose for Praluent is 75 mg administered subcutaneously once every 2 weeks. Patients requiring larger LDL-C reduction (>60%) may be started on 150 mg once every 2 weeks, or 300 mg once every 4 weeks (monthly), administered subcutaneously.

The dose of Praluent can be individualised based on patient characteristics such as baseline LDL-C level, goal of therapy, and response. Lipid levels can be assessed 4 to 8 weeks after treatment initiation or titration, and dose adjusted accordingly (up-titration or down-titration). If additional LDL-C reduction is needed in patients treated with 75 mg once every 2 weeks or 300 mg once every 4 weeks (monthly), the dosage may be adjusted to the maximum dosage of 150 mg once every 2 weeks."

7.2 RATIONALE

In the RMP approved by the EMA's PRAC, dated 23 September2015, a PASS was implemented as part of pharmacovigilance plan of the RMP for Praluent, in response to PRAC request.

At that time, only 2 dosage regimens, 75 mg once every two weeks and 150 mg once every two weeks, were approved in European Union; therefore, this drug utilization study was designed to assess, in Europe, the effectiveness of the dosing recommendation included in the labeling for these 2 approved dosage regimens to avoid very low LDL-C levels; however, a new dosage regimen of 300 mg once every 4 weeks (monthly) was approved in European Union and the updated SmPC was approved on 14 November 2016 (6). Consequently, the study design was updated to reflect the administration of the new approved dosage regimen in a real world setting.

8 RESEARCH QUESTION AND OBJECTIVES

8.1 PRIMARY OBJECTIVE

The primary objective of this study is to assess the effectiveness of the Praluent (brand name of alirocumab) dosing recommendations for the 3 dosage regimens approved to date, ie, 75 mg once every two weeks, 150 mg once every two weeks, and 300 mg once every 4 weeks (monthly) to avoid very low LDL-C levels.

8.2 SECONDARY OBJECTIVES

The secondary objective of this study is to describe the pattern of Praluent utilization in real-world clinical practice with respect to the dosing recommendations in the labelling of the 3 dosage regimens approved to date, ie, 75 mg once every two weeks, 150 mg once every two weeks, and 300 mg once every 4 weeks (monthly) to avoid very low LDL-C levels.

9 RESEARCH METHODS

9.1 STUDY DESIGN

This study is a non-interventional (with regard to the therapeutic strategy), retrospective cohort study in patients who were initiated with Praluent (brand name of alirocumab), 75 mg once every two weeks, 150 mg once every two weeks, or 300 mg once every 4 weeks (monthly).

The clinical setting and data sources of the study will mirror real life management of those patients.

9.2 SETTING

This study is planned to be conducted in European countries and consists of 3 waves. Germany, United Kingdom, Belgium, and Netherlands participated in Wave 1; for Wave 2 and Wave 3, the following countries have been selected based on the extent of patient exposure estimated from EU sales data: Austria, Belgium, Germany, Italy, Netherlands, Spain, and United Kingdom in Wave 2; Austria, Belgium, Italy, Netherlands, Spain, and United Kingdom in Wave 3. The availability of essential data, in particular the LDL-C values that will allow the MAH to assess the objectives of the study, will be ensured during the physician selection. According to the feasibility assessment result, the vast majority of the responding sites in the selected countries collect LDL-C values.

9.2.1 Duration of the study

The study will be conducted in 3 waves during 3 consecutive years.

The rationale for conducting the 3 waves when treatment patterns are evaluated across 3 different cohorts of Praluent prescribers and their patients is as follows:

- To confirm the effectiveness of the SmPC dosing recommendations risk minimization measures observed in the repeated waves.
- To observe the trend in practice over time, if any, by comparing findings across the 3 waves.
- Using 3 waves will also allow getting preliminary data available sooner, with the earliest availability at the end of the first wave.

After the first Praluent prescription identified during the eligibility period (Mar to Jun 2017 for Wave 1, Jul 2017 to Jun 2018 for Wave 2, and Jul 2018 to Jun 2019 for Wave 3), the observation period will last 6 months for each patient: from their first prescription to 6 months later, at the latest until the end of December 2017, 2018 and 2019, respectively.

After the end of the 6-month observation period, submission of appropriate documentation to Regulatory Authorities (if applicable according to local regulations) and/or Ethics Committees will be performed, in parallel, the physicians will be enrolled and informed of the main purpose of the study and upon all relevant approvals are obtained, the patients will be selected up to the first quarter (Q1) of 2019, 2020, and 2021 following the observation period, respectively.

The data will be collected retrospectively from the second quarter (Q2) 2018 to Q1 2019 in Wave 1, from Q1 2019 to Q1 2020 in Wave 2 and from Q1 2020 to Q1 2021 in Wave 3, respectively. Please see details in Figure 1 and Figure 2.

Figure 1 - Annual study progress in Wave 1

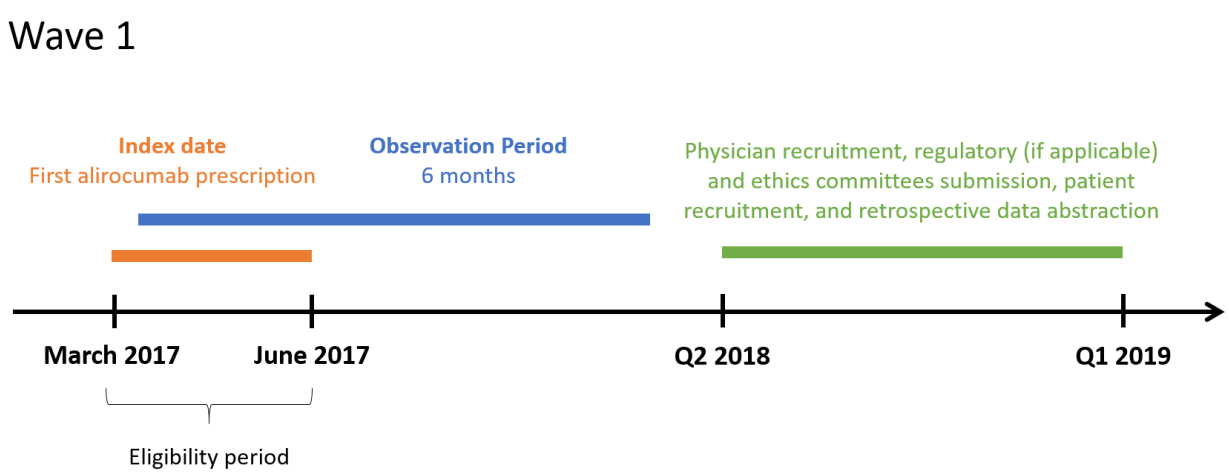
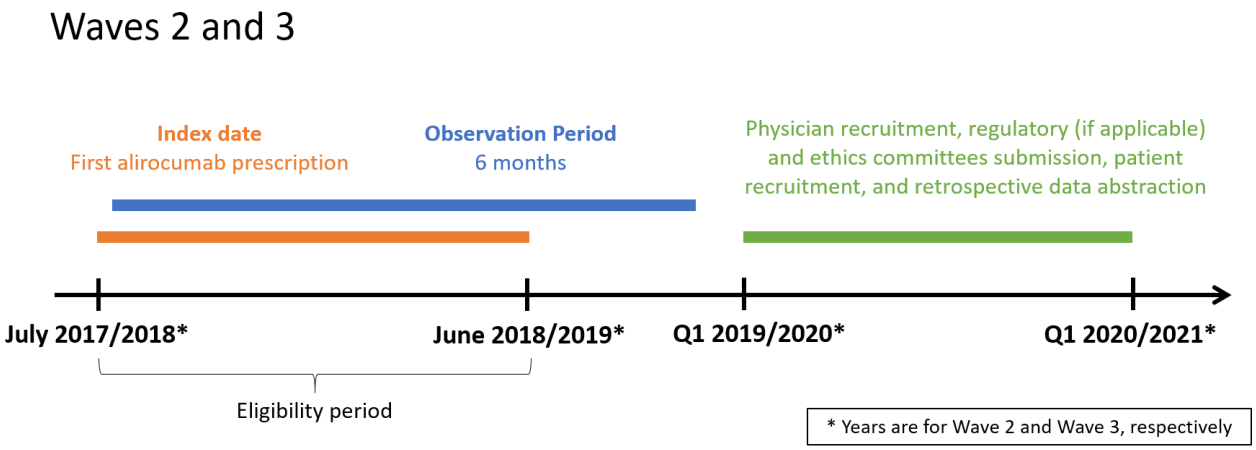


Figure 2 - Annual study progress in Waves 2 and 3



9.2.2 Eligibility criteria

9.2.2.1 Inclusion criteria

Physicians who meet the following inclusion criterion will be eligible to participate in this study:

I 01. At least one initial prescription of Praluent during the eligibility period.

Eligible patients for retrospective data collection will be those meeting the following criteria:

I 02. Initiated with Praluent following a first prescription during the eligibility period.

I 03. Signed written informed consent, if it is required by the country.

9.2.2.2 Exclusion criteria

Physicians who meet one or more of the following exclusion criteria will be excluded from this study:

E 01. Have participated in any randomized clinical trials with Praluent (alirocumab).

E 02. Have participated in a previous wave of this study.

Patients who meet one or more of the following exclusion criteria will be excluded from this study:

E 03. Have participated in any randomized clinical trials with Praluent (alirocumab).

E 04. Medical chart not retrievable, empty or missing.

9.2.3 Analysis populations

The analysis population will consist of all patients included in the study and meeting all inclusion criteria. This population will be the eligible population.

Physicians who included at least one patient in the patient analysis population will be part of the physicians' analysis population.

9.2.4 Modalities of recruitment

9.2.4.1 Physician selection

National prescriber databases containing health care professionals' information and their prescribing information, will be used to identify sites in each selected country.

For each wave, a 3-step process will be followed: identification from prescription database(s), selection, and remote recruitment.

- **Identification**: sites' prescribing volume of Praluent will be identified via Xponent database (or equivalent databases of prescriptions received in pharmacies). Additional databases will be selected in each country of interest to better identify the prescribers. Then, physicians/practices/institutions (depending on each country's data privacy limitations) with Praluent prescription during the eligibility period will be identified via OneKey database (or similar databases of physicians and/or hospital information). The prescribing physicians will be specialists (mainly, but not limited to, cardiologists, endocrinologists and internists) and/or general practitioners.

  The clusters and physicians that have the highest likelihood of having prescribed Praluent and of participating in the study will be contacted regardless of their level of prescription. Representativeness of study sample with respect to the prescription level will be assessed a posteriori in the analysis phase (details in Section 9.7.3).
- **Selection:** the selection of physicians/practices/institutions will be performed based on availability of eligible patients. The selection process will be summarized by country in the study reports.
  - A physician can only participate in 1 wave of this study, and no more than 2 physicians from the same practice/institution can participate in each wave of this study.
  - Physicians who have participated in any randomized clinical trials with Praluent (alirocumab) will be excluded from this study.
- **Recruitment**: physicians will then be recruited remotely (over the phone or by e-mail) after the end of the 6-month observational period:
  - The physician will be informed on the main purpose of the study, ie, assessing the effectiveness of the SmPC dosing recommendation to avoid very low LDL-C, collecting key characteristics and treatment approaches for Praluent-treated patients in a real world setting, and on the general design of the study (CRF, electronic platform). The physician will be informed that there is no need to interview his/her patients in order to conduct the study, except to get their consent in order to collect their data retrospectively, when informed consent is required by local regulation. Data availability from the 6-month observation period, and particularly critical variables such as LDL-C values, will be secured at the time of site selection through a questionnaire.
- A total of 20 physicians in Wave 1 and 61 physicians in Wave 2 were enrolled across all the participating countries. About 36 to 63 physicians are expected to be enrolled in Wave 3.

The detailed physician selection process will be described in a separate study plan which will be generated at study launch and updated during the conduct of the study, describing each wave separately.

It is likely that physicians who participate in this study may be different from those who do not with respect to specialty. It is anticipated that specialists are more likely to participate. The specialty, level of prescriptions, and reason for refusal (if available) will be described for the physicians who do not accept participation in the study.

9.2.4.2 Patient selection

Following site activation and staff training, the site staff will compile a patient roster from their prescription records according to the eligibility period.

For sites with more than 8 potential eligible patients, sites are asked to list their potential patients and assign them each a consecutive number. The CRO will use a random selection tool that randomly orders the previously consecutive numbers and instructs the sites which numbers were ranked as top 8. The site will look back at their list of patients and will enroll the patients with the assigned numbers that were ranked as the top 8. Should any of these 8 patients not be eligible for enrollment, the patient assigned to the next number (ie, ranked 9th) from the randomization tool will be approached.

When required by local regulation, site staff will contact patients for consent. The site might be facing the following scenarios:

- Remote consent for the patients who are not scheduled to return to the office within 1 month time. The site will contact the patient by phone to explain the study and will send the Informed Consent Form (ICF) to the patients who have interest to return, signed and dated. Patients will have the opportunity to ask questions over the phone and they will be able to decide freely if they wish to participate.
- Face to face consent for patients who will return to the office within 1 month. The ICF will be signed and dated during this visit.

Site staff will keep a patient log to track anonymous information on the patients who refuse to participate (please see Section 9.6.4).

For each participating physician, up to 8 patients will be randomly enrolled. If the number of patients treated by physician is less than 8, no random selection will be needed. If there are 2 physicians from the same practice/institution participating in the same wave of the study, the combined total number of patients selected from these 2 physicians will be limited to 10 and a random selection of 10 patients will be performed.

Patients who have participated in any randomized clinical trials of Praluent (alirocumab) will be excluded from this study.

9.3 VARIABLES

Physicians' characteristics will be collected at the time of physician recruitment.

All patient variables from the index date (the date of the first prescription of Praluent) to the end of the observational period will be retrospectively collected:

- Patient characteristics (please refer to Section 9.3.2).
- Prescriptions of Praluent and other lipid-lowering drugs in the observational period.

- LDL-C value prior to or on the index date and all LDL-C values during the observation period.
- Any adverse event identified in the patient record during the retrospective chart review (please refer to Section 11).

9.3.1 Physician characteristics

Physician level of Praluent prescription, specialty and/or setting type, and localities will be collected. The physician will also be asked if he is/was involved in another observational study of Praluent.

9.3.2 Patient characteristics

1. Demographics: age, sex.
2. Height, weight, and body mass index (where available).
3. Smoking status (ie, Never Smoker, Former Smoker, or Current Smoker).
4. Medical history: at baseline (prior to or on the index date):
   (1) Diagnosis of hypercholesterolemia,
   (2) Type of familial hypercholesterolemia,
   (3) Clinical atherosclerotic cardiovascular disease (ASCVD) that includes acute coronary syndromes, or history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, ischemic stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin,
   (4) Hypertension,
   (5) Diabetes,
   (6) Congestive heart failure,
   (7) Arrhythmia,
   (8) Chronic kidney disease (Stage 3 or 4).

9.3.3 Prescriptions of Praluent

1. Date of initial prescription,
2. Dose and dosing frequency,
3. Number of doses prescribed,
4. Number of renewals, date(s) of renewal(s), and dosage and dosing frequency at renewals,
5. Reason for any Praluent dosage regimen modification.

9.3.4 Discontinuation of Praluent, if relevant

1. Date of discontinuation;
2. Reason for discontinuation:

   (1) Description of reason, if available.

   (2) Unspecified.

9.3.5 Prescription of other lipid lowering drugs

Prescription of other PCSK-9 inhibitors, statins, ezetimibe, bile acid-binding resins, nicotinic acid and fibrates, at the time of the index prescription of Praluent and any prescriptions during the observational period:

1. Generic name of drug (international nonproprietary name [INN]);
2. Date of prescription;
3. Dose;
4. Dosing frequency.

9.3.6 LDL-C values

The most recent value prior to or on the index date (baseline) and all values in the observational period:

1. Date of the test.
2. Value of LDL-C.

9.3.7 Adverse events

An adverse event (AE) is any untoward medical occurrence in a patient or in a clinical investigation subject administered a pharmaceutical product, and which does not necessarily have a causal relationship with that treatment. An adverse event can thus be any abnormal laboratory finding, symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not caused by that product.

Adverse events will be collected from the initiation of Praluent until the end of the 6-month observational period with the following details:

1. Nature of AE, such as hospitalization, onset of new disease, a new symptom, worsening of an existing condition, or lab abnormalities…
2. Start date/end date and outcome
3. Action taken with Praluent, if any: discontinuation, delay, or dose change.

9.3.8 Date on which the patient is no longer managed by the treating physician

Date on which the patient is no longer managed by the treating physician will be collected, if it is applicable.

9.4 DATA SOURCES

As soon as the ICF is signed and dated by the patient, the data abstraction can be started. Hence, data from medical records (either EMRs or paper source files) for each participating patient will be extracted and completed by site personnel and/or trained and authorized external abstractors using an e-CRF.

For patients in whom Praluent will be initiated by a given physician, and who will then be followed by another physician, all efforts will be made to collect data from these multiple caregivers.

9.5 STUDY SIZE

9.5.1 Determination of sample size

According to the global pool of Phase 2 and Phase 3 studies, 42.7% of patients treated with Praluent (alirocumab) had at least 1 value of LDL-C <25 mg/dL[1], regardless of the dose of Praluent received and the baseline LDL–C level. Compared to what is expected in the real clinical practice, this percentage is probably overestimated as the very low LDL-C levels occurred mostly during the Long Term study in which patients were initiated and maintained at 150 mg throughout the study, independent of the LDL-C baseline, to evaluate the long term safety of Praluent administered at the highest dose. In Wave 1 of the study, a total of 61 patients had at least one LDL-C value available during the 6-month observation period (irrespective of baseline LDL-C data availability); among those, three patients (4.9%) had an LDL-C level of <25mg/dL.

The following table shows the exact 95% confidence intervals for a range of possible proportions of patients with very low LDL-C value for different study sizes (<25 mg/dL or <0.65 mmol/L). For the global analysis gathering the 3 waves with total number of patients ranging from approximately 454-574 and assuming approximately 5% of the patients will have an LDL-C level of <25 mg/dl based on the observed data for Wave 1, the half-width will range from 1.85% (95% CI = 3.4, 7.1) to 2.1% (95%CI=3.2, 7.4) for the observed proportion of 5% (Table 3), which is deemed sufficient.

[1] In the clinical trials, only patients who achieve 2 consecutive calculated LDL-C <25 mg/dL were monitored according to a specific process and only these figures were presented in each CSR and submitted files.

Table 3 - Exact 95% confidence intervals for different study sizes and possible proportions of patients with very low LDL-C level (%)

% patients with very low LDL-C	Number of Patients						
%	68	135	251	255	454	574	875 (total number planned in 2018)
1	0 , 7.1	0.1 , 4.5	0.2 , 3.2	0.2 , 3.1	0.3 , 2.4	0.4 , 2.2	0.5, 1.9
2	0.1 , 8.8	0.4 , 6	0.7 , 4.6	0.7 , 4.6	0.9 , 3.8	1 , 3.5	1.2, 3.2
5[a]	**1.2 , 13.2**	**2 , 10.2**	**2.7 , 8.5**	**2.7 , 8.4**	**3.2 , 7.4**	**3.4 , 7.1**	**3.7, 6.7**
10	4 , 19.7	5.5 , 16.3	6.6 , 14.4	6.6 , 14.4	7.4 , 13.1	7.7 , 12.8	8.1, 12.2
20	11.3 , 31.5	13.6 , 27.7	15.2 , 25.5	15.3 , 25.4	16.4 , 24	16.8 , 23.5	17.4, 22.8
30	19.5 , 42.3	22.4 , 38.5	24.4 , 36.1	24.4 , 36	25.8 , 34.4	26.3 , 33.9	27.0, 33.2
42.7[b]	**30.8 , 55.3**	**34.2 , 51.5**	**36.5 , 49.1**	**36.5 , 49.0**	**38.1 , 47.4**	**38.6 , 46.9**	**39.4, 46.1**
50	37.6 , 62.4	41.3 , 58.7	43.6 , 56.4	43.7 , 56.3	45.3 , 54.7	45.8 , 54.2	46.6, 53.4
70	57.7 , 80.5	61.5 , 77.6	63.9 , 75.6	64.0 , 75.6	65.6 , 74.2	66.1 , 73.7	66.8, 73.0
90	80.3 , 96	83.7 , 94.5	85.6 , 93.4	85.6 , 93.4	86.9 , 92.6	87.2 , 92.3	87.8, 91.9

a Of note, we expect to observe a lower percentage based on the findings of Wave 1. In Wave 1 of the study, a total of 61 patients had at least one LDL-C value available during the 6- month observation period (irrespective of baseline LDL-C data availability); among those, three patients (4.9%) had an LDL-C level of <25mg/dL.

b 42.7% is the percentage of patients with at least one very low LDL-C (<25 mg/dL or <0.65 mmol/L) observed in the Phase 2 and 3 trials.

9.5.2 Sample size

In the initial plan, it was planned to recruit 1200 patients in total for the 3 waves in the selected European countries, depending on the reimbursement status of Praluent in each country, ie, about 400 patients per wave.

According to the feasibility results, the number of physicians might be limited in each country. The initial estimate was that a minimum of 100 physicians were needed to reach the recruitment goal of 400 patients per wave. It was anticipated that given the uncertainty of Praluent market penetration in each country, the number of sites might need to be adjusted in order to reach the target of 400 patients per wave.

In 2018, the MAH encountered challenges in Wave 1 recruitment that prevented it from reaching the target sample size in the anticipated timeframe. Despite the remediation actions taken by the MAH, the site enrollment projections demonstrated that the initial plan of recruiting 400 patients from 100-138 sites for Wave 1 could not be accomplished due to continued lower than expected positive site response rate, low Praluent prescriptions, and limited patient eligibility period of 4 months from March 2017 to June 2017 for the first Praluent prescription. Therefore, the MAH decreased the projected number of sites and patients enrolled in Wave 1 to 25 sites and 75 patients, as base case (or at the minimum), and 30 sites and 90 patients, as best case, assuming an average of 3 patients per site. Reducing the number of patients in Wave 1 to 75 impacted the precision of the proportion estimate; the half-width of the 95% confidence interval was enlarged from a maximum half-width of 4.9% to 11.8%, which was still deemed sufficient at that stage in the study. For Wave 2 and Wave 3, minimum 90 sites and 400 patients were deemed feasible for enrollment at that time.

Twenty sites enrolled 68 patients in Wave 1 and 61 sites enrolled 251 patients in Wave 2. Although the remediation actions as outlined in Amended protocol 01 (December 21, 2018) (Annex 3) are being taken during Wave 3 enrollment, the target total sample size of 875-890 will not be reached at the end of the recruitment period of the Wave 3. Based on the current projection, the total number of sites enrolled in Wave 3 is expected to be ranging from 36 to 63 due to both recruitment challenges and the impact of Coronavirus disease 2019 (COVID-19) at the time of sites selection, and these sites are expected to enroll 135 to 255 patients. Best efforts will be made to enroll as many eligible patients as possible, not limiting to 255 in Wave 3. The total number of patients enrolled in this study is expected to range from approximately 454 to 574 (Table 1).

9.6 DATA MANAGEMENT

9.6.1 Data collection schedule

Data will be retrospectively collected after the end of each of the 3 observation periods and after the physicians have been selected and recruited for participation.

9.6.2 Data collected

Please refer to Section 9.3.

9.6.3 Site/Physicians questionnaire

Physicians who will not accept to participate will be described (specialty and level of prescriptions, reason for refusal, where available).

For physicians who will accept to participate, a physician questionnaire will be put in place to collect the physician's data mentioned in Section 9.3.1, and the potential availability of critical variables, such as LDL-C values, that need to be collected. An ad hoc question will be included in the Site Information Questionnaire used at Site Selection in order to qualify sites for participation.

9.6.4 Patient/Subject tracking log

A tracking log will be used to specify the reason for non-inclusion of the non-enrolled patients. To comply with data privacy requirement, data collected on the tracking log will be fully anonymous:

- Patient number (#): 1, 2….
- Included: Yes/No.
- Reason for non-inclusion.

9.6.5 Patient data

Data collected are mentioned in Section 9.3.

9.7 DATA ANALYSIS

This section provides specifications for preparation of final Statistical Analysis Plan (SAP), which will be issued prior to database lock of the first wave. Any differences compared to this statistical section should be identified and documented in final SAP.

9.7.1 Primary analysis

Descriptive analyses will be conducted for each wave separately. In addition, analyses will be conducted using the entire data of all 3 waves.

Point estimates of proportions and 95% confidence intervals will be calculated.

Data will be summarized using mean, first quartile, median, third quartile, standard deviation and range for continuous parameters and counts, percentages and 95% confidence intervals if needed for categorical parameters. The analyses will be performed, overall, by countries, and for specific analyses (starting dose of Praluent, occurrence of very low LDL-C level) will also be presented based on baseline LDL-C levels.

The following descriptive analyses will be presented on the eligible population:

A. Occurrence of very low LDL-C level

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

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

1. The proportion of patients who have at least 1 very low LDL-C level during the 6-month observational period:
   (1) In the whole analysis population,
   (2) According to baseline LDL-C level (<70; 70 to <100; 100 to <130; 130 to <160; 160 to <190; ≥190mg/dL),
   (3) According to Praluent starting dose.
2. All occurrences of very low LDL-C levels will be classified according to the Praluent regimen received at the time of the corresponding LDL-C test.

B. Evolution of LDL-C level after the occurrence of very low LDL-C level

1. Among the patients who have a LDL-C level of <25 mg/dL (0.65 mmol/L) at any dose, the proportions of patients whose LDL-C level returns to ≥25 mg/dL (0.65 mmol/L) within 8 weeks after the lab test, if data available, and at any time until the end of the 6-month observational period after index date, respectively.
   (1) Overall,
   (2) By the action of dosage regimen modification or discontinuation of Praluent, or change in dosing frequency of Praluent, or lowering doses of other lipid-lowering drugs, or discontinuation of other lipid-lowering drugs.
2. Same analysis will be conducted for the patients who have LDL-C level <15 mg/dL (0.39 mmol/L).

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

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

Among the patients who have a very low LDL-C level at a specific dosage regimen, within 8 weeks after the lab test and at any time until the end of the 6-month observational period after index date, respectively:

(1) The proportion of patients for whom the dose of Praluent is changed to another dose regimen,
(2) The proportion of patients for whom Praluent is discontinued,
(3) The proportion of patients for whom the dosing frequency of Praluent is changed at least once,
(4) The proportion of patients for whom the doses of other lipid-lowering drugs are decreased at least once,
(5) The proportion of patients for whom other lipid-lowering drugs are discontinued,
(6) The proportion of patients for whom no change in Praluent treatment or dose and/or other lipid-lowering drugs have been made.

9.7.2 Secondary analysis

A. The starting dose of Praluent

1. The proportion of patients for whom Praluent is started at 75 mg Q2W, 150 mg Q2W, or 300 mg Q4W:
   (1) In the whole analysis population;
   (2) According to baseline LDL-C level:
      a) <70 mg/dL (<1.81 mmol/L),
      b) 70 to <100 mg/dL (2.59 mmol/L),
      c) 100 to <130 mg/dL (3.37 mmol/L),
      d) 130 to <160 mg/dL (4.14 mmol/L),
      e) 160 to <190 mg/dL (4.92 mmol/L),
      f) ≥190 mg/dL (4.92 mmol/L).
   (3) According to diagnosis of heterozygous familial hypercholesterolemia, ASCVD, diabetes and chronic kidney disease.
2. Mean baseline LDL-C level by starting dose.

B. Modification of the dosage regimen of Praluent

1. The proportion of patients for whom the dosage regimen of Praluent is modified during the 6-month observational period.

   An estimate of the event rate at the end of the 6 months by a Kaplan-Meier approach.
2. Among the patients for whom the dosage regimen of Praluent is modified from the initial dose during the 6-month observational period:
   (1) The median time to dosage regimen modification estimated using time-to-event approach (Kaplan Meier methodology),
   (2) The mean LDL-C levels prior to and at least 4 weeks after the dosage regimen modification respectively,
   (3) The proportion of patients for whom the dosage regimen is adjusted back to the initial regimen.

C. Timing of LDL-C tests

1. The mean time from the first prescription of Praluent to a LDL-C test in patients having a LDL-C test after initiation of Praluent and the median time estimated using a Kaplan-Meier approach in all patients having a follow-up,
2. The mean time from a dosage regimen modification to a LDL-C test in patients having a LDL-C test after initiation of Praluent and the median time estimated using a Kaplan-Meier approach in all patients having a follow-up.

D. Discontinuation of Praluent

1. Proportion of patients for whom Praluent is discontinued during the 6-month observational period after index date:
   (1) Overall,
   (2) By starting dose.
2. Among the patients for whom Praluent is discontinued:
   (1) Proportion of patients on each dose regimen (75 mg Q2W versus 150 mg Q2W versus 300 mg Q4W) prior to discontinuation,
   (2) Proportions of patients who had LDL-C <25 mg/dL (0.65 mmol/L) and <15 mg/dL (0.39 mmol/L) prior to discontinuation, respectively,
   (3) Proportion of patients according to each reason for discontinuation, if available,
   (4) Proportion of patients who restart Praluent in the 6-month observational period.

E. Reason for Praluent prescription

Proportion of patients with LDC-C levels ≥70 mg/dL with statins +/- other lipid lowering therapies and having at least one criterion of a high or very high cardiovascular risk.

F. Adverse events

Number and proportion of patients with AE during the observational period will be presented:

1. Overall.
2. AEs that are co-reported with a subsequent change in the Praluent administration (ie, it is written in the medical chart that the Praluent administration is changed due to the AE, please refer to Section 11 for AE details).

9.7.3 Sensitivity analysis regarding the physicians selection

Physicians who are/were involved in an observational study on Praluent are allowed to participate in this study. If these physicians provided at least 15% of the patients in this study then, to assess if this constitutes a bias, all analyses will be conducted separately in patients who were managed by them and in patients who were managed by physicians who had never participated in an observational study on Praluent.

The MAH plans to assess the representativeness of study sample with respect to the level of prescription a posteriori in the analysis phase. This analysis will stratify data by physician usage patterns to understand how they might impact dosing recommendations and assess the effectiveness of the Praluent dosing recommendations with regard to the occurrence of low LDL-C levels and will consist of:

a) The MAH will be collecting information on the level of prescription via a case report form (CRF) on the enrolled physicians. The final selected study sample of Praluent prescribers will be compared to the population of Praluent prescribers

identified from the Xponent or equivalent databases, with respect to the level of prescription.

b) If the groups (ie, high, medium or low prescribers) are not balanced in a similar way, and if representativeness cannot be assumed, results will be presented by stratifying the level of prescription in each interim report and the final study report.

c) As deemed appropriate, statistical techniques will be applied in the analysis phase to ensure the groups are representative with respect to the level of prescription.

9.7.4 Interim analysis

A separate descriptive analysis will be performed for each wave separately (1, 2, and 3) once the 6-month observation period data have been retrospectively collected, so that any potential concern can be addressed earlier.

In addition, analyses will be conducted using all the data obtained from the 3 waves and will be included in the final report.

9.8 QUALITY CONTROL

9.8.1 Data collection, validation and data quality control at MAH/CRO delegated by the MAH level

Data will be collected using electronic CRF. The e-CRFs will be completed directly by site personnel and/or by a trained external medical record abstractor through a secure, easy to use and reliable web-based electronic data capture (EDC) platform. As an optional service requested by sites or as required to complete data abstractions within the defined time period, it is assumed that the CRO delegated by the MAH will perform data abstractions visits.

The computerized handling of the data by the MAH after receipt of the CRFs may generate additional requests to which the participating physician is obliged to respond by confirming or correcting the data questioned in the EDC. The requests with their responses will be appended to the CRFs held by the physician and the MAH.

Additional details regarding data collection and validation procedures will be detailed in appropriate operational documents.

9.8.2 Data quality control at site level

Type of data quality control (monitoring visit and/or phone QC) and the percentage of the sites that will be controlled are developed in this section.

Initiation visits: once all regulatory approvals and contracts are in place, a remote initiation visit per site will be conducted. Sites will be trained on the study protocol and procedures during this visit.

Monitoring visits: the monitoring approach employs a combination of remote and for cause monitoring visits in case quality risks are identified (eg, missing data, delays in entering the data in the system, delay in answering queries).

Data QC will be performed in 10% of the active sites (which have enrolled at least one patient) chosen at random in each country. If specific issues are identified in some sites or countries (see above), the percentage of QC in the concerned site/country or in all sites/countries must be appropriately increased and corrective actions must be set up.

Quality control will be performed by qualified designated personnel in each country.

The methodology of data QC and appropriate consecutive corrective actions will be detailed in the study manual.

9.9 LIMITATIONS OF THE RESEARCH METHODS

Selection bias

Potential limitations of the study design include physicians' enrollment bias. It is likely that physicians who participate in this study may be different from those who do not with respect to specialty. It is anticipated that specialists are more likely to participate. Efforts will be made to ensure an appropriate representation of physician specialty in the study.

A random selection of patients at the practice level will alleviate potential selection bias and limit notably channeling bias.

The clusters and physicians that have the highest likelihood of having prescribed Praluent and of participating in the study will be contacted regardless of their level of prescription. Representativeness of study sample with respect to the prescription level will be assessed a posteriori in the analysis phase (Section 9.7.3).

In order to avoid bias due to the awareness of the study objectives, a different group of physicians that has not participated in any previous waves of the study will be selected.

The quality of medical charts review

As this study involves multiple physicians from different countries, the quality and quantity of medical information available from medical charts may vary by clinics and hospitals. Additionally, medical charts may not be obtained from all patients or physicians. Data availability on 6-month observation period, in particular availability of critical variables, will be secured at the time of site selection through a questionnaire.

Strategies to prevent missing data will be put in place, such as:

- Collecting only critical data elements to minimize site burden.
- Including "not applicable" and "not done" on case report forms to differentiate those from values that are truly unknown.

- Training of sites and data abstractors regarding data collection.
- Checking for pattern of missing data at regular intervals and addressing any issues with targeted operational strategies.

Medical chart review will be conducted to abstract data; as such there will be no direct patient contact involved.

Data from the observational period will be collected in a retrospective way. The retrospective approach avoids influencing physicians in their prescribing behavior as only patients already treated with Praluent will be considered. No guidance on treatments is given in the study protocol.

9.10 OTHER ASPECTS

Not applicable.

10 PROTECTION OF HUMAN SUBJECTS

10.1 RESPONSIBILITIES OF THE HEALTH CARE PROVIDERS

The Health Care Provider will perform the study in accordance with this protocol, applicable local regulations and international guidelines.

It is the Health Care Provider's responsibility to obtain written informed consent from patients prior to inclusion in the study, to fill in the CRF and to record all data pertinent to the investigation. She/he will ensure that the information reported in the CRF is precise and accurate. Where allowed and feasible, a trained external medical record abstractor can also complete the e-CRFs through a secure, easy to use and reliable web-based EDC platform.

Health Care Provider, and under the Health Care Provider's responsibility, should fully inform the patient of all pertinent aspects of the study including the written information. All patients should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient's retrospective data collection, the written ICF has to be signed, name filled in and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written ICF will be provided to the patient.

The ICF and the Information Sheet used by the Health Care Provider for obtaining the Patient's Informed Consent must be reviewed and approved by the MAH/CRO delegated by the MAH prior to submission to the appropriate Institutional Review Board/Independent Ethics Committee (IRB/IEC) for approval/favorable opinion.

10.2 RESPONSIBILITIES OF MAH/CRO DELEGATED BY THE MAH

The MAH/CRO delegated by the MAH is responsible for taking all reasonable steps and providing adequate resources to ensure the proper conduct of the study.

The MAH/CRO delegated by the MAH is responsible for:

- Local submission(s) complying with data protection rules.
- Providing the material for the study including translations into local language.
- Recruitment and remuneration of the participating physicians.
- Data collection and quality check.
- Data analyses.
- Providing the interim and final reports as requested.

10.3 ETHICAL, REGULATORY AND ADMINISTRATIVE RULES

10.3.1 Ethical principles

This study will be conducted in accordance with the principles laid by the 18th World Medical Assembly (Helsinki, 1964) and all subsequent amendments.

10.3.2 Laws and regulations

This study will be conducted in accordance with the Guideline on good pharmacovigilance practices (GVP) Module VIII-Post-authorisation safety studies; EMA/813938/2011 (7).

Each participating country should locally ensure all necessary regulatory submissions (eg, IRB/IEC) are performed in accordance with local regulations including local data protection regulations.

10.3.3 Data protection

The patient's personal data and physician’s personal data which may be included in the MAH/CRO delegated by the MAH database shall be treated in compliance with all local applicable laws and regulations.

When archiving or processing personal data pertaining to the physician and/or to the patients, the MAH/CRO delegated by the MAH shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

10.3.4 Insurance

Insurance certificate is not needed for observational studies with non-interventional procedures, except if required by local law. Participating countries may contract insurance according to local specific requirements. The process for obtaining insurance will be detailed in the study manual, if appropriate.

10.3.5 Secrecy agreement

All material, information (oral or written) and unpublished documentation provided to the physician (or any action carried out by the MAH/CRO delegated by the MAH on their behalf), including the present protocol and the CRF, are exclusive property of the MAH/CRO delegated by the MAH.

These materials or information (both global and partial) cannot be given or disclosed by the physicians or by any person of her/his group to unauthorized persons without the prior formal written consent of the MAH/CRO delegated by the MAH.

The physician shall consider as confidential all the information received, acquired or deduced during the study and will take all necessary steps to ensure that there is no break of confidentiality, other than for information to be disclosed by law.

10.3.6 Record retention

The physician shall arrange for the retention of study documentation until the end of the study. In addition the physician will comply with specific local regulations/recommendations with regards to patient record retention.

It is recommended that the physician retains the study documents at least five years (5) after the completion or discontinuation of the study, unless otherwise specified in the Physician Agreement in line with additional standards and/or local laws.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

10.3.7 Discontinuation of the study

The MAH/CRO delegated by the MAH can decide at any time and for any reason to discontinue the study. If in agreement with EMA, the decision will be communicated in writing to the participating physician.

Similarly, should the physician decide to withdraw from the study, she/he will have to inform the MAH/CRO delegated by the MAH in writing.

If appropriate, according to local regulations, Ethic Committee(s) (IRB/IEC) and Competent Authorities should be informed.

10.3.8 MAH/CRO delegated by the MAH audits and inspections by competent authorities

The physician agrees to allow the MAH/CRO delegated by the MAH auditors/Competent Authorities inspectors to have direct access to his/her study records for review, being understood that this personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information. In case no ICF is signed, access to the source document is not allowed.

The physician will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the competent authorities will be communicated by the physician to the MAH/CRO delegated by the MAH.

The physician shall take appropriate measures required by the MAH/CRO delegated by the MAH to take corrective actions for all problems found during the audit or inspections.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

In this study, medical chart review will be conducted to retrospectively collect data. Therefore, safety monitoring and safety reporting on an individual case level is not required by European Pharmacovigilance Guidelines (8). Reports of adverse events/reactions should only be summarized in the study report.

In this study, any adverse event identified in the patient record during the 6-month observational period will be collected regardless of seriousness or relationship to Praluent.

Adverse events will be listed separately in the following items:

- Adverse events that are suspected to be the reason for Praluent discontinuation.
- Adverse events recorded during the time preceding drug discontinuation or dose decrease (up to 1 month between AE and discontinuation).
- Other adverse events identified during the retrospective chart review and that have occurred at any other time point during treatment with Praluent.

Of note, “very low LDL-C” will not be considered as an adverse event in this study.

It is not possible to document these events and/or follow up the cases in a time manner beyond the information found in the medical charts given the retrospective data collection. In consequence, none of these AEs will be captured in the MAH Pharmacovigilance database nor reported to the agency in the time frame as defined in the GVP module VI (8). Instead, these events will be included and summarized in the interim and the final study reports.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1 OWNERSHIP AND USE OF DATA AND STUDY RESULTS

No use of the data will be possible without the authorization of the MAH/CRO delegated by the MAH conducting the study.

12.2 PUBLICATIONS

The protocol and final report of results will be submitted to the EMA and other appropriate entities according to the guidelines for PASS (7).

Annual interim reports and a final report will be submitted to EMA as applicable. The first interim report will be performed for Wave 1 and submitted in Q3 2019. The second interim report will be performed for Wave 2 and submitted in Q3 2020. The final report will include the results of Wave 3 and the overall results and be submitted in Q3 2021.

MAH is responsible for presentations and/or publications.

All manuscript/abstract/presentation must be submitted to the internal review of the MAH at least forty-five (45) calendar days in advance of submission. The MAH may request that the MAH's name and/or names of one or several of its employees appear or do not appear in such publication.

The MAH can delay publication or communication for a limited time in order to protect the confidentiality or proprietary nature of any information contained therein.

Any publication has to be disclosed onto the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) site within 2 weeks of acceptation by a Journal.

13 REFERENCES

1. Brunzell JD, Davidson M, Furberg CD, Goldberg RB, Howard BV, Stein JH, et al. Lipoprotein management in patients with cardiometabolic risk: consensus conference report from the American Diabetes Association and the American College of Cardiology Foundation. J Am Coll Cardiol. 2008;51(15):1512-24.

2. Brown MS, Goldstein JL. A receptor-mediated pathway for cholesterol homeostasis. Science. 1986;232(4746):34-47.

3. SAR236553/REGN727-Alirocumab [Investigator's Brochure, 13th edition] Tarrytown, NJ, Chilly-Mazarin, FR; Regeneron Pharmaceuticals, Sanofi-avenitis Recherche & Developpement. 2019 Oct 18.

4. Risk management plan for PRALUENT (Alirocumab), version 5.1 dated 6-Dec-2019.

5. Praluent [Summary of product characteristics]. Paris, FR: sanofi-aventis groupe; 2020 June 02

6. Praluent [Summary of product characteristics]. Paris, FR: sanofi-aventis groupe; 2016 Nov 14, p. 69.

7. European Medicines Agency (EMA), Heads of Medicines Agencies (HMA). Guideline on good pharmacovigilance practices (GVP), Module VIII – Post-authorisation safety studies; EMA/813938/2011 Rev 1. 2013 Apr 09. p. 27.

8. European Medicine Agency (EMA), Heads of Medicines Agencies (HMA). Guideline on good pharmacovigilance practices (GVP), Module VI – Management and reporting of adverse reactions to medicinal products. EMA/873138/2011 Rev 1. 2014 Sep 08. p. 90.

14 ANNEXES

Annex 1 List of stand-alone documents

Not applicable.

Annex 2 ENCePP checklist for study protocols

Study title:
A drug utilization study (DUS) of alirocumab in Europe to assess the effectiveness of the dosing recommendation to avoid very low LDL-C levels

Study reference number:
OBS14697

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[2]	☒	☐	☐	15, 18, 23
1.1.2 End of data collection[3]	☒	☐	☐	15, 18, 23
1.1.3 Study progress report(s)	☐	☒	☐	
1.1.4 Interim progress report(s)	☒	☐	☐	15, 18, 42
1.1.5 Registration in the EU PAS register	☐	☒	☐	
1.1.6 Final report of study results.	☒	☐	☐	15, 18, 42

Comments:

[2] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[3] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	3, 10, 20
2.1.2 The objective(s) of the study?	☒	☐	☐	3, 11, 21
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	12, 24, 26
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	12, 22
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	14 Section9.7.1 and 9.7.2
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	12, 24, 25
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	15, 23
4.2.2 Age and sex?	☐	☒	☐	
4.2.3 Country of origin?	☒	☐	☐	3, 12, 22
4.2.4 Disease/indication?	☐	☒	☐	
4.2.5 Co-morbidity?	☐	☒	☐	
4.2.6 Seasonality?	☐	☒	☐	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	24, 25

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	29
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	24
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☒	☐	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	27
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	35

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	38
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	26
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	27-29
8.1.3 Covariates?	☒	☐	☐	32

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	Section 9.3
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	Section 9.3
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	Section 9.3
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☒	☐	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☒	☐	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☒	☐	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☒	☐	

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	13, 29, 31

Comments:

No power calculation is performed because no hypothesis is tested but precisions of proportion estimates are provided for several sample sizes that seem reachable, per country, or overall.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☒	☐	
10.2 Is the choice of statistical techniques described?	☐	☒	☐	
10.3 Are descriptive analyses included?	☒	☐	☐	32-35
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for adjusting for confounding?	☐	☒	☐	
10.6 Does the plan describe methods addressing effect modification?	☐	☒	☐	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	38
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☒	☐	
11.3 Are methods of quality assurance described?	☒	☐	☐	36
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	36
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	36
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	36
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☒	☐	
12.3 Does the protocol address other limitations?	☐	☒	☐	

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	15, 18, 22
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	40

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	16

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	42
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	42

Comments:

Name of the main author of the protocol: _ Isabela Batsu_____

Date: / /

Signature: _____

Annex 3 Protocol amendment history

The amended protocol 01 and 02 are for all countries and the Protocol Amendment Summary of Changes Table for the current amendment is located in Section 5.

AMENDED PROTOCOL 01 (21-DEC-2018)

OVERALL RATIONALE FOR THE AMENDMENT

The site enrollment projections demonstrate that the initial plan of recruiting 400 patients from 100-138 sites for Wave 1 cannot be accomplished due to continued lower than expected positive site response rate, low Praluent prescriptions, and limited patient eligibility period of 4 months from March 2017 to June 2017 for the first Praluent prescription. Therefore, it is planned to decrease the projected number of sites and patients enrolled in Wave 1 to 25 sites and 75 patients, as base case (or at the minimum), and 30 sites and 90 patients, as best case, assuming an average of 3 patients per site.

Furthermore, the study design for Waves 2 and 3 is modified to increase the likelihood of enrolling sites and patients as follows:

1. Increase the eligibility period from 4 months to 12 months to increase the possibility of enrolling the target number of patients, while preserving the original timelines for interim and final reporting.

	Original protocol	New strategy to be applied
Wave 2	Mar-Jun 2018	Jul 17-Jun 2018
Wave 3	Mar-Jun 2019	Jul 18-Jun 2019

2. Eliminate random selection process: the clusters and physicians that have the highest likelihood of having prescribed Praluent and of participating in the study will be contacted regardless of their level of prescription. Representativeness of study sample with respect to the level of prescription will be assessed a posteriori in the analysis phase.
3. Selection of countries will depend on the extent of patient exposure estimated from EU sales data.
4. Select additional databases in each country of interest to better identify the prescribers.
5. For Wave 2 and Wave 3, minimum 90 sites and 400 patients are deemed feasible for enrollment.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 4 Abstract and Section 9.5 Study size	Decreased the projected number of sites and patients enrolled in Wave 1 to 25 sites and 75 patients, as base case (or at the minimum), and 30 sites and 90 patients, as best case, assuming an average of 3 patients per site	Recruitment challenges encountered in Wave 1 due to continued lower than expected positive site response rate, low Praluent prescriptions, and limited patient eligibility period
Section 4 Abstract, Section 6 Milestones, and Section 9.2.1 Duration of the study	Increased the eligibility period from 4 months to 12 months	To increase the possibility of enrolling the target number of patients
Section 4 Abstract, Section 9.2.4.1 Physician selection, Section 9.7.3 Sensitivity analysis regarding the physicians selection, and Section 9.9 Limitations of the research methods	Random selection of physicians was eliminated. Representativeness of study sample with respect to the level of prescription will be assessed a posteriori in the analysis phase	Eliminate random selection of physicians to increase the likelihood of enrolling sites and patients
PASS Information, Section 4 Abstract, and Section 9.2 Setting	Added the following text: for Wave 2 and Wave 3, selection of countries will depend on the extent of patient exposure estimated from EU sales data	To clarify the selection of countries in Wave 2 and Wave 3 will depend on the extent of patient exposure estimated from EU sales data
Section 9.2.4.1 Physician selection	Added the following text: additional databases will be selected in each country of interest to better identify the prescribers	To better identify the prescribers
Section 9.2.4.2. Patient selection	Included the process of random selection of patients	To include details on random selection of patients
Section 4 Abstract and Section 9.5.2 Sample size	For Wave 2 and Wave 3, number of sites decreased from 100-125 to at least 90	For Wave 2 and Wave 3, minimum 90 sites and 400 patients are deemed feasible for enrollment
Section 9.7.1 Primary analysis	A Cochran Mantel Haenszel test to compare percentages of patients with at least one very low LDL-C between the three different regimens of Praluent received at the time of low LDL-C and the baseline LDL-C was removed	The study is not stratified by baseline LDL-C and the initial dose may depend on the baseline LDL-C value which may be a confounding factor that cannot be controlled; therefore, the between-group statistical test will not be used
Section 9.7.1 Primary analysis and Section 9.7.2 Secondary analysis	Changed the baseline LDL-C level category of ≥160 mg/dL to two categories of 160 to <190 mg/dL and ≥190 mg/dL	To update the LDL-C level categories
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

Signature Page
obs14697-16-1-1-pass-amended-protocol02

Approve & eSign	[redacted]
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