2. 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 Date: 10 August 2021 Authors: [redacted]
Keywords	Praluent, alirocumab, drug utilization study, low-density lipoprotein, hypercholesterolemia.
Rationale and background	Praluent® (brand name of alirocumab) has been approved in the European Union (EU) since 23 September 2015 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 low-density lipoprotein cholesterol (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. Upon this approval, Sanofi was requested to conduct a DUS, with an objective to assess the effectiveness of dosing recommendation as per the product information to avoid very low low-density lipoprotein-cholesterol (LDL-C) levels. This request was included in the Risk Management Plan (RMP) as a category 3 Post-authorization Safety Study (PASS) (MEA019). The initial protocol version 1 is dated 08 March 2018 (approved by the Committee for Medicinal Products for Human Use (CHMP) 25 January 2018), Amended protocol 01 dated 21 December 2018, and Amended protocol 02 dated 09 July 2020. The usual starting dose for alirocumab is 75 mg administered subcutaneously once every two weeks (Q2W). Patients requiring larger LDL-C reduction (>60%) may be started on 150 mg Q2W, or 300 mg once every four weeks (Q4W) (monthly), administered subcutaneously.
Research question and	The primary objective of this DUS was to assess the effectiveness of the Praluent (brand name of alirocumab) dosing recommendations for the three dosage regimens

objectives	approved to date, i.e., 75 mg Q2W, 150 mg Q2W, and 300 mg Q4W (monthly) to avoid very low LDL-C levels. The secondary objective was to describe the pattern of Praluent utilization in real-world clinical practice with respect to the dosing recommendations in the labeling of the three dosage regimens approved to date, i.e., 75 mg Q2W, 150 mg Q2W, and 300 mg Q4W to avoid very low LDL-C levels.
Study design	This study is a non-interventional (with regard to the therapeutic strategy), retrospective cohort study in patients who were initiated with Praluent 75 mg Q2W, 150 mg Q2W, or 300 mg Q4W. Physicians were informed of the main purpose of the study and, upon all relevant approvals being obtained, the physicians and patients were enrolled between the second quarter (Q2) of 2018 up to the first quarter (Q1) of 2019 for Wave 1, between Q1 2019 to Q1 2020 in Wave 2 and between Q1 2020 to Q1 2021 in Wave 3. The observation period lasted six months for each patient, starting from their first Praluent prescription, identified during the eligibility period (March to June 2017 for Wave 1, July 2017 to June 2018 for Wave 2, and July 2018 to June 2019 for Wave 3) to six months later, at the latest until December 2017, 2018 and 2019, respectively. Patients were enrolled retrospectively and data during the above-described observational period were collected retrospectively from Q3 2018 to Q1 2019 in Wave 1, from Q2 2019 to Q1 2020 in Wave 2 and from Q2 2020 to Q1 2021 in Wave 3.
Setting	The clinical setting and data sources of the study mirrors real life management of these patients. The study consisted of three waves, conducted during three consecutive years. Wave 1 was conducted in Belgium, Germany, the Netherlands, and the United Kingdom (UK); Wave 2 in Austria, Belgium, Germany, Italy, the Netherlands, Spain, and the UK; and Wave 3 in Austria, Belgium, Italy, the Netherlands, Spain, and the UK. Therefore, the cumulative results of Wave 1, 2, and 3 include patients from Austria, Belgium, Germany, Italy, the Netherlands, Spain, and the UK. This is the final study report, which describes the cumulative results of Wave 1, 2, and 3. In addition, the results of the last wave only, i.e., Wave 3, are included. The results of Wave 1 and 2 were described in previous reports.

Subjects and study size	National prescriber databases containing data on health care professionals and their prescribing information were used to identify potential physicians in each selected country. For Wave 3, a sample of 255 patients was estimated to result in a half-width of 6.3% for the 95% confidence interval (CIs) around an expected 42.7% of patients with at least one value of LDL-C <25 mg/dL. The total number of patients enrolled in Wave 1, 2, and 3 was expected to range from 454 to 574 patients; a sample of 574 patients was estimated to result in a half-width of 4.2% for the 95% CIs around an expected 42.7% of patients with at least one value of LDL-C <25 mg/dL. Inclusion criteria for patients included having initiated Praluent following a first prescription during the eligibility period and having signed the written informed consent, if needed as per local regulatory requirements. Exclusion criteria for patients included participation in any randomized clinical trial with Praluent and their medical chart being not retrievable. For physicians, the inclusion criterion was to have at least prescribed one initial prescription of Praluent during the eligibility period and the exclusion criteria included participation in any randomized clinical trial with Praluent and participation in a previous wave of this study.
Variables and data sources	Physicians' characteristics were collected at the time of their recruitment. Medical chart reviews were conducted retrospectively to collect data during the 6-month observation period following the date of the first prescription of Praluent (index date) for each patient. Such data included: (1) patient characteristics, (2) prescriptions of Praluent and other lipid-lowering drugs in the observation period, (3) LDL-C values, and (4) adverse events (AEs). The data sources consisted of medical records (either electronic medical records or paper source files). Data were collected using an electronic case report form (eCRF).
Results	**Physician and Patient Characteristics** Across the three waves, 130 physicians enrolled 534 patients, including 20 physicians and 68 patients in Wave 1, 61 physicians and 276 patients in Wave 2, and 49 physicians and 190 patients in Wave 3. The most frequent primary specialties of the enrolled physicians were cardiology (43.8%) and internal medicine (23.1%). The physicians who enrolled patients are based in the UK (23.1%, n=30), the Netherlands (16.2%, n=21),

Germany (13.1%, n=17), Italy (13.1%, n=17), Spain (12.3%, n=16), Belgium (11.5%, n=15), and Austria (10.8%, n=14). The initial Praluent dosage regimen was 75 mg Q2W for 313 patients (58.6%) and 150 mg Q2W for 218 patients (40.8%). No patient initiated Praluent on the 300 mg Q4W dosage. Three patients had initiated either another dosage of Praluent at initial prescription or the initiating dosage was unknown.

Baseline LDL-C Values

Of the 534 enrolled patients, baseline LDL-C measurements were available for 486 patients (91.0%); among those, the mean baseline LDL-C value was 159.35 mg/dL (Standard Deviation [SD]= 56.09). The mean baseline LDL-C value was lower in Wave 3 (145.03 mg/dL [SD=49.79]) compared to Wave 1 (166.41 mg/dL [SD=57.65]) and Wave 2 (163.75 mg/dL [SD=52.80]).

Among 313 patients of the 75 mg Q2W cohort (i.e., initial Praluent dosage of 75 mg Q2W), 289 (92.3%) patients had a baseline LDL-C measurement. The mean baseline LDL-C value was 151.69 mg/dL (SD=50.73). Six patients had a baseline LDL-C value between 19 and 70 mg/dL; five were prescribed Praluent due to statin intolerance and one patient because statin alone was not effective. All six patients had a relevant diagnosis, including non-familial hypercholesterolemia (n=4), coronary heart disease, and mixed dyslipidemia.

Among 218 patients of the 150 mg Q2W cohort, 194 (89.0%) patients had a baseline LDL-C measurement. The mean baseline LDL-C value was 170.44 mg/dL (SD=59.73). Two patients had a baseline LDL-C value between 55 and 70 mg/dL; one was prescribed Praluent due to statin intolerance and had a diagnosis of heterozygous familial hypercholesterolemia and one was prescribed Praluent due to the medical conditions (peripheral arterial disease, stent, and significantly elevated lipoprotein(a) levels).

In Wave 1, 2 and 3, the mean baseline LDL-C value was higher among patients who were prescribed the 150 mg Q2W Praluent dosage compared to the patients who were prescribed the 75 mg Q2W Praluent dosage.

Follow-up LDL-C Values

A total of 466 (87.3%) of the 534 patients had at least one post-baseline LDL-C value

available during the 6-month observation period (irrespective of baseline LDL-C data availability). The mean LDL-C levels steadily decreased from baseline at Month 1 and Month 6. The mean LDL-C was 97.74 mg/dL (SD=56.53) at Month 1 (n=103) and 72.45 mg/dL (SD=36.19) at Month 6 (n=140). The trend of decreasing mean LDL-C levels over the 6-month observation period was consistent across the waves.

Despite the month-to-month varying availability of LDL-C values (related to a different set of patients for which the mean LDL-C level was calculated each month), only numerical changes were observed in the mean LDL-C level over time after the patients initiated treatment with Praluent.

In the 75 mg Q2W cohort, the mean LDL-C levels decreased between baseline (151.69 mg/dL; SD: 50.73; n=289) and Month 1 (101.98 mg/dL; SD=56.04; n=52) and further at Month 2 (75.89 mg/dL; SD=35.29; n=69) and remained similar between Month 3 (80.66 mg/dL; SD=43.09; n=97) and Month 6 (72.66 mg/dL; SD=33.75; n=92). In the 150 mg Q2W cohort, the mean LDL-C levels steadily decreased between baseline (170.44 mg/dL; SD=59.73; n=194) and Month 4 (64.15 mg/dL; SD=38.10; n=55) and remained similar at Month 5 (68.53 mg/dL; SD=50.34; n=37) and 6 (72.05 mg/dL; SD=40.82; n=48).

The mean baseline LDL-C level was lower among the 75 mg Q2W cohort compared to the 150 mg Q2W cohort, but after baseline, the mean LDL-C levels were similar or slightly lower among the 150 mg Q2W cohort.

Very Low LDL-C Values

Among the 466 patients with at least one post-baseline LDL-C value during the 6-month observation period, 38 patients (8.2%; 95% CI: 5.8, 11.0) had an LDL-C level <25 mg/dL, including nine patients (1.9%; 95% CI: 0.9, 3.6) with an LDL-C level <15 mg/dL. A higher percentage of patients with very low LDL-C levels (<25 mg/dL) was observed in Wave 3 (11.3%; 18 of 160 patients) compared to Wave 1 (4.9%; three of 61 patients) and 2 (6.7%; 15 of 225 patients); corresponding percentage for LDL-C levels <15 mg/dL were 1.6% in Wave 1 (n=1), 1.8% in Wave 2 (n=4), and 2.5% in Wave 3 (n=4).

Twenty-four (63.2%) of the 38 patients with a post-baseline LDL-C level of <25 mg/dL

initiated Praluent on the 150 mg Q2W dosage levels (including seven patients who experienced LDL-C level of <15 mg/dL). Most of the 38 patients (63.2%; n=24, including 15 patients from the 150 mg Q2W cohort) had a baseline LDL-C level below 130 mg/dL.

Among the 38 patients for whom a post-baseline LDL-C level <25 mg/dL was reported, 30 patients had no change in treatment dose of Praluent or other lipid-lowering drugs after the very low LDL-C test in the 6-month observation period. Among the other eight patients, two patients had a modification in the Praluent dosage regimen (including a modification from 150 mg Q2W to 75 mg Q2W and a temporary discontinuation from 150 mg Q2W with a later modification to 300 mg Q4W), four patients had a decrease in other lipid-lowering drugs, and two patients discontinued another lipid-lowering drug after the measurement of the LDL-C value <25 mg/dL.

Subsequent LDL-C levels after the measurement of very low post-baseline levels were reported for nine patients including two patients who reached LDL-C level <15 mg/dL. For seven of these nine patients (77.8%), an increase in LDL-C level above 25 mg/dL was recorded within six months from the occurrence of LDL-C level <25 mg/dL, including three patients (33.3%) for whom the increase was observed within eight weeks. For four of the seven patients (57.1%) with an increase in LDL-C level above the 25 mg/dL, there had been no change in lipid-lowering treatments (including Praluent).

For both patients with the LDL-C value of <15 mg/dL, the LDL-C level was recorded to increase to above 15 mg/dL within six months. One of these patients returned to above 25 mg/dL within eight weeks. Both patients had changes in lipid-lowering treatments prior to the subsequent LDL-C test.

The percentage of patients experiencing a post-baseline very low LDL-C level did not differ notably according to the prescription levels of the physicians (based on the number of patients to whom Praluent was prescribed in the previous calendar year).

Praluent Indication

Nearly all patients had a diagnosis or condition in their medical history (98.7%); this was observed in Wave 1, 2 and 3 with respectively 100%, 99.2% and 97.9% of patients with a relevant diagnosis or condition. The most common conditions were clinical

atherosclerotic cardiovascular disease (ASCVD) (59.2%), non-familial hypercholesterolemia (52.5%), hypertension (46.4%), familial hypercholesterolemia (36.2%), diabetes mellitus (17.4%), and mixed dyslipidemia (9.2%).

The most frequently reported indications for Praluent prescription were non-familial hypercholesterolemia (52.1%) and familial hypercholesterolemia (35.8%). Among the patients who initiated Praluent on the 75 mg Q2W dose, 53.4% had a diagnosis of non-familial hypercholesterolemia and 31.9% a diagnosis of familial hypercholesterolemia reported as the indication for Praluent prescription. In patients who initiated Praluent on the 150 mg Q2W dose, 50.5% had a diagnosis of non-familial hypercholesterolemia and 41.3% a diagnosis of familial hypercholesterolemia reported as the indication for Praluent prescription.

Permanent Praluent Discontinuation

Twenty-three (4.3%) patients permanently discontinued Praluent during the 6-month observational period. None of these patients had very low LDL-C levels before discontinuation, but one patient had LDL-C <25 mg/dL after switching from Praluent to Repatha® (evolocumab). Of the 23 patients who permanently discontinued Praluent, nine (39.1%) patients initiated Praluent on the 75 mg Q2W dose and 14 (60.9%) patients initiated Praluent on 150 mg Q2W. Among the 21 (91.3%) patients with a known reason for discontinuation, 15 patients discontinued Praluent due to an AE (65.2%), three due to lack of LDL-C reduction (13.0%), two due to patient decision (8.7%), and one reported to be not applicable (4.3%).

Praluent Dosage Regimen Modification

Among the 534 patients, 63 (11.8%) patients had at least one Praluent dosage regimen modification, including 54 patients who initiated Praluent on 75 mg Q2W and nine patients who initiated Praluent on 150 mg Q2W. By wave, Praluent dosage modifications were less common in Wave 3 (6.8%) compared to Wave 1 (11.8%) or Wave 2 (16.3%). Among the 63 patients with at least one modification, there were:

- Fifty-two patients (82.5%) with a modification from 75 mg Q2W to 150 mg Q2W
- Six patients (9.5%) with a modification from 150 mg Q2W to 75 mg Q2W

- Five patients (7.9%) with a modification from 150 mg Q2W to 300 mg Q4W
- Two patients (3.2%) with a modification from 75 mg Q2W to 75 mg Q4W
- One patient (1.6%) with a modification from 75 mg Q4W to 150 mg Q4W
- One patient (1.6%) with a modification from 150 mg Q4W to 300 mg Q4W
- One patient (1.6%) with a modification from 150 mg Q4W to 150 mg Other (once every six weeks)
- One patient (1.6%) with a modification from 300 mg Q4W to 150 mg Q4W

The most common primary reason for Praluent dosage modification was physician decision among patients who initiated on 75 mg Q2W (n=25, 46.3%) and among patients who initiated on 150 mg Q2W (n=5, 55.6%). Among the 75 mg Q2W cohort, lack of LDL-C reduction was the second most common primary reason for dosage modification (n=20, 37.0%) and among the 150 mg Q2W cohort, this was AEs (n=4, 44.4%).

Other Lipid-Lowering Drugs

Other lipid-lowering drugs were prescribed to 353 (66.1%) patients in addition to Praluent at enrollment or any time during the 6-month observation period; this percentage was observed to be slightly higher in Wave 3 (74.7%) compared to Wave 1 (60.3%) and Wave 2 (61.8%). The number (%) of patients on other lipid-lowering drugs was 153 (70.2%) patients in the 150 mg Q2W cohort and 199 (63.6%) in the 75 mg Q2W cohort. Overall, the most frequently reported lipid-lowering drug was ezetimibe, in 281 (79.6%) patients, followed by atorvastatin in 89 (25.2%) patients and rosuvastatin in 79 (22.4%) patients. Ezetimibe was prescribed as a monotherapy or as add on to statin.

Adverse Events

Ninety-seven (18.2%) of 534 patients reported a total of 179 AEs during the 6-month observation period; 50 (16.0%) of the 313 patients who initiated Praluent at the 75 mg Q2W dosage experienced 91 AEs and 47 (21.6%) of the 218 patients who initiated Praluent on the 150 mg Q2W dosage experienced 88 AEs. No AEs were reported for the three patients who initiated either another dosage of Praluent at initial prescription or

	with initiating dosage unknown. By wave, it was observed that the percentage of patients experiencing at least one AE was higher in Wave 1 (22.1%) compared to Wave 2 (18.7%) and Wave 3 (15.3%). Five patients (1.2%) experienced 11 AEs that led to Praluent dose reduction. In addition, 20 patients (3.7%) experienced 29 AEs that led to Praluent interruption or withdrawal.
Discussion	The results from this study provide some insights on the effectiveness of the Praluent dosing recommendations to avoid very low LDL-C and the patterns of Praluent utilization in real-world clinical practice. Only 38 (8.2%; 95% CI: 5.8, 11.0) of the patients experienced a post-baseline very low LDL-C level (<25 mg/dL). The percentage of patients with very low LDL-C levels (<25 mg/dL) was lower in Wave 1 (4.9%; 95% CI: 1.0, 13.7) and Wave 2 (6.7%; 95% CI: 3.8, 10.8) compared to Wave 3 (11.3%; 95% CI: 6.8, 17.2). Consistent with Praluent dosing recommendations and consistent across the waves, patients who initiated treatment with the 150 mg Q2W dose had higher baseline LDL-C values than patients who initiated treatment with the 75 mg Q2W dose. Participating physicians also followed the Praluent dosing recommendations regarding up-titration when LDL-C reduction is not sufficient; especially in Wave 3, where all modifications were up-titrations from 75 mg Q2W to 150 mg Q2W. Consistent across the waves, the Praluent dosage regimen and other concomitant lipid-lowering drugs dosage was not changed for most patients who experienced a very low LDL-C level. There were nine patients with records of very low LDL-C levels who had subsequent values of LDL-C levels available. Among seven (78%) of these nine patients, an LDL-C level above 25 mg/dL was observed after the very low LDL-C level within the 6-month observation period. Among these seven patients, four patients (57.1%) had a spontaneous return to higher LDL-C values without change in any lipid-lowering treatment and three patients had a modification in Praluent or other lipid-lowering drugs. Despite the precautions taken to select physicians representative of the prescribers of Praluent in the selected countries, the findings may not be entirely representative of the level of prescription, specialty and/or setting type due to the limited sample size of the

	study. Results showed that compliance to the posology recommended in the EU summary of product characteristics (SmPC) was satisfactory and consistent across the 3 waves. This high degree of compliance was efficient to limit the occurrence of very low LDL-C levels. Furthermore, the percentage of patients experiencing a post-baseline very low LDL-C level was not found to notably differ according to the prescription level of the physicians.
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