HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PRALUENT safely and effectively. See full prescribing information for PRALUENT.

PRALUENT® (alirocumab) injection, for subcutaneous use

Initial U.S. Approval: 2015

RECENT MAJOR CHANGES

Indications and Usage (1.1, 1.2) 4/2019

Dosage and Administration (2.1) 8/2018

INDICATIONS AND USAGE

PRALUENT is a PCSK9 (proprotein convertase subtilisin kexin type 9) inhibitor antibody indicated:

• to reduce the risk of myocardial infarction, stroke, and unstable angina requiring hospitalization in adults with established cardiovascular disease. (1.1)

• as adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for the treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia) to reduce low-density lipoprotein cholesterol LDL-C. (1.2)

DOSE AND ADMINISTRATION

The recommended starting dose of PRALUENT is 75 mg once every 2 weeks administered subcutaneously, since the majority of patients achieve sufficient LDL-C reduction with this dosage. An alternative starting dosage for patients who prefer less frequent dosing is 300 mg once every 4 weeks (monthly). (2.1)

If the LDL-C response is inadequate, the dosage may be adjusted to the maximum dosage of 150 mg administered every 2 weeks. (2.1)

FULL PRESCRIBING INFORMATION: CONTENTS

1 INDICATIONS AND USAGE

1.1 Prevention of Cardiovascular Events

PRALUENT® is indicated to reduce the risk of myocardial infarction, stroke, and unstable angina requiring hospitalization in adults with established cardiovascular disease. (1.1)

1.2 Primary Hyperlipidemia (including heterozygous familial hypercholesterolemia)

PRALUENT is indicated as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for the treatment of adults with primary hyperlipidemia to reduce low-density lipoprotein cholesterol (LDL-C). (1.2)

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The recommended dose of PRALUENT in patients with HeFH undergoing LDL apheresis is 150 mg once every 2 weeks. PRALUENT can be administered without regard to timing of apheresis. (2.1)

DOSE FORMS AND STRENGTHS

• Injection: 75 mg/mL or 150 mg/mL solution in a single-dose pre-filled pen (3)

• Injection: 75 mg/mL or 150 mg/mL solution in a single-dose pre-filled syringe (3)

CONTRAINDICATIONS

History of a serious hypersensitivity reaction to PRALUENT. (4)

WARNINGS AND PRECAUTIONS

Allergic Reactions: Hypersensitivity reactions (e.g., pruritus, rash, urticaria), including some serious events (e.g., hypersensitivity vasculitis and hypersensitivity reactions requiring hospitalization), have been reported with PRALUENT treatment. If signs or symptoms of serious allergic reactions occur, discontinue treatment with PRALUENT, treat according to the standard of care, and monitor until signs and symptoms resolve. (5.1)

ADVERSE REACTIONS

The most commonly occurring adverse reactions (≥5% of patients treated with PRALUENT and occurring more frequently than with placebo) are nasopharyngitis, injection site reactions, and influenza. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sanofi at 1-800-633-1610 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 04/2019
Follow aseptic injection technique every time PRALUENT is administered.

Administer PRALUENT by subcutaneous injection into the thigh, abdomen, or upper arm using a single-dose pre-filled pen or single-dose pre-filled syringe.

Rotate the injection site with each injection.

To administer the 300 mg dose, give two 150 mg PRALUENT injections consecutively at two different injection sites.

Do NOT inject PRALUENT into areas of active skin disease or injury such as sunburns, skin rashes, inflammation, or skin infections.

Do NOT co-administer PRALUENT with other injectable drugs at the same injection site.

3 DOSE FORMS AND STRENGTHS

PRALUENT is a clear, colorless to pale yellow solution available as follows:
Injection: Single-dose pre-filled pen
75 mg/mL
150 mg/mL
Injection: Single-dose pre-filled syringe
75 mg/mL
150 mg/mL

4 CONTRAINDICATIONS

PRALUENT is contraindicated in patients with a history of a serious hypersensitivity reaction to PRALUENT. Reactions have included hypersensitivity vasculitis and hypersensitivity reactions requiring hospitalization. See Warnings and Precautions (5.1).

5 WARNINGS AND PRECAUTIONS

5.1 Allergic Reactions

Hypersensitivity reactions (e.g., pruritus, rash, urticaria), including some serious events (e.g., hypersensitivity vasculitis and hypersensitivity reactions requiring hospitalization), have been reported with PRALUENT treatment. If signs or symptoms of serious allergic reactions occur, discontinue treatment with PRALUENT, treat according to the standard of care, and monitor until signs and symptoms resolve [see Contraindications (4)].

6 ADVERSE REACTIONS

The following adverse reactions are also discussed in the other sections of the labeling:

Allergic Reactions [See Warnings and Precautions (5.1)].

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Common Adverse Reactions

The data in Table 1 are derived from 9 primary hyperlipidemia placebo-controlled trials that included 2476 patients treated with PRALUENT 75 mg and/or 150 mg every 2 weeks, including 2135 exposed for 6 months and 1999 exposed for more than 1 year (median treatment duration of 65 weeks). The mean age of the population was 59 years, 40% of the population were male, and 3% were Asian.

Adverse reactions reported in at least 2% of PRALUENT-treated patients, and more frequently than in placebo-treated patients, are shown in Table 1.

Table 1: Adverse Reactions Occurring in Greater Than or Equal to 2% of PRALUENT-Treated Patients and More Frequently Than with Placebo

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Placebo (N=1276)</th>
<th>PRALUENT (N=2476)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>11.1%</td>
<td>11.3%</td>
</tr>
<tr>
<td>Injection site reactions$</td>
<td>5.1%</td>
<td>7.2%</td>
</tr>
<tr>
<td>Influenza</td>
<td>4.6%</td>
<td>5.7%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>4.6%</td>
<td>4.8%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4.4%</td>
<td>4.7%</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>3.8%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>3.4%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>2.4%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>2.7%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Cough</td>
<td>2.3%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Confusion</td>
<td>1.3%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>1.6%</td>
<td>2.1%</td>
</tr>
</tbody>
</table>

75 mg every 2 weeks and 150 mg every 2 weeks combined
$ Includes erythema/redness, itching, swelling, pain/tenderness

Adverse reactions led to discontinuation of treatment in 5.3% of patients treated with PRALUENT and 5.1% of patients treated with placebo. The most common adverse reactions leading to treatment discontinuation in patients treated with PRALUENT were allergic reactions (0.6% versus 0.2% for PRALUENT and placebo, respectively) and elevated liver enzymes (0.3% versus <0.1%).

In an analysis of ezetimibe-controlled trials in which 864 patients were exposed to PRALUENT for a median of 27 weeks and 618 patients were exposed to ezetimibe for a median of 24 weeks, the types and frequencies of common adverse reactions were similar to those listed above.

In a cardiovascular outcomes trial in which 9451 patients were exposed to PRALUENT for a median of 21 months and 9443 patients were exposed to placebo for a median of 32 months, common adverse reactions (greater than 5% of patients treated with PRALUENT and occurring more frequently than placebo) included non-cardiac chest pain (7.0% PRALUENT, 6.8% placebo), nasopharyngitis (6.0% PRALUENT, 5.6% placebo), and myalgia (5.6% PRALUENT, 5.3% placebo).

Local Injection Site Reactions

In a pool of placebo-controlled trials evaluating PRALUENT 75 mg and/or 150 mg administered every 2 weeks (Q2W), local injection site reactions including erythema/redness, itching, swelling, and pain/tenderness were reported more frequently in patients treated with PRALUENT (7.2% versus 5.1% for PRALUENT and placebo, respectively).

Few patients discontinued treatment because of these reactions (0.2% versus 0.4% for PRALUENT and placebo, respectively), but patients receiving PRALUENT had a greater number of injection site reactions, had more reports of associated symptoms, and had reactions of longer average duration than patients receiving placebo.

In a 48-week placebo-controlled trial evaluating PRALUENT 300 mg every 4 weeks (Q4W) and 75 mg Q2W, in which all patients received an injection of drug or placebo every 2 weeks to maintain the blind, local injection site reactions were reported more frequently in patients treated with PRALUENT 300 mg Q4W as compared to those receiving PRALUENT 75 mg Q2W or placebo (16.6%, 9.6%, and 7.9%, respectively). Three patients (0.7%) treated with PRALUENT 300 mg Q4W discontinued treatment due to local injection site reactions versus no patients (0%) in the other 2 treatment groups.

In a cardiovascular outcomes trial, local injection site reactions were reported in 3.8% of patients treated with PRALUENT versus 2.1% patients treated with placebo, and led to permanent discontinuation in 26 patients (0.3% versus 3 patients [<0.1%], respectively).

Allergic Reactions

Allergic reactions were reported more frequently in patients treated with PRALUENT than in those treated with placebo (8.6% versus 7.8%). The proportion of patients who discontinued treatment due to allergic reactions was higher among those treated with PRALUENT (0.6% versus 0.2%). Serious allergic reactions, such as hypersensitivity, nummular eczema, and hypersensitivity vasculitis were reported in patients using PRALUENT in controlled clinical trials [see Warnings and Precautions (5.1)].

Lever Enzyme Abnormalities

In the primary hyperlipidemia trials, liver-related disorders (primarily related to abnormality of the assay) were reported in 2.5% of patients treated with PRALUENT and 1.8% of patients treated with placebo, leading to treatment discontinuation in 0.4% and 0.2% of patients, respectively. Increases in serum transaminases to greater than 3 times the upper limit of normal occurred in 1.7% of patients treated with PRALUENT and 1.4% of patients treated with placebo.

Low LDL-C Values

In the placebo-controlled and active-controlled primary hyperlipidemia trials using an every 2 week or every 4 week dosing interval, 914 PRALUENT-treated patients had two consecutive calculated LDL-C values <25 mg/dL, and 335 had two consecutive calculated LDL-C values <15 mg/dL. LDL-C values <25 mg/dL and <15 mg/dL were observed more frequently in patients treated with the PRALUENT 150 mg Q2W or 300 mg Q4W dosing regimens compared with patients receiving statins (e.g., maximally tolerated statins) were not made in response to low LDL-C values in these trials, and PRALUENT dosing was not modified or interrupted on this basis.

In a cardiovascular outcomes trial, 4305 PRALUENT-treated patients had two consecutive calculated LDL-C values <25 mg/dL, and 782 had two consecutive calculated LDL-C values <15 mg/dl. Because PRALUENT dosing was decreased or discontinued in the event of two consecutive LDL-C values <15 mg/dL in this trial, the effects of prolonged very low LDL-C with PRALUENT are unknown.

In published genetic studies as well as clinical and observational trials with lipid lowering therapies, an increased risk of new onset of diabetes has been associated with lower levels of LDL-C.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity with PRALUENT. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to PRALUENT in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In a cardiovascular outcomes trial, 5.5% (504/9091) of patients treated with PRALUENT 75 mg and/or 150 mg every 2 weeks (Q2W) had anti-drug antibodies (ADA) detected after initiating treatment compared with 1.6% (149/9097) of patients treated with placebo. Persistent ADA responses, defined as at least 2 consecutive post-baseline samples with positive ADA separated by at least a 16-week period, were observed in 0.7% of patients treated with PRALUENT and 0.4% of patients treated with placebo. Neutralizing antibody (NAb) responses were observed in 0.5% of patients treated with PRALUENT and in <0.1% of patients treated with placebo. Efficacy based on reductions in LDL-C was mostly similar in patients with or without ADA. However, some patients treated with PRALUENT with persistent or neutralizing antibodies experienced attenuation in LDL-C efficacy.

A higher incidence of injection site reactions were observed in patients with treatment-emergent ADA compared to patients without ADA (523 vs 253%). In a pool of ten placebo-controlled and active-controlled trials of patients treated with PRALUENT 75 mg and/or 150 mg Q2W as well as in a separate clinical study of patients treated with PRALUENT 75 mg Q2W or 300 mg every 4 weeks (including some patients with dose adjustment to 150 mg Q2W), the incidence of detecting ADA and NAb was similar to the results from the trial described above.

The long-term consequences of continuing PRALUENT treatment in the presence of ADA are unknown.

6.3 Postmarketing Experience

The following adverse reactions have been reported during postapproval use of PRALUENT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Alirocumab is a human monoclonal antibody that binds to proprotein convertase subtilisin kexin type 9 (PCSK9). PCSK9 binds to the low-density lipoprotein receptors (LDLR) on the surface of hepatocytes to promote LDLR degradation within the liver. LDLR is the primary receptor that clears circulating LDL, therefore the decrease in LDLR levels by PCSK9 results in higher blood levels of LDL-C. By inhibiting the binding of PCSK9 to LDLR, alirocumab increases the number of LDLRs available to clear LDL, thereby lowering LDL-C levels.

12.2 Pharmacodynamics
Alirocumab reduced free PCSK9 in a concentration-dependent manner. Following a single subcutaneous administration of alirocumab 75 or 150 mg, maximal suppression of free PCSK9 occurred within 4 to 8 hours. Free PCSK9 concentrations returned to baseline when alirocumab concentrations decreased below the limit of quantitation.

12.3 Pharmacokinetics
Absorption
After subcutaneous (SC) administration of 75 mg to 300 mg alirocumab, median times to maximum serum concentrations (tmax) were 3–7 days. The pharmacokinetics of alirocumab after single SC administration of 75 mg into the abdomen, upper arm, or thigh were similar. The absolute bioavailability of alirocumab after SC administration was about 85% as determined by population pharmacokinetics analysis. A slightly greater than dose proportional increase was observed, with a 2.1-fold to 2.7-fold increase in total alirocumab concentration for a 2-fold increase in median human steady state AUC exposure.

Distribution
Following IV administration, the volume of distribution was about 0.04 to 0.05 L/kg indicating that alirocumab is distributed primarily in the circulatory system.

Metabolism and Elimination
Specific metabolism studies were not conducted, because alirocumab is a protein. Alirocumab is expected to degrade to small peptides and individual amino acids. In clinical studies where alirocumab was administered in combination with atorvastatin or rosvastatin, no relevant changes in statin concentrations were observed in the presence of alirocumab, indicating that alirocumab does not affect CYP3A4 and CYP2C9 and transporter proteins such as P-gp and OATP were not affected by alirocumab.

Two elimination phases were observed for alirocumab. At low concentrations, the elimination is predominately through saturable binding to target (PCSK9), while at higher concentrations the elimination of alirocumab is largely through a non-saturable proteolytic pathway.

Based on a population pharmacokinetic analysis, the median apparent half-life of alirocumab at steady state was 17 to 20 days in patients receiving alirocumab at subcutaneous doses of 75 mg Q2W or 150 mg Q2W.

Specific Populations
A population pharmacokinetic analysis was conducted on data from 2799 patients. Age, body weight, gender, race, and creatinine clearance were found not to significantly influence alirocumab pharmacokinetics. No dose adjustments are recommended for these demographics.

Pediatric
PLAURENT has not been studied in pediatric patients [see Use in Specific Populations (8.6)].

8.6 Renal Impairment
No dose adjustment is needed for patients with mild or moderately impaired renal function. No data are available in patients with severe renal impairment. [See Clinical Pharmacology (12.3).]

8.7 Hepatic Impairment
No dose adjustment is needed for patients with mild or moderate hepatic impairment. No data are available in patients with severe hepatic impairment. [See Clinical Pharmacology (12.3).]

11 DESCRIPTION
Alirocumab is a human monoclonal antibody (IgG1 isotype) that targets proprotein convertase subtilisin kexin type 9 (PCSK9). Alirocumab is a PCSK9 inhibitor produced by recombinant DNA technology in Chinese Hamster Ovary cell suspension culture. Alirocumab is manufactured as a single entity in a single-dose pre-filled pen or single-dose pre-filled syringe supplied in a 5 mL single-use vial, which contains 50 mg of alirocumab in a single-use vial with a needleless injection in a single-dose pre-filled pen or single-dose pre-filled syringe is supplied in a sterilized, Type-1 clear glass syringe. The needle shield is not made with natural rubber latex.
13.2 Animal Toxicology and/or Pharmacology

During a 13-week toxicology study of 75 mg/kg once weekly alirocumab in combination with 40 mg/kg once daily atorvastatin in adult monkeys, there were no effects of PRALUENT on the humoral immune response to keyhole limpet hemocyanin (KLH) after one to two months at exposures 100-fold greater than the exposure at the maximum recommended human dose of 150 mg every two weeks, based on AUC.

14 CLINICAL STUDIES

14.1 Prevention of Cardiovascular Events

Study 1 (ODYSSEY OUTCOMES, NCT01663402) was a multicenter, double-blind, placebo-controlled trial in 18,924 adult patients (9462 PRALUENT; 9462 placebo) followed for up to 5 years. Patients had an acute coronary syndrome (ACS) event 4 to 52 weeks prior to randomization and were treated with a lipid-modifying—therapy (LMT) regimen that was statin-intensive (defined as atorvastatin 40 or 80 mg, or rosuvastatin 20 or 40 mg) or at maximally tolerated dose of a statin, with or without other LMT. Patients were randomized to receive either PRALUENT 75 mg every two weeks (Q2W) or placebo Q2W. The PRALUENT 300 mg Q4W dose [see Dosage and Administration (2.1)] was not evaluated in this study.

At month 2, if additional LDL-C lowering was required based on pre-specified LDL-C criteria (LDL-C ≥50 mg/dL), PRALUENT was adjusted to 150 mg Q2W. For patients who had their dose adjusted to 150 mg Q2W and who had two consecutive LDL-C values below 25 mg/dL, down-titration from 150 mg Q2W to 75 mg Q2W was performed. Patients on 75 mg Q2W who had two consecutive LDL-C values below 15 mg/dL were switched to placebo in a blinded fashion. Approximately 2615 (27.7%) of 9451 patients treated with PRALUENT required dose adjustment to 150 mg Q2W. Of these 2615 patients, 805 (30.8%) were down-titrated to 75 mg Q2W. Overall, 730 (7.7%) of 9451 patients switched to placebo.

A total of 99.5% of patients were followed for survival until the end of the trial. The median follow-up duration was 33 months. The mean age at baseline was 59 years (range 39–92), with 25% women, and 27% at least 65 years old. The trial population was 79% Caucasian, 3% Black, and 13% Asian; 17% identified as Hispanic/Latino ethnicity. The index ACS event was a myocardial infarction in 83% of patients and unstable angina in 17% of patients. Prior to the index ACS event, 19% had prior myocardial infarction and 23% had coronary revascularization procedures (CABG/PCI). Selected additional baseline risk factors included hypertension (30.8%) were down-titrated to 75 mg Q2W. Overall, 730 (7.7%) of 9451 patients switched to placebo.

The Kaplan-Meier estimates of the cumulative incidence of the primary endpoint over time is presented in Figure 1.

14.2 Primary Hyperlipidemia (including heterozygous familial hypercholesterolemia)

Study 2 (ODYSSEY LONG TERM, NCT01507831) was a multicenter, double-blind, placebo-controlled trial that randomly assigned 1553 patients to PRALUENT 150 mg Q2W and 788 patients to placebo. All patients were taking maximally tolerated doses of statins with or without other lipid-modifying therapy, and required additional LDL-C reduction. The mean age was 61 years (range 18–89); 38% were women, 93% were Caucasian, 3% were Black, and 5% were Hispanic/Latino. The average LDL-C at baseline was 122 mg/dL. The proportion of patients who prematurely discontinued study drug prior to the 24-week primary endpoint was 8% among those treated with PRALUENT and 8% among those treated with placebo.

At week 24, the treatment difference between PRALUENT and placebo in mean LDL-C percent change was -58% (95% CI: -61%, -56%; p-value: <0.0001). For additional results see Table 3 and Figure 2.

Table 2: Cardiovascular Outcomes in Patients with Established Cardiovascular Disease

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>PRALUENT N=9462</th>
<th>Placebo N=9462</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>Incidence Rate per 100 Patient Years (95% CI)</td>
<td>n (%)</td>
<td>Incidence Rate per 100 Patient Years (95% CI)</td>
</tr>
<tr>
<td>CHD death</td>
<td>205 (2.2%)</td>
<td>0.8 (0.7 to 0.9)</td>
<td>0.8 (0.7 to 0.9)</td>
</tr>
<tr>
<td>Non-fatal MI†</td>
<td>626 (6.6%)</td>
<td>2.4 (2.2 to 2.6)</td>
<td>2.8 (2.6 to 3.0)</td>
</tr>
<tr>
<td>Fatal or non-fatal ischemic stroke§</td>
<td>111 (1.2%)</td>
<td>0.4 (0.3 to 0.5)</td>
<td>1.52 (1.6%)</td>
</tr>
<tr>
<td>Unstable angina requiring hospitalization§</td>
<td>37 (0.4%)</td>
<td>0.1 (0.1 to 0.2)</td>
<td>0.2 (0.2 to 0.3)</td>
</tr>
</tbody>
</table>

Components of the Primary Composite Endpoint†

<table>
<thead>
<tr>
<th>Mortality Endpoint (not statistically significant per pre-specified method to control for type I error)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
</tr>
</tbody>
</table>

†Cox-proportional hazards model with treatment as a factor and stratified by geographic region
‡Primary composite endpoint defined as: time to first occurrence of coronary heart disease death, non-fatal myocardial infarction, fatal and non-fatal ischemic stroke, or unstable angina requiring hospitalization
§First occurrence of specified event at any time; patients may have experienced more than one adjudicated event
$Statistical testing performed outside hierarchy; therefore not considered statistically significant

Table 3: Mean Percent Change from Baseline and Difference* from Placebo in Lipid Parameters at Week 24 in ODYSSEY LONG TERM

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>LDL-C</th>
<th>Total-C</th>
<th>Non-HDL-C</th>
<th>Apo B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>PRALUENT (150 mg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference from placebo (LS Mean) (95% CI)</td>
<td>-58 (-61, -56)</td>
<td>-36 (-37, -34)</td>
<td>-50 (-52, -47)</td>
<td>-51 (-53, -48)</td>
</tr>
</tbody>
</table>

*Difference is PRALUENT minus Placebo

A pattern-mixture model approach was used with multiple imputation of missing post-treatment values based on a patient’s own baseline value and multiple imputation of missing on-treatment values based on a model including available on-treatment values.

Figure 2: Mean Percent Change from Baseline in LDL-C Over 52 Weeks in Patients on Maximally Tolerated Statin Treated with PRALUENT 150 mg Q2W and Placebo Q2W (ODYSSEY LONG TERM)

<table>
<thead>
<tr>
<th>Time point (Weeks)</th>
<th>LDL-C</th>
<th>Non-HDL-C</th>
<th>Apo B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (N=788)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRALUENT (N=1553)</td>
<td>1</td>
<td>0.4</td>
<td>1.5</td>
</tr>
</tbody>
</table>

a The means were estimated based on all randomized patients, with multiple imputation of missing data taking into account treatment adherence.

b Number of patients with observed data.
Study 3 (ODYSSEY COMBO I, NCT01644175) was a multicenter, double-blind, placebo-controlled trial that randomly assigned 209 patients to PRALUENT and 107 patients to placebo. Patients were taking maximally tolerated doses of statins with or without other lipid-modifying therapy, and required additional LDL-C reduction.

The mean age was 63 years (range 39–87), 34% were women, 82% were Caucasian, 16% were Black, and 11% were Hispanic/Latino. Mean baseline LDL-C was 102 mg/dL. The proportion of patients who prematurely discontinued study drug prior to the 24-week primary endpoint was 11% among those treated with PRALUENT and 12% among those treated with placebo.

At week 12, the mean percent change from baseline in LDL-C was -45% with PRALUENT compared to 1% with placebo, and the treatment difference between PRALUENT 75 mg Q2W and placebo in mean LDL-C percent change was -46% (95% CI: -53%, -39%).

At week 12, if additional LDL-C lowering was required based on pre-specified LDL-C criteria, PRALUENT was up-titrated to 150 mg Q2W for the remainder of the trial. The dose was up-titrated to 150 mg Q2W in 32 (17%) of 191 patients treated with PRALUENT for at least 12 weeks. At week 24, the mean percent change from baseline in LDL-C was -44% with PRALUENT and -2% with placebo, and the treatment difference between PRALUENT and placebo in mean LDL-C percent change was -43% (95% CI: -50%, -36%; p-value: <0.0001).

Studies 4 (ODYSSEY FH I, NCT01623115) and 5 (ODYSSEY FH II, NCT01709500) were multicenter, double-blind, placebo-controlled trials that, combined, randomly assigned 490 patients to PRALUENT and 245 patients to placebo. The trials were similar with regard to both design and eligibility criteria. All patients had HeFH, were taking a maximally tolerated dose of statin with or without other lipid-modifying therapy, and required additional LDL-C reduction. The diagnosis of HeFH was made either by genotyping or clinical criteria ("definite FH" using either the Simon Broome or WHO/Dutch Lipid Network criteria). The mean age was 52 years (range 20–87), 45% were women, 94% were Caucasian, 1% were Black, and 3% were Hispanic/Latino. The average LDL-C at baseline was 141 mg/dL.

Considering both trials together, the proportion of patients who prematurely discontinued study drug prior to the 24-week primary endpoint was 6% among those treated with PRALUENT and 4% among those treated with placebo.

At week 12, the treatment difference between PRALUENT 75 mg Q2W and placebo in mean LDL-C percent change was -48% (95% CI: -52%, -44%).

At week 12, if additional LDL-C lowering was required based on pre-specified LDL-C criteria, PRALUENT was up-titrated to 150 mg Q2W for the remainder of the trial. The dose was up-titrated to 150 mg Q2W in 32 (17%) of 191 patients treated with PRALUENT for at least 12 weeks. At week 24, the mean percent change from baseline in LDL-C was -44% with PRALUENT and -2% with placebo, and the treatment difference between PRALUENT and placebo in mean LDL-C percent change was -43% (95% CI: -50%, -36%; p-value: <0.0001). The LDL-C-lowering effect was sustained to week 52.

For additional results see Table 4 and Figure 3.

Table 4: Mean Percent Change from Baseline and Difference from Placebo in Lipid Parameters at Week 12 and Week 24 in Patients with HeFH (ODYSSEY FH I and FH II Pooled)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>LDL-C</th>
<th>Total-C</th>
<th>Non-HDL-C</th>
<th>Apo B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 12 (Mean Percent Change from Baseline)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>5</td>
<td>4</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>PRALUENT (75 mg)</td>
<td>-43</td>
<td>-27</td>
<td>-38</td>
<td>-34</td>
</tr>
<tr>
<td>Difference from placebo (LS Mean) (95% CI)</td>
<td>-48</td>
<td>-31</td>
<td>-42</td>
<td>-36</td>
</tr>
<tr>
<td>Week 24 (Mean Percent Change from Baseline)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>7</td>
<td>5</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>PRALUENT (75/up 150 mg)</td>
<td>-47</td>
<td>-30</td>
<td>-42</td>
<td>-40</td>
</tr>
<tr>
<td>Difference from placebo (LS Mean) (95% CI)</td>
<td>-54</td>
<td>-36</td>
<td>-49</td>
<td>-42</td>
</tr>
</tbody>
</table>

*pDifference is PRALUENT minus Placebo
†A pattern-mixture model approach was used with multiple imputation of missing post-treatment values based on a patient’s own baseline value and multiple imputation of missing on-treatment values based on a model including available on-treatment values
‡Dose was up-titrated to 150 mg Q2W in 196 (42%) patients treated for at least 12 weeks

Study 6 (ODYSSEY HIGH FH, NCT01617655) was a multicenter, double-blind, placebo-controlled trial that randomly assigned 72 patients to PRALUENT 150 mg Q2W and 35 patients to placebo. Patients had HeFH with a baseline LDL-C ≥180 mg/dL while taking a maximally tolerated dose of statin with or without other lipid-modifying therapy. The mean age was 51 years (range 18–68), 47% were women, 88% were Caucasian, 2% were Black, and 6% were Hispanic/Latino. The average LDL-C at baseline was 198 mg/dL.

The proportion of patients who discontinued study drug prior to the 24-week primary endpoint was 10% among those treated with PRALUENT and 0% among those treated with placebo.

At week 24, the mean percent change from baseline in LDL-C was -43% with PRALUENT and -7% with placebo, and the treatment difference between PRALUENT and placebo in mean LDL-C percent change was -36% (95% CI: -49%, -24%; p-value: <0.0001).

Study 7 (ODYSSEY CHOICE I, NCT01926782) was a multicenter, double-blind, placebo-controlled trial that randomly assigned 458 patients with primary hyperlipidemia to PRALUENT 300 mg Q4W, 115 patients to PRALUENT 75 mg Q2W, and 230 patients to placebo. Patients were stratified based on whether or not they were treated concomitantly with statin.

The mean age was 61 years (range 21–88), 42% were women, 87% were Caucasian, 11% were Black, and 3% were Hispanic/Latino. The proportion of patients who discontinued study drug prior to the 24-week primary endpoint was 12% among those treated with PRALUENT and 0% among those treated with placebo.

In the cohort of patients on background statin, the mean LDL-C at baseline was 113 mg/dL. At week 12, the treatment difference between PRALUENT 300 mg Q4W and placebo in mean percent change in LDL-C from baseline was -54% (97.5% CI: -61%, -48%), and the treatment difference between PRALUENT 75 mg Q2W and placebo in mean percent change in LDL-C was -43% (97.5% CI: -53%, -35%) (Figure 4).

The means were estimated based on all randomized patients, with multiple imputation of missing data taking into account treatment adherence.

Number of patients with observed data.

Study 7 (ODYSSEY CHOICE I, NCT01926782) was a multicenter, double-blind, placebo-controlled trial that randomly assigned 458 patients with primary hyperlipidemia to PRALUENT 300 mg Q4W, 115 patients to PRALUENT 75 mg Q2W, and 230 patients to placebo. Patients were stratified based on whether or not they were treated concomitantly with statin.

The mean age was 61 years (range 21–88), 42% were women, 87% were Caucasian, 11% were Black, and 3% were Hispanic/Latino. The proportion of patients who discontinued study drug prior to the 24-week primary endpoint was 12% among those treated with PRALUENT and 0% among those treated with placebo.

In the cohort of patients on background statin, the mean LDL-C at baseline was 113 mg/dL. At week 12, the treatment difference between PRALUENT 300 mg Q4W and placebo in mean percent change in LDL-C from baseline was -54% (97.5% CI: -61%, -48%), and the treatment difference between PRALUENT 75 mg Q2W and placebo in mean percent change in LDL-C was -43% (97.5% CI: -53%, -35%) (Figure 4).

*The means were estimated based on all randomized patients, with multiple imputation of missing data taking into account treatment adherence.

Figure 2: Mean Percent Change from Baseline in LDL-C Over 52 Weeks in Patients with HeFH on Maximally Tolerated Statin Treated with PRALUENT 75/150 mg Q2W and Placebo Q2W (ODYSSEY FH I and FH II Pooled)

*The means were estimated based on all randomized patients, with multiple imputation of missing data taking into account treatment adherence.
At week 12, if additional LDL-C lowering was required based on pre-specified LDL-C criteria, PRALUENT was adjusted to 150 mg Q2W in approximately 20% of patients treated with PRALUENT for at least 12 weeks. At week 24, the treatment difference between initial assignment to PRALUENT 300 mg Q2W and placebo in mean percent change in LDL-C from baseline was -56% (97.5% CI: -62%, -49%; p-value: <0.0001), and the treatment difference between initial assignment to PRALUENT 75 mg Q2W and placebo in mean percent change in LDL-C from baseline was -48% (97.5% CI: -57%, -39%).

In the cohort of patients not treated with a concomitant statin, the mean LDL-C at baseline was 142 mg/dL. The treatment difference between PRALUENT and placebo were similar to the cohort of patients treated with a concomitant statin.

Study 9 (ODYSSEY COMBO II, NCT01644188) was a multicenter, double-blind, placebo-controlled trial that randomly assigned 479 patients with HeFH who were undergoing LDL apheresis to PRALUENT 150 mg Q2W (N=41) or placebo (N=21). Patients were treated in combination with their usual LDL apheresis schedule for 6 weeks. The mean age was 59 years (range 27–79), 42% were women, 97% were Caucasian, 3% were Black, and 0% were Hispanic/Latino. The mean LDL-C at baseline, measured before the apheresis procedure, was 181 mg/dL. The proportion of patients who discontinued study drug prior to the 6-week endpoint was 2% among those treated with PRALUENT 150 mg Q2W and 5% among those treated with placebo. At week 6, the mean percent change from baseline in pre-apheresis LDL-C was -53% in patients in the PRALUENT group compared to 1% in patients who received placebo.

Study 8 (ODYSSEY ESCAPE, NCT02326620) was a multicenter, double-blind, placebo-controlled trial that randomly assigned patients with HeFH who were undergoing LDL apheresis to PRALUENT 150 mg Q2W (N=41) or placebo (N=21). Patients were treated in combination with their usual LDL apheresis schedule for 6 weeks. The mean age was 59 years (range 27–79), 42% were women, 97% were Caucasian, 3% were Black, and 0% were Hispanic/Latino. The mean LDL-C at baseline, measured before the apheresis procedure, was 181 mg/dL. The proportion of patients who prematurely discontinued study drug prior to the 24-week primary endpoint was 9% among those treated with PRALUENT and 10% among those treated with ezetimibe.

At week 12, the mean percent change from baseline in LDL-C was -50% with PRALUENT compared to -22% with ezetimibe, and the treatment difference between PRALUENT and ezetimibe in mean LDL-C percent change was -28% (95% CI: -32%, -23%; p-value: <0.0001). At week 24, the mean percent change from baseline in LDL-C was -45% with PRALUENT compared to -19% with ezetimibe, and the treatment difference between PRALUENT and ezetimibe in mean LDL-C percent change was -26% (95% CI: -33%, -23%; p-value: <0.0001).

PRALUENT is available in cartons containing 1 or 2 pre-filled pens and 1 or 2 pre-filled syringes. PRALUENT is designed to deliver 1 mL of 75 mg/mL or 150 mg/mL solution. PRALUENT is available in cartons containing 1 or 2 pre-filled pens and 1 or 2 pre-filled syringes. Each pre-filled pen or pre-filled syringe of PRALUENT is designed to deliver 1 mL of 75 mg/mL or 150 mg/mL solution.

Pack Size | 75 mg/mL Pre-filled Pen | 150 mg/mL Pre-filled Pen
--- | --- | ---
Pack of 1 pen | NDC 0024-5901-01 | NDC 0024-5902-01
Pack of 2 pens | NDC 0024-5901-02 NDC 7273-5901-2 | NDC 0024-5902-02 NDC 7273-5902-2

Pack Size | 75 mg/mL Pre-filled Syringe | 150 mg/mL Pre-filled Syringe
--- | --- | ---
Pack of 1 syringe | NDC 0024-5903-01 | NDC 0024-5904-01
Pack of 2 syringes | NDC 0024-5903-02 | NDC 0024-5904-02
What should I tell my healthcare provider before using PRALUENT?

Before you start using PRALUENT, tell your healthcare provider about all your medical conditions, including allergies, and if you:

• are pregnant or plan to become pregnant. It is not known if PRALUENT will harm your unborn baby. Tell your healthcare provider if you become pregnant while taking PRALUENT.

Pregnancy Registry. There is a pregnancy registry for women who take PRALUENT during pregnancy. The purpose of this registry is to collect information about your health and your baby’s health. You can talk to your healthcare provider or contact 1-877-311-8972 or go to https://mothertobaby.org/ongoing-study/praluent/ to enroll in this registry or get more information.

• are breastfeeding or plan to breastfeed. You and your healthcare provider should decide if you will take PRALUENT or breastfeed. You should not do both without talking to your healthcare provider first.

Tell your healthcare provider or pharmacist about any prescription and over-the-counter medicines you are taking or plan to take, including natural or herbal remedies.

How should I use PRALUENT?

• See the detailed “Instructions for Use” that comes with this patient information about the right way to prepare and give your PRALUENT injections.

• Use PRALUENT exactly as your healthcare provider tells you to use it.

• PRALUENT comes as a single-dose (1 time) pre-filled pen (autoinjector), or as a single-dose pre-filled syringe. Your healthcare provider will prescribe the type and dosage that is best for you.

• If your healthcare provider decides that you or a caregiver can give the injections of PRALUENT, you or your caregiver should receive training on the right way to prepare and administer PRALUENT. Do not try to inject PRALUENT until you have been shown the right way by your healthcare provider or nurse.

• PRALUENT is injected under the skin (subcutaneously) every 2 weeks or every 4 weeks (monthly).

• If your healthcare provider prescribes you the monthly dose, you will give yourself 2 separate injections in a row, using a different syringe or pen for each injection and two different injection sites.

• Do not inject PRALUENT together with other injectable medicines at the same injection site.

• Always check the label of your pen or syringe to make sure you have the correct medicine and the correct dose of PRALUENT before each injection.

• If you forget to use PRALUENT or are not able to take the dose at your regular time, inject your missed dose as soon as you remember, within 7 days. Then, if you inject every 2 weeks take your next dose in 2 weeks from the day you missed your dose or if you inject every 4 weeks take your next dose in 4 weeks from the day you missed your dose. This will put you back on your original schedule.

• If you missed a dose by more than 7 days and you inject every 2 weeks wait until your next scheduled dose to re-start PRALUENT or if you inject every 4 weeks start a new schedule from the time you remember to take your dose. If you are not sure when to re-start PRALUENT, ask your healthcare provider or pharmacist.

• If you use more PRALUENT than you should, talk to your healthcare provider or pharmacist.

• Do not stop using PRALUENT without talking with your healthcare provider. If you stop using PRALUENT, your cholesterol levels can increase.

What are the ingredients in PRALUENT?

Active ingredient: alirocumab

Inactive ingredients: histidine, polysorbate 20, sucrose, and Water for Injection, USP.

What are the possible side effects of PRALUENT?

PRALUENT can cause serious side effects, including:

• allergic reactions. PRALUENT may cause allergic reactions that can be severe and require treatment in a hospital. Call your healthcare provider or go to the nearest hospital emergency room right away if you have any symptoms of an allergic reaction including a severe rash, redness, severe itching, a swollen face, or trouble breathing.

The most common side effects of PRALUENT include: redness, itching, swelling, or pain/tenderness at the injection site, symptoms of the common cold, and flu or flu-like symptoms.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of PRALUENT. Ask your healthcare provider or pharmacist for more information. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of PRALUENT.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use PRALUENT for a condition for which it was not prescribed. Do not give PRALUENT to other people, even if they have the same symptoms that you have. It may harm them.

This Patient Information summarizes the most important information about PRALUENT. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about PRALUENT that is written for health professionals.

For more information about PRALUENT, go to www.PRALUENT.com or call 1-844-PRALUENT (1-844-772-5836).

What are the ingredients in PRALUENT?

• Active ingredient: alirocumab

• Inactive ingredients: histidine, polysorbate 20, sucrose, and Water for Injection, USP.

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This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: April 2019

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