**INDICATIONS AND USAGE**

PRALUENT® is indicated:
- To reduce the risk of myocardial infarction, stroke, and unstable angina requiring hospitalization in adults with established cardiovascular disease. (1)
- As adjunct to diet, alone or in combination with other low-density lipoprotein cholesterol (LDL-C)-lowering therapies, in adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH), to reduce LDL-C. (1)
- As an adjunct to other LDL-C-lowering therapies in adult patients with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C. (1)

**DOSAGE AND ADMINISTRATION**

- In adults with established cardiovascular disease or with primary hyperlipidemia, including HeFH (2.1):
  - The recommended starting dose of PRALUENT is either 75 mg once every 2 weeks or 300 mg once every 4 weeks administered subcutaneously. (2.1)
  - For patients receiving PRALUENT 300 mg every 4 weeks, measure LDL-C just prior to the next scheduled dose, because LDL-C can vary between doses in some patients. (2.1)
  - If the LDL-C response is inadequate, the dosage may be adjusted 150 mg subcutaneously every 2 weeks. (2.1)
- In adults with HeFH undergoing LDL apheresis or in adults with HoFH (2.1):
  - The recommended dose of PRALUENT is 150 mg once every 2 weeks administered subcutaneously. (2.1)
  - PRALUENT can be administered without regard to the timing of LDL apheresis. (2.1)
  - Assess LDL-C when clinically appropriate. The LDL-lowering effect of PRALUENT may be measured as early as 4 weeks after initiation. (2.1)
  - Administer PRALUENT subcutaneously into areas of the thigh, abdomen, or upper arm that are not tender, bruised, red, or indurated. Rotate injection sites for each administration. (2.3)
  - To administer the 300 mg dose, give two 150 mg PRALUENT injections consecutively at two different injection sites. (2.3)

**DOSE FORMS AND STRENGTHS**

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

**CONTRAINDICATIONS**
Common (>5% of patients treated with PRALUENT and more frequently than placebo) adverse reactions in adults with:
- Primary hyperlipidemia: nasopharyngitis, injection site reactions, and influenza. (6)
- Established cardiovascular disease: non-cardiac chest pain, nasopharyngitis, and myalgia. (6)

**ADVERSE REACTIONS**

To report SUSPECTED ADVERSE REACTIONS, contact Regeneron at 1-844-734-6643 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Revised: 04/2021
• To administer the 300 mg dose, give two 150 mg PRALUENT injections consecutively at two different injection sites.

3 Doseage Forms and Strengths

PRALUENT injection is a clear, colorless to pale yellow solution available as follows:

- 75 mg/mL single-dose pre-filled pen
- 150 mg/mL single-dose pre-filled pen

4 Contraindications

PRALUENT is contraindicated in patients with a history of a serious hypersensitivity reaction to alirocumab or any of the excipients in PRALUENT. Hypersensitivity vasculitis, angioedema, and hypersensitivity reactions requiring hospitalization have occurred [see Warnings and Precautions (5.1)].

5 Warnings and Precautions

5.1 Hypersensitivity Reactions

Hypersensitivity reactions, including hypersensitivity vasculitis, angioedema, and other hypersensitivity reactions requiring hospitalization, have been reported with PRALUENT treatment. The proportion of patients discontinuing treatment due to serious hypersensitivity reactions occurred more frequently in patients treated with PRALUENT compared to patients treated with placebo (0.2% versus 0.4% for PRALUENT and placebo, respectively). The proportion of patients discontinuing treatment due to other hypersensitivity reactions was also 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.

6 Adverse Reactions

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

• Hypersensitivity Reactions [see Warnings and Precautions (5.1)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates 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.

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 patients were women, 90% were White, 4% were Black or African American, and 3% were Asian.

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

Table 1: Adverse Reactions Occurring in ≥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 spams</td>
<td>2.4</td>
<td>2.5</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>Contusion</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>

† 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 (primarily related to 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 7557 patients were exposed to PRALUENT 300 mg every 4 weeks for a median of 2 years, 2.1% of patients treated with PRALUENT and 2.3% of patients treated with placebo discontinued treatment due to adverse events. In a cardiovascular outcomes trial, 5.5% (504/9091) of patients treated with PRALUENT 75 mg or 150 mg every 2 weeks 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 <0.1% of patients treated with placebo.

More frequent adverse reactions compared to placebo included:

- Injection site reactions
- Headache
- Dyspepsia
- Anorexia
- Flatulence
- Diarrhea
- Myalgia
- Upper respiratory tract infection
- Urinary tract infection
- Nasopharyngitis
- Upper respiratory tract infection
- Cough

A higher incidence of injection site reactions were observed in patients with treatment-emergent ADA compared to patients who were ADA negative (7.5% vs 3.6%). In a pool of ten placebo-controlled and active-controlled trials of patients treated with PRALUENT 75 mg and/or 150 mg every 2 weeks as well as in a separate clinical study of patients treated with PRALUENT 75 mg every 2 weeks or 300 mg every 4 weeks (including some patients with dose adjustment to 150 mg every 2 weeks), the incidence of detecting ADA and NAB was similar to the results from the trials described above.

7 Use in Specific Populations

7.1 Pregnancy

Risk Summary

Available data from clinical trials and postmarketing reports on PRALUENT use in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects. There are no data on the risk for other adverse maternal or fetal outcomes. In animal reproduction studies, there were no effects on embryo-fetal development when rats were subcutaneously administered alirocumab during organogenesis at dose exposures up to 12-fold the exposure at the maximum recommended human dose. In monkey studies, suppression of the humoral immune response was observed in infant monkeys when alirocumab was dosed during organogenesis to parturition at dose exposures 13-fold the exposure at the maximum recommended human dose of 150 mg every two weeks.

Anomalies in development of the offspring were observed in one animal study when alirocumab was administered during organogenesis and pregnancy. In a primate study with a dosing regimen of up to 12-fold the maximum recommended human daily dose of 150 mg every two weeks. Measurable alirocumab serum concentrations were observed in the infant monkeys at doses up to 81-fold the maximum recommended human dose of 150 mg every two weeks. The clinical relevance of these observations to human infants is unknown. The long-term consequences of continuing PRALUENT treatment in the presence of pregnancy are unknown.

8.1 Pregnancy

Data

Animal data

In Sprague Dawley rats, no effects on embryo-fetal development were observed when alirocumab was dosed at up to 75 mg/kg/dose by the subcutaneous route on gestation days 6 through 15. In Sprague Dawley rats, no teratogenic effects were observed when alirocumab was administered at doses of 2.5, 12.5, and 120 mg/kg/dose both before and during organogenesis and pregnancy. In Sprague Dawley rats, no effects on embryo-fetal development were observed when alirocumab was dosed at up to 75 mg/kg/dose by the subcutaneous route on gestation days 6 through 15. In Sprague Dawley rats, no teratogenic effects were observed when alirocumab was administered at doses of 2.5, 12.5, and 120 mg/kg/dose both before and during organogenesis and pregnancy.
In cynomolgus monkeys, suppression of the humoral immune response to keyhole limpet hemocyanin (KLH) antigen was observed in infant monkeys at 4 to 6 months of age when alirocumab was dosed during organogenesis at 15 mg/kg/week and 75 mg/kg/week by the subcutaneous route, corresponding to 13-fold and 81-fold the human exposure at the maximum recommended human dose of 150 mg every two weeks, based on serum AUC.

8.2 Lactation

Risk Summary

There is no information regarding the presence of alirocumab in human milk, the effects on the breastfed infant, or the effects on milk production. The development and health benefits of breastfeeding should be considered along with the mother’s clinical need for PRALUENT and any potential adverse effects on the breastfed infant from PRALUENT or from the underlying maternal condition. Human IgG is present in human milk, but published data suggest that breastmilk IgG antibodies do not enter the neonatal and infant circulation in substantial amounts.

8.4 Pediatric Use

The safety and effectiveness of PRALUENT have not been established in pediatric patients.

8.5 Geriatric Use

In controlled trials, 3683 patients treated with PRALUENT were ≥65 years of age and 734 patients treated with PRAVUENT were ≥75 years of age. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

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 (12.2)].

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 (12.2)].

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 contains two disulfide-linked heavy chains, each covalently linked to two light chains. The heavy chain is linked to the PCSK9 binding site within the antibody. Alirocumab has an approximate molecular weight of 146 kDa.

PRALUENT is a sterile, preservative-free, clear, colorless to pale yellow solution for subcutaneous use. PRALUENT 75 mg/mL or 150 mg/mL solution for subcutaneous injection in a single-dose pre-filled pen is supplied in a siliconized 1 mL Type-1 clear glass syringe.

Each 75 mg/mL pre-filled pen contains 75 mg alirocumab, histidine (8 mM), polysorbate 20 (0.1 mg), sucrose (100 mg), and Water for Injection USP, to pH 6.0.

Each 150 mg/mL pre-filled pen contains 150 mg alirocumab, histidine (6 mM), polysorbate 20 (0.1 mg), sucrose (100 mg), and Water for Injection USP, to pH 6.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Alirocumab is a human monoclonal antibody that binds to proprotein convertase subtilisin kexin type 9 (PCSK9). Alirocumab binding to the low-density lipoprotein (LDL) receptors (LDLR) on the surface of hepatocytes to promote LDLR degradation within the liver. By inhibiting the binding of PCSK9 to LDLR, alirocumab increases the number of LDLR 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 administration of 75 to 300 mg alirocumab, median times to maximum serum concentrations ([Cmax]) were 3-7 days. The pharmacokinetics of alirocumab after single subcutaneous administration of 75 mg into the abdomen, upper arm, or thigh were similar. The absolute bioavailability of alirocumab after subcutaneous 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 concentrations for a 2-fold increase in dose from 75 mg every 2 weeks to 150 mg every 2 weeks. Monthly dose normalized exposure with 300 mg every 4 weeks by the subcutaneous route, corresponding to 103-fold the 150 mg every 2 weeks exposure at the maximum recommended human dose of 150 mg every two weeks, based on serum AUC.

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 17.1 days at steady state was 17.4 days in patients receiving alirocumab at subcutaneous doses of 75 mg every 2 weeks or 150 mg every 2 weeks.

Specific Populations

Population pharmacokinetic analysis was conducted on data from 2739 patients. Age, body weight, gender, race, and creatinine clearance were found not to significantly influence alirocumab pharmacokinetics.

Renal Impairment

Since monoclonal antibodies are not known to be eliminated via renal pathways, renal function is not expected to impact the pharmacokinetics of alirocumab.

No data are available in patients with severe renal impairment.

Drug-Drug Interactions

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.

13.2 Animal Toxicology and/or Pharmacology

In 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

Adult Patients with Established Cardiovascular Disease

Study 1 (ODYSSEY OUTCOMES, NCT01663402) was a multicenter, double-blind, placebo-controlled trial in 16,924 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 or placebo once every two weeks. 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 every 2 weeks for patients who had their dose adjusted to 150 mg every 2 weeks and who had two consecutive LDL-C values below 50 mg/dL. Owing to a 2.1-fold to 2.7-fold increase in total alirocumab concentrations for a 2-fold increase in dose from 75 mg every 2 weeks to 150 mg every 2 weeks was performed. Patients on 75 mg every 2 weeks who had two consecutive LDL-C values below 50 mg/dL, were switched to placebo in a blinded fashion. Approximately 2615 (27.7%) of 9451 patients treated with PRALUENT required dose adjustment, with 150 mg every 2 weeks for 751 patients, 2615 patients, 806 (30.8%) were down-titrated to 75 mg every 2 weeks. 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% ≥65 years of age. The trial population was 79% White, 3% Black, and 13% Asian; 17% identified as Hispanic/Latino ethnicity. The index ACS event was a myocardial infarction in 85% of patients and unstable angina in 17% of patients. Prior to the index ACS event, 9% had prior myocardial infarction and 23% had coronary revascularization procedures (CABG/PCI). Selected additional baseline risk factors included hypertension (65%), diabetes mellitus (25%), New York Association class 1 or II congestive heart failure (15%), and age ≥70 years (15%); 75% of participants were receiving statin-based therapy with or without other LMT at randomization. The mean LDL-C value at baseline was 92.4 mg/dL.

PRALUENT significantly reduced the risk for the primary composite endpoint (time to first occurrence of coronary heart disease death, non-fatal myocardial infarction, fatal or non-fatal ischemic stroke, or unstable angina requiring hospitalization; p=0.0003). The results are presented in Table 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>Incidence Rate per 100 Patient Years</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Primary composite endpoint†</td>
<td>903 (9.5%)</td>
<td>3.5 (3.3 to 3.8)</td>
<td>1052 (11.2%)</td>
</tr>
</tbody>
</table>
Primary Hyperlipidemia

Study 2 (ODYSSEY LONG TERM, NCT01507831) was a multicenter, double-blind, placebo-controlled trial that randomly assigned 1553 patients to PRALUENT 150 mg every 2 weeks 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 diagnosis of HeFH was made either by genotyping or using either the Simon Broome or WHO/Dutch Lipid Network 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 White, 1% were Black, and 3% were Hispanic/Latino. The average LDL-C at baseline was 141 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 3: Mean Percent Change from Baseline and Difference* from Placebo in Lipid Parameters at Week 24 in ODYSSEY LONG TERM† (continued)

<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 (n=788)</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>PRALUENT 150 mg (n=1553)</td>
<td>-58</td>
<td>-36</td>
<td>-49</td>
<td>-50</td>
</tr>
<tr>
<td>Difference from placebo (LS Mean)</td>
<td>-58</td>
<td>-36</td>
<td>-50</td>
<td>-51</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 Maximal Tolerated Statin Treated with PRALUENT 150 mg Every 2 Weeks and Placebo Every 2 Weeks (ODYSSEY LONG TERM)
### 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>Placebo (n=245)</td>
<td>5</td>
<td>4</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>PRALUENT 75 mg (n=490)</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>(32, -44)</td>
<td>(31, -26, -39, -38)</td>
<td>(36, -39, -35)</td>
<td></td>
</tr>
<tr>
<td>Placebo (n=245)</td>
<td>7</td>
<td>5</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>PRALUENT 75 mg/150 mg (n=490)</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>(37, -50)</td>
<td>(36, -33, -39)</td>
<td>(34, -45, -42)</td>
<td></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
‡ Dose was up-titrated to 150 mg every 2 weeks in 196 (42%) patients treated for at least 12 weeks

**Figure 3: 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 Every 2 Weeks and Placebo every 2 weeks (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
- Number of patients with observed data

Study 6 (ODYSSEY HIGH FH, NCT01617655) was a multicenter, double-blind, placebo-controlled trial that randomly assigned 72 patients to PRALUENT 150 mg every 2 weeks and 51 patients to placebo. Placeholders had HeFH with a baseline LDL-C ≥160 mg/dL while taking a maximally tolerated dose of statin with or without other lipid-modifying therapy. The mean age was 51 years (range 18-80), 47% were women, 88% were White, 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%, -22%; 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 every 4 weeks, 115 patients to PRALUENT 75 mg every 2 weeks, 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 White, 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 300 mg every 4 weeks, 14% among those treated with PRALUENT 75 mg every 2 weeks, and 15% 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 every 4 weeks 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 every 2 weeks and placebo in mean percent change in LDL-C was -44% (97.5% CI: -53%, -35%) (Figure 4).

**Figure 4: Mean Percent Change from Baseline in LDL-C up to Week 12 in Patients on Concomitant Statin Treated with PRALUENT 75 mg Every 2 Weeks, PRALUENT 300 mg Every 4 Weeks or Placebo**

- 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 every 2 weeks for the remainder of the trial. The dose was adjusted to 150 mg every 2 weeks in approximately 20% of patients treated with PRALUENT 75 mg every 2 weeks or 300 mg every 4 weeks for at least 12 weeks. At week 24, the treatment difference between initial assignment to PRALUENT 300 mg every 4 weeks 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 every 2 weeks 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 was similar to the cohort of patients treated with a concomitant statin.

Study 8 (ODYSSEY ESCAPE, NCT02326220) was a multicenter, double-blind, placebo-controlled trial that randomly assigned 479 patients with HeFH who were undergoing LDL apheresis to PRALUENT 150 mg every 2 weeks (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 White, 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 every 2 weeks and 5% among those treated with placebo. At week 6, the mean percent change from baseline in pre-apheresis LDL-C was -33% in patients in the PRALUENT group compared to 1% in patients who received placebo.

Study 9 (ODYSSEY COMBO II, NCT01644188) was a multicenter, double-blind, ezetimibe-controlled trial that randomly assigned 479 patients to PRALUENT 75 mg every 2 weeks/150 mg every 2 weeks and 241 patients to ezetimibe 10 mg/day. Patients were taking a maximally tolerated dose of a statin and required additional LDL-C reduction.

The mean age was 62 years (range 29-88), 26% were women, 85% were White, 4% were Black, and 3% were Hispanic/Latino. Mean baseline LDL-C was 107 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.
Study 11 (ODYSSEY HoFH, NCT03156621) was a multicenter, double-blind, placebo-controlled trial that randomly assigned 45 adult patients to PRALUENT 150 mg every 2 weeks and 24 adult patients to placebo. Patients were taking maximally tolerated doses of statins with or without other lipid-lowering therapy and required additional LDL-C reduction.

Randomization was stratified by LDL apheresis treatment status. The diagnosis of HoFH was made by either clinical diagnosis, which included a history of an untreated total cholesterol concentration >500 mg/dL together with either xanthoma before 10 years of age or with a history of total cholesterol >250 mg in both parents, or by genetic testing. The mean age was 43 years (range 19-81), 51% were women, 78% were White, 3% were Black, 17% were Asian, and 5% were identified as Hispanic/Latino ethnicity. Mean baseline LDL-C was 283 mg/dL, with 97% on statins, 72% on ezetimibe, and 14% on lomitapide. No patient discontinued from the study prior to the 12-week primary endpoint.

At week 12, the treatment difference between PRALUENT and placebo in mean LDL-C percent change from baseline was -36% (95% CI: -51% to -20%; p < 0.0001) (see Figure 5). For the effect of PRALUENT on lipid parameters as compared to placebo, see Table 5.

Table 5: Effect of PRALUENT on Lipid Parameters in Patients with HoFH (LS Mean Percent Change from Baseline to Week 12 in ODYSSEY HoFH)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>LDL-C</th>
<th>Apo B</th>
<th>Non-HDL-C</th>
<th>Total Cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=24)</td>
<td>-27</td>
<td>9</td>
<td>-8</td>
<td>-7</td>
</tr>
<tr>
<td>PRALUENT 150 mg every 2 weeks (n=45)</td>
<td>-36</td>
<td>-30</td>
<td>-33</td>
<td>-27</td>
</tr>
<tr>
<td>Difference from placebo (LS Mean (95% CI))</td>
<td>-51, -20</td>
<td>-42, 17</td>
<td>-48, 18</td>
<td>-39, -14</td>
</tr>
</tbody>
</table>

Table 5: Effect of PRALUENT on Lipid Parameters in Patients with HoFH (LS Mean Percent Change from Baseline to Week 12 in ODYSSEY HoFH)

16 HOW SUPPLIED/STORAGE AND HANDLING
PRALUENT injection is a clear, colorless to pale yellow solution, supplied as follows:

<table>
<thead>
<tr>
<th>Strength</th>
<th>Package Size</th>
<th>NDC</th>
</tr>
</thead>
<tbody>
<tr>
<td>75 mg/mL single-dose pre-filled pen</td>
<td>1 pen</td>
<td>61755-020-01</td>
</tr>
<tr>
<td></td>
<td>2 pens</td>
<td>61755-020-02</td>
</tr>
<tr>
<td>150 mg/mL single-dose pre-filled pen</td>
<td>1 pen</td>
<td>61755-021-01</td>
</tr>
<tr>
<td></td>
<td>2 pens</td>
<td>61755-021-02</td>
</tr>
</tbody>
</table>

The needle shield is not made with natural rubber latex.
Store in a refrigerator at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light. Do not freeze. Do not shake.
PRALUENT may be kept at room temperature up to 77°F (25°C) in the original carton for 30 days. If not used within the 30 days, discard PRALUENT.

17 PATIENT COUNSELING INFORMATION
Advising the patient to read the FDA-Approved Patient Labeling (Patient Information and Instructions for Use).

Pregnancy
Advising women who are exposed to PRALUENT during pregnancy that there is a pregnancy safety study that monitors pregnancy outcomes. Encourage these patients to report their pregnancy to Regeneron at 1-844-734-6643 [see Use in Specific Populations (8.1)].

Hypersensitivity Reactions
Inform patients that serious hypersensitivity reactions (e.g., angioedema) have been reported in patients treated with PRALUENT. Advise patients on the symptoms of hypersensitivity reactions and instruct them to discontinue PRALUENT and seek medical attention promptly, if such symptoms occur.

Administration
Provide guidance to patients and caregivers on proper subcutaneous injection technique and how to use the pre-filled pen. Inform patients that it may take up to 20 seconds to inject PRALUENT. Inform patients the pre-filled pen should be allowed to warm to room temperature for 30 to 40 minutes prior to use if refrigerated.

Manufactured by:
Regeneron Pharmaceuticals, Inc.
Tarrytown, NY 10591
U.S. License # 1760
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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). Your healthcare provider will prescribe the 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 give 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 pen for each injection and 2 different injection sites.
- Do not inject PRALUENT together with other injectable medicines at the same injection site.
- Always check the label of your pen 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 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. Stop using PRALUENT and 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
  - hives
  - severe itching
  - trouble breathing
  - swelling of the face, lips, throat, or tongue

The most common side effects of PRALUENT include:

- redness, itching, swelling, pain, or tenderness at the injection site
- symptoms of the common cold
- 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.