Drug Use Research & Management Program
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New Drug Evaluation: Redemplo (plozasiran), subcutaneous injection

Date of Review: August 2026
Generic Name: Plozasiran

End Date of Literature Search: 04/15/26
Brand Name (Manufacturer): REDEMPLO (Arrowhead Pharmaceuticals)
Dossier Received: yes

Plain Language Summary:

- REDEMPLO (plozasiran) is a new medicine used to reduce triglyceride levels in patients with a genetic condition causing very high triglyceride levels. This condition is called Familial Chylomicronemia Syndrome. People with very high triglyceride levels of 1000 mg/dL or higher have increased risk for inflammation of the pancreas, known as pancreatitis.
- There is only one other medication that works like plozasiran to reduce triglyceride levels in this condition. Dietary and fat restrictions are currently the only other recommended treatments. These dietary restrictions are difficult for patients to maintain.
- In one study, plozasiran injected subcutaneously, or under the skin, every 3 months reduced triglyceride levels by a meaningful amount when compared to placebo over 12 months in patients who were also following a low-fat diet.
- Side effects with plozasiran include an increase in blood sugars, injection site reactions, and nausea.
- We recommend plozasiran will be covered for people with familial chylomicronemia syndrome who are enrolled in the fee-for-service Oregon Health Plan after a prior authorization request by the prescriber is approved.

Research Questions:

1. Is there evidence demonstrating the efficacy of plozasiran in reducing triglyceride (TG) levels and episodes of acute pancreatitis in patients with Familial Chylomicronemia Syndrome (FCS)?
2. Is there evidence that plozasiran is safe for reducing TG levels and episodes of acute pancreatitis in patients with FCS?
3. Are there specific subpopulations for which plozasiran is better tolerated or more effective when used for FCS?

Conclusions:

- There is low-quality evidence that plozasiran at the FDA-approved dose of 25 mg subcutaneous (SC) every 3 months lowers TG levels significantly more than placebo at 10 months (least squares mean [LSM] difference -59%; 95% confidence interval [CI] -90 to -28; $p<0.001$) in participants with FCS.[1]
- There is low-quality evidence that plozasiran resulted in a nominal decrease in pancreatitis in adults with FCS (5 subjects in placebo group versus 2 in the pooled plozasiran group; odds ratio [OR] 0.17; 95% CI 0.03 to 0.94).[1] Given the small of subjects with pancreatitis events, the precise magnitude of risk reduction is uncertain.

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- There is insufficient evidence for the long-term safety of plozasiran. Safety concerns include elevated hepatic transaminases and hyperglycemia. There were low rates of serious adverse events and discontinuations due to adverse events in one small trial (n=75) in adults with FCS.
- There is supportive data from two phase 2 trials that plozasiran 25 mg every 12 weeks results in clinically meaningful reduction in TG levels in patients with moderate hypertriglyceridemia (TG level 150-499 mg/dL) and severe hypertriglyceridemia (TG level ≥ 500 mg/dL) without FCS on background lipid lowering therapy.[2,3] At the time of this review, plozasiran is not FDA-approved for this indication and phase 3 trials are ongoing. There is insufficient evidence that plozasiran lowers the risk of cardiovascular events or pancreatitis in patients with moderate to severe hypertriglyceridemia.
- There are no studies comparing the efficacy or safety of plozasiran to olezarsen for the treatment of FCS.

Recommendations:
- Make plozasiran as non-preferred in the "*Other Dyslipidemia Drug*" preferred drug list (PDL) class. Review costs in executive session.
- Include plozasiran in the apolipoprotein C-III clinical prior authorization criteria to ensure it is used according to supporting evidence and FDA labeling **(Appendix 3**).

Background:
Familial chylomicronemia syndrome is a rare autosomal recessive genetic disorder that causes a deficiency in lipoprotein lipase (LPL) enzyme activity through inactivation of the LPL gene resulting in persistence of triglyceride rich chylomicrons.[4] Although the onset of symptoms usually occurs in childhood or adolescence, FCS is often underdiagnosed or the diagnosis is delayed. Up to 30% of patients with FCS remain undiagnosed until adulthood.[4] FCS affects an estimated 1 to 13 individuals per 1,000,000 in the United States and is characterized by severely elevated chylomicrons and plasma TGs and an increased risk of pancreatitis.[4,5] Clinical presentation includes a TG level greater than 885 mg/dL repeatedly, or a one-time greater than 1000 mg/dL, lack of response to standard treatments, and history of acute pancreatitis. Patients have a 60% to 90% lifetime risk of pancreatitis. There is often a lack of other secondary risk factors, such as obesity and diabetes. Other manifestations can include eruptive cutaneous xanthomas, lipemia retinalis, episodic abdominal pain, and hepatosplenomegaly.[4,5]

Genetic testing remains the gold standard for diagnosing FCS. The North American Familial Chylomicronemia Score (NAFCS) calculator was developed to use clinical criteria to determine a diagnosis of FCS and may be useful for patients who have not been tested genetically or in whom genetic testing was inconclusive.[4] The calculator is recommended only when patients are not responsive to fibrates and high-dose omega-3 fatty acids (< 20% reduction in TGs). The NAFCS calculator includes the following variables: young age of onset, BMI less than 25 kg/m^2, history of abdominal pain or pancreatitis, absence of secondary risk factors, persistent fasting TG greater than 885 mg/dL, TG to total cholesterol ratio greater than 3.5 mg/dL, apolipoprotein B (apoB) < 1 g/L, and nonresponse to conventional medications.[4]

The goal of treatment in FCS is to prevent acute pancreatitis and reduce plasma TG levels to less than 885 mg/dL. There is no current evidence-based definitive TG target and there are no high-quality clinical guidelines addressing FCS. There are currently no Food and Drug Administration (FDA)-approved treatments for FCS. Standard triglyceride-lowering treatments with fibrates, niacin, and omega-3 fatty acids are typically not effective in FCS due to a lack of LPL activity in FCS patients. Standard of care remains a restrictive low-fat diet (< 20 grams daily) to reduce the accumulation of chylomicrons, physical activity, and complete avoidance of alcohol. While standard lipid-lowering drugs are generally not effective for patients with FCS as they have no impact on chylomicron metabolism, they may be beneficial in patients with concomitant risk factors for atherosclerotic cardiovascular disease (ASCVD).[4,5]

Inhibiting APOC3 reduces TG levels by enhancing LPL activity and reducing serum apolipoprotein C-III protein, a key regulator of TG metabolism. Volanesorsen is an APOC3 inhibitor approved in Europe for the treatment of FCS. It was not approved in the United States because of concerns about thrombocytopenia.[4] In

December 2024, Olezarsen was the first FDA-approved treatment for FCS in adults. It is an antisense oligonucleotide targeting apolipoprotein C-III (APOC3) mRNA to reduce APOC3 production. Olezarsen was approved through expedited approval pathways, including fast-track, breakthrough therapy, and priority review.[5] Olezarsen is a second generation APO3 inhibitor targeting hepatic APOC3 mRNA. It has the same chemical composition as volanesorsen but differs with the addition of a triantennery N-acetyl galactosamine, which allows for lower dosing. Olezarsen 80 mg subcutaneous once monthly lowered TG levels more than placebo at 6 months (difference -43.5%; 95% CI -69.1 to -17.9; p<0.001) in subjects with FCS with insufficient evidence on decreasing pancreatitis and no effect on LDL-C.[6] There is supportive data that olezarsen 50 mg and 80 mg reduce TG levels in patients with moderate hypertriglyceridemia (TG level 150-499 mg/dl) at high cardiovascular (CV) risk and severe hypertriglyceridemia (TG level ≥ 500 mg/dl) without FCS on background lipid lowering therapy.[7,8] At the time of this review, olezarsen is not FDA approved for this indication, but a supplemental new drug application has been submitted to FDA.

Also targeting APOC3, Plozasiran is a small interfering RNA (siRNA) that degrades APOC3 mRNA through RNA interference, resulting in increased clearance of serum TGs. It was FDA approved in November 2025 for the treatment of FCS in adults through expedited FDA approval pathways.[9] There is no data comparing plozasiran to olezarsen and neither drug has demonstrated a reduction in cardiovascular or clinical outcomes.

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations. Pharmacology and Pharmacokinetic Properties are listed in **Appendix 2**.

Clinical Efficacy:
Plozasiran 25 mg administered subcutaneously every 3 months received approval based on one randomized, phase 3, double-blind, controlled trial (**Table 1**). Subjects were randomized 2:1 to plozasiran 25 mg or volume matched placebo or plozasiran 50 mg or volume-matched placebo subcutaneously every 3 months for 12 months.[1] Adults 18 years of older with FCS and fasting TG levels greater than 880 mg/dL with and without a history of pancreatitis were included. Subjects with both genetically confirmed and clinical diagnoses were included. A clinical diagnosis included fasting TG level greater than 1000 mg/dL and one of the following: recurrent episodes of acute pancreatitis, recurrent hospitalizations for abdominal pain, childhood pancreatitis, or family history of hypertriglyceridemia-induced pancreatitis.[1] The FDA typically requires 2 adequate and well controlled trials to provide substantial evidence for efficacy. However, the FDA allowed one study due to the rarity of the condition and lack of alternative treatment options for FCS.[9]

If the study participant was not already following a low-fat diet, they were enrolled in a 4-week dietary run-in period. Subjects were instructed to consume no more than 20 g of fat per day, and alcohol use was discouraged.[1] Of the 123 screened subjects, 75 were randomized to plozasiran or placebo. The most common reason for screen failure was not meeting the TG requirement or diagnosis of FCS. Seventy-three percent of the enrolled population was White, the median TG level was 2044 mg/dL, and 49% were enrolled based on a previous genetic confirmation.[1] Thirty four subjects had a clinical diagnosis of FCS that was not genetically confirmed. Most subjects (88%) had a previous episode of pancreatitis.[1]

The percent change in baseline TG level was -80% with plozasiran 25 mg (LSM difference -59%; 95% CI -90 to -28), -78% with plozasiran 50 mg (LSM difference -53%; 95% CI -83 to -22), and -17% with placebo, resulting in a statistically significant mean difference in both treatment groups.[1] There were also statistically significant differences in percent change from baseline in APO3 for both plozasiran 25 mg (LSM difference -95%; 95% CI -108.3% to -72.7%) and plozasiran 50 mg (LSM difference -93.4%; 95% CI -109.4% to -77.4%) compared to placebo at month 10.[1] Subgroup analysis demonstrated a similar treatment effect in those with genetically confirmed FCS and clinically diagnosed FCS. Plozasiran resulted in an increase in low density lipoprotein (LDL) from baseline compared to placebo.

There was a total of 9 positively adjudicated acute pancreatitis events, occurring in 5 (20%) subjects in the placebo group and in 2 (4%) in the pooled plozasiran groups (OR 0.17; 95% CI 0.03 to 0.94; p=0.03).[1] Given the small of subjects with pancreatitis events, the precise magnitude of risk reduction is uncertain.

Two phase 2 trials in adults with severe hypertriglyceridemia (TG ≥ 500 mg/dL) (n=226) and moderate hypertriglyceridemia (TG ≥ 150 mg/dL and ≤ 400 mg/dL) (n=353) were used by the FDA as confirmatory evidence.[2,3] Subjects with a history of clinical ASCVD or an elevated 10-year ASCVD risk score were required to be on appropriate lipid lowering therapy according to standard of care. There were high rates of screening failures in both trials (66.2% in severe hypertriglyceridemia trial and 52% in moderate hypertriglyceridemia).[9] Both trials demonstrated statistically significant reductions in TG levels from baseline at week 24 with plozasiran administered subcutaneously every 12 weeks (total of 2 doses given). In moderate hypertriglyceridemia, the placebo-adjusted percent change in fasting TG from baseline to week 24 was -56% (95% CI -65.1 to -46.8) and in severe hypertriglyceridemia, the difference was -53.1% (95% CI -65.1% to -38). There are ongoing phase 3 trials evaluating plozasiran for moderate and severe hypertriglyceridemia.

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Acute pancreatitis
2) Hospitalization due to pancreatitis
3) Serious adverse events
4) Study withdrawal due to an adverse event
5) Reduction in TG level

Primary Study Endpoint:

1) Percent change in fasting triglyceride level from baseline to month 10

Table 1. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Endpoints	ARR/NNH	Risk of Bias/ Applicability
1. Palisade Study[1] Phase 3, DB, PC, RCT	1. Plozasiran 25 mg SC Q 3 months 2. Plozasiran 50 mg SC Q 3 months 3. placebo * 4-week run-in period for diet stabilization prior to randomization 12 months	Demographics: 51% women, 73% white, mean age 46 years, median TG 2044 mg/dL, 59% genetically confirmed FCS, 88% h/o pancreatitis Key Inclusion Criteria: -Genetically or clinically confirmed diagnosis of FCS -Fasting TG ≥880 mg/dL, refractory to standard lipid lowering therapy -Age ≥18 years old - ≤ 20g of fat/ day Key Exclusion Criteria: -Active pancreatitis - HbA1c ≥ 9% - AST/ALT > 3 x ULN - Bilirubin > 1.5 x ULN -eGFR < 30 ml/min - Coagulopathy - Malignancy within 2 years - Active HIV, HCV, or HBV - Use of GLP-1 - NYHA Class II, III, or IV HF or EF < 30% - > 14 units of alcohol per week	ITT: 1. 26 2. 24 3. 25 PP: 1. 23 2. 22 3. 19 Attrition: 1. 3 (12%) 2. 2 (8%) 3. 6 (24%)	Primary Endpoint: Percent change in fasting TG from baseline at Month 10 1. -80% 2. -78% 3. -17% Mean difference: 25 mg vs placebo: -59% 95% CI, -90 to -20; P<0.0001 50 mg vs. Placebo: -53%; 95% CI, -83 to -22; p=0.0002 Secondary Endpoint: Acute Pancreatitis (pooled plozasiran vs. pooled placebo) Plozasiran: 2 (4%) Placebo: 5 (25%) OR 0.17; 95% CI 0.03 to 0.94; p=0.03	N/A N/A	Discontinued due to AE: 1. 2 (7.7%) 2. 1 (4.2%) 3. 0 Serious adverse effects: 1. 5 (19%) 2. 2 (8%) 3. 7 (28%)	NS NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear; randomized using an interactive web response system, allocation performed using a block randomization algorithm; small numbers resulted in imbalances at baseline in TG lowering therapy and percent of subjects with diabetes Performance Bias: Low; double blinded using matching placebo volume. Detection Bias: Low; blinded assessors for adjudication of pancreatitis Attrition Bias: Low; low overall attrition and similar between groups. Reporting Bias: Low. Protocol available online and all outcomes prespecified. Other Bias: High. Study financially supported by drug manufacturer. Arrowhead Pharmaceuticals involved in data interpretation and preparation of manuscript. **Applicability**: Patient: Rare disease limits sample size. 54% of screened patients did not meet randomization criteria. FCS is often present in adolescents, who were excluded. The 4-week diet stabilization run-in period limits applicability. Intervention: Doses selected based on phase 1 studies. However, no clear dose response in phase 3 study and only the 25 mg dose was FDA approved. Comparator: Placebo group comparator appropriate Outcomes: Reduction in TG levels is a surrogate outcome. Uncertainty around magnitude of benefit on acute pancreatitis. Setting: 58 centers in 21 countries; 12% of subjects from the United States.

Abbreviations : ACS = acute coronary syndrome; AE = adverse events; ALT = alanine aminotransferase; ARR = absolute risk reduction; ASCVD = atherosclerotic cardiovascular disease; AST = aspartate aminotransferase; CI = confidence interval; CV = cardiovascular; DC = discontinuation; DB = double-blind; EF = ejection fraction; eGFR = estimated glomerular filtration rate; FCS = Familial Chylomicronemia Syndrome; GLP-1 = glucagon like peptide-1; HbA1c = hemoglobin A1c; HBV = hepatitis B virus; HCV = hepatitis C virus; HF = heart failure; HIV = human immunodeficiency virus; ITT = intention to treat; LSM = least squares mean; MC = multicenter; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not

reported; NYHA = New York heart association; OR = odds ratio; PC = placebo controlled; PP = per protocol; RR: rate ratio; SAE = serious adverse events; SC = subcutaneous; TG = triglyceride; ULN = upper limit of normal.

Clinical Safety:

In the small pivotal study, plozasiran was well tolerated. Common side effects that occurred more frequently than placebo are included in **Table 2.** Side effects of concern with plozasiran include hyperglycemia, elevated in liver transaminases, and increases in LDL-C. In the pivotal trial, there were 3 discontinuations due to adverse events in subjects receiving plozasiran and none in subjects receiving placebo. Two of the discontinuations were due to hyperglycemia. Average fasting glucose and HbA1c values increased by 7.6 mg/dl and 0.33%, respectively in the plozasiran 25 mg group.[9] There were more subjects receiving plozasiran who experienced a composite hyperglycemia outcome consisting of adverse events, new antidiabetic medication, and laboratory values in a subgroup without diabetes compared to placebo (40% vs. 20%), suggesting worsening glycemic control with plozasiran.[9] Plozasiran was associated with mean increases in ALT, (alanine aminotransferase) AST (asparte aminotransferase), and direct bilirubin within the first 3 months, which stabilized, and remained on average within normal range. Increases in LDL-C of 125% from baseline was noted in the FCS population treated with plozasiran 25 mg compared to 46% in those treated with placebo. Despite increases in the LDL-C, the average LDL-C value at Month 12 was less than 50 mg/dL.[9]

The proportion of subjects reporting serious adverse events was 28% in the placebo, 19% in the 25 mg plozasiran group, and 8% in the plozasiran 50 mg group. While thrombocytopenia is a safety concern of antisense oligonucleotides, platelet levels remained unchanged from baseline and there was no difference in the frequency of thrombocytopenia between plozasiran and placebo. The safety of plozasiran has not been established in pediatric patients with FCS.

Table 2: Adverse reactions that occurred in > 10 % of patients and at a higher frequency than placebo[10]

Adverse reaction	Plozasiran (n=43)	Placebo (n=23)
Hyperglycemia	10 (20%)	2 (8%)
Headache	8 (16%)	2 (8%)
Nausea	7 (14%)	2 (8%)
Injection site reaction	1 (4%)	5 (10%

References:

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6. Stroes ESG, Alexander VJ, Karwatowska-Prokopczuk E, et al. Olezarsen, Acute Pancreatitis, and Familial Chylomicronemia Syndrome. *The New England journal of medicine.* 2024;390(19):1781-1792.
7. Bergmark BA, Marston NA, Prohaska TA, et al. Targeting APOC3 with Olezarsen in Moderate Hypertriglyceridemia. *The New England journal of medicine.* 2025;393(13):1279-1291.
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Appendix 1: Prescribing Information Highlights

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

REDEMPLO (plozasiran) injection, for subcutaneous use
Initial U.S. Approval: 2025

----------INDICATIONS AND USAGE----------
REDEMPLO is an apolipoprotein C-III *(apoC-III)*-directed small interfering ribonucleic acid (siRNA) indicated as an adjunct to diet to reduce triglycerides in adults with familial chylomicronemia syndrome (FCS). (1)

----------DOSAGE AND ADMINISTRATION----------
- The recommended dosage of REDEMPLO is 25 mg injected subcutaneously once every 3 months. (2.1)
- Inject REDEMPLO subcutaneously into the front of the thigh or abdomen. The outer area of the upper arm can be used as an injection site if a healthcare provider or caregiver administers the injection. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Injection: 25 mg/0.5 mL solution in a single-dose pre-filled syringe. (3)

----------CONTRAINDICATIONS----------
None. (4)

----------ADVERSE REACTIONS----------
Most common adverse reactions in REDEMPLO treated patients (incidence ≥10% of patients treated with REDEMPLO and >5% more frequently than with placebo) are hyperglycemia, headache, nausea, and injection site reaction. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Arrowhead Pharmaceuticals Inc. at 1-844-REDEMPLO (1-844-733-3675), or https://arrowheadpharma.com/safetyreporting, or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

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

Revised: 11/2025

Appendix 2. Pharmacology and Pharmacokinetic Properties.[10]

Parameter	
Mechanism of Action	Plozasiran is an siRNA conjugated with GalNAc that binds and degrades ApoC-III mRNA through the RNA interference mechanism resulting in reduced levels of hepatic and serum ApoC-III protein. Reduction of serum and liver ApoC-III protein leads to increased clearance of plasma TGs
Oral Bioavailability	N/A; subcutaneous administration
Distribution and Protein Binding	Volume of distribution is 146 L; Plozasiran is 78% protein bound
Elimination	16% - 19% excreted in the urine
Half-Life	3 to 4 hours
Metabolism	Plozasiran is primarily metabolized by nucleases to shorter oligonucleotides of varying lengths.

Abbreviations: ApoC-III - apolipoprotein C-III; L – liter; N/A – not applicable; RNA - Ribonucleic acid; siRNA – small interfering RNA; TG - triglyceride

APOLIPOPROTEIN C-III (APOC3) Inhibitors

Goal(s):

- Promote use of APOC3 Inhibitors that is consistent with medical evidence and FDA-approved indications.
- Promote use of high value products.

Length of Authorization:

Up to 12 months

Requires PA:

- Olezarsen (Tryngolza)
- Plozasiran (Redemplo)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. Is this a request for renewal of a previously approved prior authorization?	**Yes**: Go to **Renewal Criteria**	**No**: Go to #2
2. What diagnosis is being treated?	Record ICD10 code. Go to #3	
3. Is the medication prescribed by or in consultation with a specialist in familial chylomicronemia syndrome (FCS)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Does the patient have a diagnosis of familial chylomicronemia syndrome (FCS), confirmed by genetic testing? Please submit a copy of the genetic testing results	**Yes**: Go to #5	**No:** Go to #7

Approval Criteria		
5. Does the patient have a current triglyceride level of 1000 mg/dL or greater within the previous 6 months?	**Yes:** Go to #6 **Recent TG Level**_____ **Date** _____	**No:** Pass to RPh. Deny; medical appropriateness
6. Does the patient agree to adhere to a low-fat diet (≤ 20 g of fat per day)?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the request for an FDA-approved indication?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Does the patient have clinically diagnosed severe hypertriglyceridemia with triglyceride levels ≥ 500 mg/dL on at least 2 occasions within the previous 6 months?	**Yes:** Go to #9 **Recent TG Level**_____ **Date** _____	**No:** Pass to RPh. Deny; medical appropriateness
9. Is the patient on maximally tolerated statin therapy?	**Yes:** Go to #10	**No: No:** Pass to RPh. Deny; medical appropriateness
10. Has the patient failed to have adequate benefit with (triglycerides remain > 500 mg/dl), or have a contraindication to, an adequate trial (at least 8 weeks) of a fibric acid derivative (fenofibrate or gemfibrozil) and high-dose omega 3 fatty acid (4 gm daily)?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there documentation of a positive clinical response (i.e. clinically meaningful reduction in triglyceride level or reduction in episodes of acute pancreatitis) within the previous 6 months?	Yes: Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness