Targeting APOC3: Redemplo Joins the Growing Landscape of Treatment for FCS

When Julie was just 18, her blood results revealed alarmingly high triglyceride levels at over 1,000 mg/dL. Two years later, she had her first acute pancreatitis attack. Although she would suffer from monthly pancreatitis flares after having her son and her triglycerides would escalate to over 10,000 mg/dL, she wouldn't receive a diagnosis of familial chylomicronemia syndrome (FCS) for years.

For too long, FCS has been an untreatable condition, but the past few years have seen landmark advancements in treatment options. Recently, the U.S. Food and Drug Administration (FDA) approved Redemplo (plozasiran) for the treatment of adults with familial chylomicronemia syndrome (FCS). Redemplo was approved only a year after the approval of Tryngolza (olezarsen) in late 2024.

Familial Chylomicronemia Syndrome: rare and misdiagnosed

Familial chylomicronemia syndrome (FCS) — also known as lipoprotein lipase deficiency — is a rare, inherited disease that impairs the body's ability to metabolize fats. Those with FCS lack functional lipoprotein lipase (LPL), the enzyme needed for breaking down fats, thus impeding the body's ability to eliminate triglycerides from the bloodstream. Normal triglyceride levels are below 150 mg/dL, but people with FCS have levels that can far surpass 880 mg/dL.

About 80% of familial hyperchylomicronemia syndrome is due to inherited defects in both alleles of the lipoprotein lipase gene. The remaining 20% is attributable to other genetic

mutations affecting lipoprotein lipase function, such as apolipoprotein C-II (APOC2), apolipoprotein A-V (APOA5), high-density lipoprotein binding protein 1 (GP1HBP1), and lipase maturation factor 1 (LMF1). All these mutations lead to the malfunctioning of the lipoprotein lipase enzyme (1).

Affecting one to ten people per million worldwide, the disorder significantly increases the risk of acute pancreatitis, a painful and potentially fatal swelling of the pancreas. Acute severe pancreatitis can also cause multi-organ failure and increase morbidity and mortality, as well as lead to chronic pancreatitis (1). These attacks often happen repeatedly, requiring multiple hospital visits.

The disease is often misdiagnosed as it shares symptoms with more common conditions, like multifactorial syndrome or MCS. Key indications of FCS are chronic fatigue, forgetfulness, spleen and liver swelling, and fatty deposits known as xanthomas that build up in the skin, especially in the arms, buttocks, and/or knees. The disease's psychological and financial burden has also contributed to patients reporting feelings of anxiety, isolation, and depression. Additionally, hypertriglyceridemia is an independent risk factor for cardiovascular diseases and other complications, including changes in mental activity, loss of memory, and difficulty concentrating (1).

Dr. Christie Ballantyne, chief of cardiovascular research at Baylor College of Medicine and principal investigator of the PALISADE trial for Redemplo, explained in an HCP Live interview that diagnosis relies on integrating genetic testing with structured clinical evaluation. He said that diagnosis is rarely based on a single finding, but rather on a coordinated interpretation of laboratory results, clinical history, and genetic data, adding that this approach speeds up referrals to lipid specialists and ensures that patients who qualify for newly approved therapies are identified efficiently.

Prior to the approval of Redemplo and Olezarsen, the only treatment options for those with FCS were to follow a highly fat-restricted diet, exercise, and eliminate alcohol and simple carbohydrates, and those in the EU have been able to receive Volanesorsen since 2019. Even with the lifestyle changes, Ballantyne said, it is still difficult for those with FCS to lower their triglycerides.

"It was frustrating that there was a genetic disorder that we simply could not treat," he said.

Ballantyne suggested that the lipid profile of anyone with pancreatitis should be checked, and that high triglycerides are a red flag for FCS. When triglycerides are over 880, patients have chylomicrons, large particles full of triglycerides from the diet, which doctors should recognize as a risk for pancreatitis.

In Julie's case, after giving birth, she was hospitalized every month for two years due to her pancreatitis episodes. She was missing precious moments with her infant son and husband. Looking for answers, she underwent multiple surgeries over the next seven years, including a

radical hysterectomy at 34 that would prevent her from having the large family she dreamed of. Still no diagnosis. No answers.

During a plasma exchange, a practitioner noticed chylomicrons in Julie's blood. She went home, researched the terms, and found information about FCS, which she brought to her lipidologist. Three months later, she was finally diagnosed with FCS.

PALISADE trial: lower triglycerides and reduced risk of pancreatitis

The approval of Redemplo, announced on November 18, 2025, marks Arrowhead Pharmaceuticals' first FDA-approved therapy. In January 2025, the FDA accepted Redemplo's New Drug Application (NDA) based on results from its PALISADE phase 3 trial, and supportive data from its phase 2 SUMMIT program.

In the press release, Christopher Anzalone, Ph.D., President and CEO at Arrowhead Pharmaceuticals, said that "The FDA approval of REDEMPLO is a transformational milestone for Arrowhead. This is a proud moment for all those involved in the discovery and development process and represents new hope for the estimated 6,500 people in the U.S. living with genetic or clinical FCS. This approval, and subsequent launch, marks the beginning of a new chapter in our journey—one rooted in our unwavering commitment to delivering life-changing therapies to patients with serious diseases."

Redemplo is a small interfering ribonucleic acid (siRNA) conjugated with N-acetylgalactosamine (GalNAc) for targeted liver delivery. Redemplo is approved as an adjunct to diet and is administered as a subcutaneous injection once every three months, which can be done at home.

It acts by suppressing the production of a specific protein called apolipoprotein C-III (APOC3), a significant component of triglyceride-rich lipoproteins (TRLs) that also regulates triglyceride metabolism. As triglyceride blood levels rise, APOC3 prevents the breakdown of TRLs by lipoprotein lipase and the uptake of TRL remnants by hepatic receptors in the liver (1). By reducing APOC3 levels, TRL clearance increases, resulting in lower blood triglyceride concentrations.

Participants in the PALISADE trial included patients who had a fasting triglyceride level of ≥880 mg/dL and a diagnosis of FCS who were willing to follow dietary counselling and local standard of care. A total of 75 participants from 18 countries were enrolled in the trial and randomly assigned to receive 25 mg or 50 mg of plozasiran, or a matching placebo, all administered once every three months for 12 months (1). The primary endpoint was the median percent change from baseline in fasting triglycerides at month 10. Secondary endpoints included incidence of acute pancreatitis, the percent change from baseline to mean values of fasting triglycerides at months 10 and 12, as well as percent changes in apoC-III and non-HDL-C at months 10 and 12 (2).

Results showed that at 10 months patients receiving the 25 mg dose had a median change in the fasting triglyceride level as compared with placebo of -59 percentage points, while the 50-mg plozasiran group had a change of -53 percentage points. Additionally, the pooled 25 mg and 50 mg group had an 83% lower risk of acute pancreatitis compared with the placebo group. These triglyceride drops were seen as early as one month and persisted throughout the 12 months. A favorable tolerability profile was observed throughout the trial, and the most common adverse reactions were hyperglycemia, headache, nausea, and injection site reaction.

Lindsey Sutton Bryan, co-founder and co-president of the FCS Foundation, said that the approval of Redemplo marks a pivotal moment for people living with familial chylomicronemia syndrome and the physicians who support them.

“Because FCS symptoms are mostly invisible, this community historically has been often overlooked and misunderstood, making their journey to effective treatment especially difficult,” she said.

Plozasiran is also being investigated in multiple SHASTA Phase 3 studies in patients with severe hypertriglyceridemia, as well as the MUIR Phase 3 study in patients with mixed hyperlipidemia. It has also been submitted to additional global regulatory authorities for review and marketing authorization.

Volanesorsen and Olezarsen: reduce triglycerides and lower the risk of pancreatitis

The first drug approved to treat FCS was Waylivra (Volanesorsen) by Ionis and Akcea, which was approved by the European Medicines Agency in 2019. It is a second-generation 2'-*O*-methoxyethyl (2'-MOE) ASO that blocks the production of apoC3 by targeting mRNA. After three months in the phase 3 study, participants had a 77% mean percentage change in triglyceride levels, compared with an 18% increase found in the placebo-receiving control group, although reduced platelet counts were a common side effect (3).

The second FCS treatment to receive regulatory approval was olezarsen (TRYNGOLZA), an antisense oligonucleotide (ASO) conjugated with GalNAc for liver targeting. The drug, approved by the US FDA in 2024, binds to and promotes the degradation of apoC3 mRNA via RNase H-mediated cleavage (4), distinct from the RNA interference mechanism used by siRNAs like Redemplo. Both ASO and siRNA therapies target apoC3 to reduce triglycerides in FCS, but they employ different RNA-targeting modalities.

Their administration frequencies differ as well, with Redemplo given every three months and Olezarsen administered once a month, while Waylivra is administered once a week for three months, then reduced to once every two weeks. Like Redemplo, however, Olezarsen and Waylivra successfully lowered triglyceride levels and reduced the risk of pancreatitis in the patients participating in their trials.

The future of FCS treatment

For those newly diagnosed with FCS, Julie said to give yourself grace. “Find your support system—family, friends, online communities. You are not alone. This disease does not define you. You can still have dreams and goals. Make plans, be flexible with adjustments, but don’t stop dreaming.”

25 years into her own health journey, Julie is still dreaming. “Having a triglyceride level under 500 makes me a little giddy. It’s exciting to think about that possibility. Fewer hospitalizations would mean everything to me. I could live. I could plan for my future… It would mean possibility.”

Ballantyne said that both Redemplo and Tryngolza have dramatically altered treatment options for patients with FCS, although it’s essential for people on these therapies to maintain a low-fat diet to benefit from lower triglycerides and reduced risk of pancreatitis.

“The dietary part is still important,” he said. “But it used to be that with the diet, they [FCS patients] couldn’t get their numbers very low. Now if they take the medication on time and follow the diet, they can get themselves in a safe zone where they’re not at risk of pancreatitis.”

“These therapies work,” he added. “Patients who [triglycerides] could not be controlled can now be controlled.”

The recent approvals of Redemplo and Tryngolza signal a new era for people living with FCS — one in which pancreatitis is no longer an inevitable outcome and triglyceride levels can finally be brought under control. For patients like Julie, these therapies offer not just clinical improvement but the chance to reclaim time, energy, and milestones once overshadowed by hospitalization and uncertainty. As awareness grows, specialists will more readily recognize the signs of FCS, and more patients can be accurately diagnosed and connected with effective treatment sooner. While careful dietary management and lifestyle changes will remain essential, the combination of these new targeted therapies with comprehensive care offers real hope that FCS may become a manageable condition rather than a life-defining burden.

References:

1. Regmi M, Rehman A. Familial Hyperchylomicronemia Syndrome. 2023 Aug 8. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan–. PMID: 31869119.
2. Watts GF, Rosenson RS, Hegele RA, Goldberg IJ, Gallo A, Mertens A, Baass A, Zhou R, Muhsin M, Hellawell J, Leeper NJ, Gaudet D; PALISADE Study Group. Plozasiran for Managing Persistent Chylomicronemia and Pancreatitis Risk. N Engl J Med. 2025 Jan 9;392(2):127-137. doi: 10.1056/NEJMoa2409368. Epub 2024 Sep 2. PMID: 39225259.

3. Witztum JL, Gaudet D, Freedman SD, Alexander VJ, Digenio A, Williams KR, Yang Q, Hughes SG, Geary RS, Arca M, Stroes ESG, Bergeron J, Soran H, Civeira F, Hemphill L, Tsimikas S, Blom DJ, O'Dea L, Bruckert E. Volanesorsen and Triglyceride Levels in Familial Chylomicronemia Syndrome. N Engl J Med. 2019 Aug 8;381(6):531-542. doi: 10.1056/NEJMoa1715944. PMID: 31390500.
4. Oligonucleotide Treatment Advances Offer Relief for Patients with Familial Chylomicronemia Syndrome. Oligonucleotide Therapeutics Society. 2025 Feb 5.