

TRYNGOLZA™ (olezarsen)

Category:

Best Product for Orphan/Rare Diseases

Company Name:

Ionis

Product/Solution Name:

TRYNGOLZA™ (olezarsen)

Compound/Tech Name:

IONIS-APOCIII-LRx

Trade Name:

TRYNGOLZA™

Corporate Name:

olezarsen

Date of Approval:

2024-12-19

Indications:

TRYNGOLZA™ (olezarsen) is indicated as an adjunct to diet to reduce triglycerides in adults with familial chylomicronemia syndrome (FCS).

Therapeutic Areas:

FCS is a rare, genetic, potentially life-threatening form of severe hypertriglyceridemia (sHTG) associated with an elevated risk of life-threatening acute pancreatitis (AP). Severely elevated triglycerides are caused by the body's inability to break down fats and remove triglycerides from the bloodstream due to an impaired function of the enzyme lipoprotein lipase (LPL). TRYNGOLZA is the first and only FDA-approved medicine for FCS.

General Information File Document upload:

[**Prescribing information TRYNGOLZA.pdf**](#)

[**FDA Approval Press Release TRYNGOLZA.pdf**](#)

[**TRYNGOLZA Ionis FDA Approval PR.pdf**](#)

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Background information and need for drug / device:

FCS is an underrecognized disease, characterized by a buildup of fat particles called chylomicrons in the blood, resulting in high triglyceride levels that are poorly controlled by previously available triglyceride-lowering therapies. In people with FCS, impaired LPL function causes the accumulation of these chylomicrons, resulting in triglyceride levels 10-100x higher than the normal level (<150 mg/dL). As a result, people with FCS experience a high risk of AP - a painful inflammation of the pancreas that often results in lengthy hospitalizations and can be fatal. Furthermore, FCS is associated with many chronic health issues such as severe, recurrent abdominal pain, fatigue and a high risk of diabetes due to damage to the pancreas. In severe cases, additional vital organs such as the heart, lungs and kidneys can be damaged. Unfortunately, as many as 65-80% of patients will experience at least one episode of AP, with a mortality rate as high as 30%.

People with FCS are advised to maintain an extremely limited, low-fat diet and can experience challenges in social settings centered around food and drink, which can add to emotional distress, social isolation, or feelings of uncertainty or hopelessness. FCS may also stop people from maintaining steady work and cause anxiety about relationships, and guilt or disappointment about missing out on events, adding to financial and psychological stress.

In the U.S., FCS is estimated to impact up to approximately 3,000 people, the vast majority of whom remain undiagnosed. As a rare disease that many patients and healthcare providers may not encounter regularly, lack of awareness can result in diagnostic delays. FCS can also be difficult to distinguish from other conditions marked by elevated triglycerides, including SHTG and multifactorial chylomicronemia syndrome (MCS). Lipid specialists are best equipped to diagnose FCS, which can be accomplished through the use of a clinical scoring system, though genetic testing is recommended to help support a diagnosis.

In December 2024, TRYNGOLZA™ (olezarsen) became the first and only FDA-approved treatment for adults with FCS as an adjunct to diet. Prior to the approval of TRYNGOLZA, the primary disease management approach for FCS was limiting daily fat intake to <20 grams, equivalent to approximately one tablespoon of olive oil. However, diet alone is often ineffective in lowering triglycerides and preventing AP and other chronic, debilitating symptoms associated with FCS.

Recognizing the significant medical need for an FCS treatment, the FDA granted Orphan Drug designation and Priority Review for TRYNGOLZA. With the FDA approval of TRYNGOLZA, those adults in the U.S. who are impacted by FCS - including patients, families and the HCPs who treat them - now have renewed hope. Olezarsen is currently undergoing review in the EU for the treatment of FCS.

Background File Document upload:

[TRYNGOLZA Ionis NEJM Balance.pdf](#)

[TRYNGOLZA Ionis Jnl ClinLipid NAFCS Validation.pdf](#)

History of the development of the solution/product:

In the early 2000s, Ionis initiated research to identify a potent apoC-III (a protein produced in the liver) antisense oligonucleotide (ASO). The catalyst for prioritizing this project was a 2008 publication about a cohort of Amish individuals who carried a loss-of-function mutation in apoC-III and had reduced plasma apoC-III and triglycerides. This got us thinking - what if we could engineer a medicine to help lower apoC-III levels, and therefore lower triglycerides, for people with severely elevated levels?

Olezarsen represents the most advanced ASO chemistry from Ionis - the pioneer in ASO R&D. Clinical trials for our previous generation medicine, volanesorsen, were the first to prove the connection between apoC-III and triglyceride levels and to demonstrate efficacy of a medicine in patients with FCS, but volanesorsen was associated with an increased risk of thrombocytopenia and the FDA did not approve it (volanesorsen was approved in the EU and other regions).

To address the safety issues of systemic delivery of volanesorsen, Ionis designed a new molecule - olezarsen - using a GalNAc conjugate to specifically target hepatocytes in the liver, to allow for less frequent (monthly vs. weekly) and lower volume dosing, as well as an improved safety profile.

TRYNGOLZA is an RNA-targeted medicine designed to lower the body's production of apoC-III, a key regulator of triglyceride metabolism. ApoC-III inhibits LPL, the primary mechanism by which plasma triglycerides are broken down and regulates the metabolism of triglyceride-rich lipoproteins through LPL pathways, which play an important role in people with FCS who have a substantial deficit of LPL activity.

TRYNGOLZA's mechanism of action is as follows:

- Selective binding to apoC-III messenger RNA
- Degradation of apoC-III messenger RNA
- Reducing serum apoC-III protein levels, resulting in reduced triglyceride levels

Ionis was the first to demonstrate that inhibition of apoC-III can substantially reduce triglyceride levels through multiple mechanisms in humans. By inhibiting apoC-III,

TRYNGOLZA promotes metabolism and hepatic clearance of triglycerides through LPL-independent and LPL-dependent pathways.

With TRYNGOLZA as adjunct to a low-fat diet, adults in the U.S. can achieve significant and substantial reductions in triglyceride levels with monthly dosing and a generally well-tolerated safety profile. Olezarsen is currently undergoing review in the EU.

- Preclinical studies of olezarsen focused on its pharmacokinetics, pharmacodynamics and safety profile. In vitro and in vivo experiments confirmed the GalNAc-conjugated ASO could effectively target hepatocytes and lower apoC-III more efficiently than unconjugated ASOs. These studies determined that olezarsen could achieve significant reduction of apoC-III at lower doses, without risk of systemic side effects.
- The Phase 3 clinical study (Balance) demonstrated a statistically significant reduction in triglyceride levels at the six-month primary endpoint in patients treated with TRYNGOLZA 80 mg. TRYNGOLZA also demonstrated continued triglyceride reduction at 12 months and a substantial, clinically meaningful reduction in AP events over 12 months. These results were published in The New England Journal of Medicine.

TRYNGOLZA exemplifies tenacious and relentless efforts to discover and develop breakthrough medicines for people suffering from serious conditions who have no other treatment options.

Development File Document upload:

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[TRYNGOLZA Ionis Circulation Paper.pdf](#)

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Why this drug or device is innovative, the broad implications for future research, and/or how it will improve the human condition:

Fifteen years ago, there was no consensus that lowering apoC-III would reduce triglycerides, or that a medicine targeting apoC-III would be effective in FCS due to the lack of LPL function. Ionis' unique and deep understanding of human biology and genetics allowed us to develop TRYNGOLZA - the result of many years of research and our long-standing commitment to deliver a breakthrough medicine for FCS.

We were the first to:

- Prove that lowering apoC-III in people with FCS could lower triglycerides
- Show that lowering triglycerides can reduce the risk of AP in people with FCS
- Demonstrate that apoC-III can lower triglyceride levels through a pathway independent of LPL activity
- Validate these associations with Phase 3 results

Nearly fifteen years of research and perseverance were the foundation for TRYNGOLZA's FDA approval. We are proud to have been the first to offer hope and clinical efficacy in the form of an FDA-approved treatment for this rare, underserved population.

There is still opportunity for continued innovation to support the ~3 million Americans with sHTG - a complex, burdensome disease defined by triglyceride levels >500 mg/dL. Though multiple medical societies urge action to treat triglycerides >500 mg/dL to reduce risk of AP and atherosclerotic cardiovascular disease, physicians often deprioritize due to limited efficacy of currently available medicines and the presence of more treatable comorbidities (i.e., type 2 diabetes/insulin resistance, obesity and metabolic disorders).

In 2025, Ionis will report data from our Phase 3 clinical program evaluating olezarsen for sHTG.

Innovation in Community

Ionis had the foresight to identify gaps in the understanding of FCS and aid in the development of resources for the FCS community, providing holistic support.

- Ionis convened an FCS advisory board, which was the first time many attendees ever spoke to another person with FCS. Subsequently, the FCS Foundation - the first U.S. FCS patient advocacy group - was formed and supported by Ionis.
- We worked to define and standardize understanding of FCS, including efforts to explain the role of disease-causing variants beyond LPL; physician education on how to identify, diagnose and manage FCS; and patient education on nutrition resources and understanding why their triglycerides are elevated.
- To help facilitate and shorten the diagnostic pathway, we launched a complimentary genetic testing program and supported the development of clinical diagnostic scoring tools in Europe and North America.
- We are proud to be the founding sponsor of the National Triglyceride Alliance, whose mission is to transform clinical practice through education and advocacy.

Innovation for the Human Condition

Since FDA approval, TRYNGOLZA-treated patients have shared they have seen improvements in their triglyceride levels. Genevie and Aaron, who each live with FCS and are working with Ionis to spread awareness, have had extremely elevated triglycerides their whole lives (higher than 2,500 mg/dL and 1,200 mg/dL, respectively) and, since treatment with TRYNGOLZA, are now both below the threshold for chylomicronemia (880 mg/dL) where the risk of AP is most acute. It's stories like these that inspire us.

Innovation File Document upload:

N/A

Please provide appropriate references (PubMed, Abstract, Website):

PubMed

Translational

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Clinical

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Antisense Platform

1. Baker BF, Xia S, Partridge W, Engelhardt JA, Tsimikas S, Crooke ST, Bhanot S, Geary RS. Safety and Tolerability of GalNAc3-Conjugated Antisense Drugs Compared to the Same-Sequence 2'-O-Methoxyethyl-Modified Antisense Drugs: Results from an Integrated Assessment of Phase 1 Clinical Trial Data. *Nucleic Acid Ther*. 2024;34:18-25. doi: 10.1089/nat.2023.0026. PMID: 38227794.

2. Baker BF, Xia S, Partridge W, Kwok TJ, Tsimikas S, Bhanot S, Geary RS. Integrated Assessment of Phase 2 Data on GalNAc3-Conjugated 2'-O-Methoxyethyl-Modified

Antisense Oligonucleotides. *Nucleic Acid Ther.* 2023;33:72-80. doi: 10.1089/nat.2022.0044. PMID: 36454263.

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