



## Drug Coverage Policy

Effective Date .....4/1/2026

Coverage Policy Number.....IP0733

Policy Title.....Tryngolza

# Familial Chylomicronemia Syndrome – Tryngolza

- Tryngolza™ (olezarsen subcutaneous injection – Ionis)

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### **INSTRUCTIONS FOR USE**

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### **OVERVIEW**

Tryngolza, an apolipoprotein C-III (APO-III)-directed antisense oligonucleotide, is indicated as an adjunct to diet to reduce triglycerides in adults with familial chylomicronemia syndrome (FCS).<sup>1</sup> It is recommended to maintain a low-fat diet ( $\leq 20$  grams of fat per day) in conjunction with Tryngolza.

Page 1 of 6

Coverage Policy Number: IP0733

## Disease Overview

FCS is an ultrarare, genetic form of severe hypertriglyceridemia that impacts 1 to 10 per 1,000,000 persons in the US. Patients with FCS may have triglyceride levels in the thousands. Of note, normal triglyceride levels are < 150 mg/dL with levels above 500 mg/dL categorized as severe hypertriglyceridemia. In general, patients with FCS do not have adequate responses to triglyceride-lowering therapies (e.g., fibrates, omega-3 fatty acids). The high triglyceride levels lead to symptoms such as severe abdominal pain, inflammation of the pancreas (acute pancreatitis), and fatty deposits in the skin. Lipemia retinalis may occur, a condition in which the retinal veins of the eyes appear milky. Patients may develop symptoms of FCS in infancy but may not have the disease be known until adulthood. FCS is caused by biallelic pathogenic variants in five known genes (i.e., lipoprotein lipase [*LPL*], glycosylphosphatidylinositol-anchored high-density lipoprotein [HDL]-binding protein 1 [*GPIHBP1*], apolipoprotein A-V [*APOA5*], apolipoprotein C-II [*APOC2*], or lipase maturation factor 1 [*LMF1*]).

## Clinical Efficacy

The efficacy of Tryngolza was evaluated in a randomized, placebo-controlled, double-blind, Phase III trial in patients with genetically identified FCS.<sup>1,2</sup> A fasting triglyceride level  $\geq$  880 mg/dL was required. At study entry, patients who received the FDA-approved dose of Tryngolza (n = 22) had baseline mean triglyceride levels of 2,613 mg/dL; the value for this parameter in patients who received placebo (n = 23) was 2,585 mg/dL. Background medications were statins (27%), omega-3 fatty acids (42%), fibrates (49%), or other lipid-lowering therapies (13%). The difference between Tryngolza 80 mg and placebo in the percent change in fasting triglycerides from baseline to Month 6 was -42.5%.

## Guidelines

Guidelines do not address Tryngolza. There are recommendations regarding the diagnosis and/or identification of FCS.<sup>3,4</sup> An expert panel (2018) states the FCS is characterized by very high plasma triglyceride concentrations (> 885 mg/dL) in the untreated state.<sup>3</sup> Patients with FCS experience physical complications including incapacitating abdominal pain, and severe recurrent acute pancreatitis. Other clinical symptoms include eruptive xanthomas, lipemia retinalis, and lower body weight. Neurologic symptoms may be present (e.g., irritability, memory problems, dementia). Pathogenic variants are also present in FCS-genes (i.e., *LPL*, *GPIHBP1*, *APOA5*, *APOC2*, or *LMF1*). An FCS score  $\geq$  10 (often referred to as the Moulin et al scoring criteria) is a strong predictor of the condition.<sup>3</sup> Also, patients with a North America Familial Chylomicronemia Syndrome (NAFCS) score  $\geq$  45 are very likely to have classical FCS.

## Coverage Policy

### Policy Statement

Prior Authorization is required for benefit coverage of Tryngolza. Because of the specialized skills required for evaluation and diagnosis of patients treated with Tryngolza as well as the monitoring required for adverse events and long-term efficacy, initial approval requires Tryngolza to be prescribed by or in consultation with a physician who specializes in the condition being treated.

**Documentation:** Documentation is required for use of Tryngolza as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory tests, medical test results, claims records, prescription receipts, and/or other information. All documentation must include patient-specific identifying information.

**Tryngolza is considered medically necessary when the following are met:**

## FDA-Approved Indication

- 1. Familial Chylomicronemia Syndrome.** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
  - A)** Patient is  $\geq 18$  years of age; AND
  - B)** Patient has a fasting triglyceride level  $\geq 880$  mg/dL at baseline [**documentation required**]; AND  
Note: This refers to baseline prior to treatment with a triglyceride-lowering medication. Examples of triglyceride-lowering medications include statins, niacin, fibrates, and omega-3 fatty acids.
  - C)** Patient meets at least ONE of the following (i, ii, or iii):
    - i.** Molecular genetic test results demonstrate biallelic pathogenic variants in at least one gene causing familial chylomicronemia syndrome [**documentation required**];  
OR  
Note: Examples of genes causing Familial Chylomicronemia Syndrome include lipoprotein lipase (*LPL*), glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (*GPIHBP1*), apolipoprotein A-V (*APOA5*), apolipoprotein C-II (*APOC2*), or lipase maturation factor 1 (*LMF1*).
    - ii.** Molecular genetic test results are inconclusive, and the patient has ONE of the following (a or b) [**documentation required**]:
      - a)** Patient has a Moulin familial chylomicronemia syndrome score  $\geq 10$ ; OR
      - b)** Patient has a North American familial chylomicronemia syndrome score  $\geq 45$ ;  
OR
    - iii.** Patient has received a clinical diagnosis of familial chylomicronemia syndrome based on the presence of ALL of the following (a, b, and c):
      - a)** Patient meets ONE of the following (1 or 2):
        - (1)** History of acute pancreatitis not caused by alcohol or cholelithiasis; OR
        - (2)** History of recurrent hospitalizations for severe abdominal pain without other explainable cause; AND
      - b)** Absence of secondary hypertriglyceridemia (e.g., obesity, uncontrolled diabetes);  
AND
      - c)** Lack of response to traditional triglyceride-lowering medications; AND  
Note: Examples of triglyceride-lowering medications include statins, niacin, fibrates, and omega-3 fatty acids.
  - D)** The medication will be used concomitantly with a low-fat diet; AND
  - E)** Medication is prescribed by a cardiologist, an endocrinologist, lipidologist, or a physician who focuses in the treatment of disorders related to severe hypertriglyceridemia.

## Conditions Not Covered

**Tryngolza for any other use is considered not medically necessary, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):**

- 1. Hypertriglyceridemia (in the absence of a confirmed diagnosis of familial chylomicronemia syndrome).** A trial evaluated Tryngolza in patients with either moderate hypertriglyceridemia and elevated cardiovascular risk or with severe hypertriglyceridemia.<sup>5</sup> However, Tryngolza is not FDA-approved for this use.<sup>1</sup>

Receipt of sample product does not satisfy any criteria requirements for coverage.

## References

1. Tryngolza™ subcutaneous injection [prescribing information]. Carlsbad, CA: Ionis; January 2025.
2. Stroes ESG, Alexander VJ, Karwatowska-Prokopczuk E, et al, for the Balance investigators. Olezarsen, acute pancreatitis, and familial chylomicronemia syndrome. *N Engl J Med.* 2024;390(19):1781-1792.
3. Moulin P, Dufour R, Averna M, et al. Identification and diagnosis of patients with familial chylomicronemia syndrome (FCS): expert panel recommendations and proposal of an "FCS score." *Atherosclerosis.* 2018;275:265-272.
4. Hegele RA, Ahmad Z, Ashraf A, et al. Development and validation of clinical criteria to identify familial chylomicronemia syndrome (FCS) in North America. *J Clin Lipidol.* 2024 Nov 12. [Online ahead of print].
5. Bergmark BA, Marston NA, Prohaska RA, et al, for the Bridge-TIMI73 investigators. Olezarsen for hypertriglyceridemia in patients at high cardiovascular risk. *N Engl J Med.* 2024;390(19):1770-1780.

## Revision Details

Type of Revision	Summary of Changes	Date
New	New policy.	06/15/2025
Annual Revision	<p><b>Familial Chylomicronemia Syndrome.</b> The requirement for a fasting triglyceride level <math>\geq</math> 880 mg/dL was clarified to state at baseline. A Note was added to clarify that baseline is prior to a triglyceride-lowering medication. For a patient with inconclusive molecular genetic test result, the option for approval for a familial chylomicronemia score <math>\geq</math> 10 was clarified to state Moulin familial chylomicronemia score. History of pancreatitis, history of eruptive xanthomas, and history of lipemia retinalis were removed as options of approval for a patient with inconclusive genetic test results. Requirements for a clinical diagnosis were added as an alternative to genetic testing if the patient meets all of the following: documentation of a fasting triglyceride level <math>\geq</math> 880 mg/dL at baseline; history of recurrent episodes of acute pancreatitis not caused by alcohol or cholelithiasis; history of recurrent hospitalizations for severe abdominal pain without other explainable cause; absence of secondary hypertriglyceridemia (for example, obesity, uncontrolled diabetes); and lack of response to traditional triglyceride-lowering medications. A Note of examples of triglyceride-lowering medications was added throughout the policy and includes statins, niacin, fibrates, and omega-3 fatty acids.</p> <p><b>Added</b> Appendix A. <i>Moulin Familial Chylomicronemia Syndrome Score Diagnostic</i></p>	02/15/2026

	<p><i>Criteria (for Patients with Fasting TGs &gt; 885 mg/dL) and Appendix B. North American Familial Chylomicronemia Syndrome Score Diagnostic Criteria</i></p> <p><b>Added</b> Appendix B. North American Familial Chylomicronemia Syndrome Score Diagnostic Criteria.</p>	
Selected Revision	<p><b>Familial Chylomicronemia Syndrome.</b> The requirement for a patient to be diagnosed by biallelic pathogenic variants, inconclusive genetic test results, or a clinical diagnosis was modified to state at least one of the following. The requirement for a fasting triglyceride level <math>\geq</math> 880 mg/dL at baseline for a clinical diagnosis was removed, along with the corresponding Note. The requirement for recurrent episodes of pancreatitis was modified to state a history of acute pancreatitis. The clinical diagnosis was modified to require one of a history of acute pancreatitis not caused by alcohol or cholelithiasis or history of recurrent hospitalizations for severe abdominal pain without other explainable cause and not both. Lipidologist was added to the specialist requirement.</p>	4/1/2026

The policy effective date is in force until updated or retired.

**Appendix A. Moulin Familial Chylomicronemia Syndrome Score Diagnostic Criteria (for Patients with Fasting TGs > 885 mg/dL).<sup>3\*</sup>**

Fasting TG levels > 885 mg/dL for three consecutive blood analyses (measured at least 1 month apart; presence of eruptive xanthoma may be used as a surrogate for high TG levels): <b>+5</b>
<ul style="list-style-type: none"> <li>Fasting TG levels &gt; 1,770 mg/dL at least once: <b>+1</b></li> </ul>
Previous TG levels < 177 mg/dL: <b>-5</b>
No secondary factor (i.e., alcohol, diabetes, metabolic syndrome, hypothyroidism, steroid therapy, and additional drugs; exceptions include pregnancy and ethinyl estradiol; if diagnosis is made during pregnancy, a second assessment is necessary to confirm diagnosis postpartum): <b>+2</b>
History of pancreatitis: <b>+1</b>
Unexplained recurrent abdominal pain: <b>+1</b>
No history of familial combined hyperlipidemia: <b>+1</b>
No response (TG decrease < 20%) to hypolipidemic treatment: <b>+1</b>
Onset of symptoms age: <ul style="list-style-type: none"> <li>&lt; 40 years: <b>+1</b></li> <li>&lt; 20 years: <b>+2</b></li> <li>&lt; 10 years: <b>+3</b></li> </ul>

TG(s) – Triglyceride(s); \* The FCS score is the sum of all items cited above and a score  $\geq$  10 suggests that FCS is very likely.

**Appendix B. North American Familial Chylomicronemia Syndrome Score Diagnostic Criteria.<sup>4†</sup>**

Characteristics Included in Patient Scenarios	Categories and Definitions for Patient Scenarios
Patient Age	<ul style="list-style-type: none"> <li>Adult: <math>\geq</math> 20 years of age</li> <li>Adolescent: <math>\geq</math> 10 to 19 years of age</li> <li>Child: <math>\geq</math> 1 to 9 years of age</li> <li>Infant: &lt; 1 year of age</li> </ul>

Hypertriglyceridemia Onset	Defined as Hypertriglyceridemia $\geq$ 440 mg/dL, categorized into early vs. late onset. <ul style="list-style-type: none"> <li>• Early onset: In infancy or childhood</li> <li>• Later onset: In adolescence or adulthood</li> </ul>
Body Mass Index	<ul style="list-style-type: none"> <li>• <math>\geq</math> 25.0 kg/m<sup>2</sup> in adults or <math>\geq</math> 85<sup>th</sup> percentile in children/adolescents</li> <li>• <math>&lt;</math> 25 kg/m<sup>2</sup> in adults or <math>&lt;</math> 85<sup>th</sup> percentile in children/adolescents</li> </ul>
Abdominal Pain/ Pancreatitis	In all scenarios, panelists assumed symptoms were related to chylomicronemia in a patient. <ul style="list-style-type: none"> <li>• No history of abdominal pain or pancreatitis</li> <li>• Recurrent abdominal pain but no history of pancreatitis</li> <li>• History of pancreatitis (with or without abdominal pain)</li> </ul>
Secondary Factors	Defined as factors that may contribute to the patient's hypertriglyceridemia. For example, lifestyle factors (e.g., high alcohol intake, ultra-processed diet), clinical conditions (e.g., non-pancreatitis induced diabetes, HIV), medications (e.g., antidepressants, antiretrovirals).* <ul style="list-style-type: none"> <li>• <math>\geq</math> One secondary factor</li> <li>• No secondary factors</li> </ul>
Fasting TG Levels	Defined fasting as routine fasting (e.g., 6 to 12 hours depending on patient age) prior to outpatient laboratory tests. Panelists assumed it did not include a scenario in which the patient had been fasting during a hospitalization for many days to control acute pancreatitis or in attempts to bring TG levels down. Panelists also assumed the patient was not yet complying with severe dietary fat restriction ( $<$ 20 g/day for adults, $<$ 10% calories from fat for adolescents and children). We categorized the last three laboratory values for adults and on the last two laboratory values for children into two categories: <ul style="list-style-type: none"> <li>• Not all severely elevated: one to two TG readings 440 to 880 mg/dL, remainder <math>&gt;</math> 880 mg/dL.</li> <li>• All severely elevated: all TG readings <math>&gt;</math> 880 mg/dL</li> </ul>
TG/TC Ratio	Defined as the ratio of TG over TC, categorized into: <ul style="list-style-type: none"> <li>• Normal/low: <math>\leq</math> 8 mg/dL</li> <li>• High: <math>&gt;</math> 8 mg/dL</li> </ul>
ApoB Reading	ApoB laboratory value, categorized into: <ul style="list-style-type: none"> <li>• Normal/high: <math>\geq</math> 1 g/L</li> <li>• Low: <math>&lt;</math> 1.0 g/L (100 mg/dL)</li> </ul>
Treatment Non-Response	In all scenarios describing patients $\geq$ 10 years old, panelists assumed fibrates and high-dose omega-3 fatty acids did not produce a sustained response in TG levels even when the patient was compliant with therapy (i.e., TG levels do not decrease by 20% or more from these treatments and do not remain reduced).

<sup>†</sup> This tool can be used to assist in the diagnosis of familial chylomicronemia syndrome. It should be utilized in patients  $\geq$  1 year of age with triglyceride (TG) levels  $\geq$  440 mg/dL. It may be useful in patients who have not yet been tested genetically for FCS, or in whom genetic testing was inconclusive. If patients  $\geq$  10 years of age, the tool should only be used for patients who are not responsive to fibrates and high-dose omega-3 fatty acids even when the patient is compliance with therapy; HIV – Human immunodeficiency virus; \* A more comprehensive list of secondary factors are available; TG – Triglyceride; TC – Total cholesterol; ApoB – Apolipoprotein B.

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