

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

218614Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	218614
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Reviewer Name(s)	Ingrid N. Chapman, PharmD, BCPS
Team Leader	Naomi Boston, PharmD
Deputy Director	Laura Zendel, PharmD
Review Completion Date	December 18, 2024
Subject	Evaluation of Need for a REMS
Established Name	olezarsen
Trade Name	Tryngolza
Name of Applicant	Ionis Pharmaceuticals, Inc
Therapeutic Class	antisense oligonucleotide
Formulation(s)	80 mg/0.8 mL solution for injection supplied in a single-dose autoinjector
Dosing Regimen	80 mg subcutaneously once monthly

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Tryngolza (olezarsen) is necessary to ensure the benefits outweigh its risks. Ionis Pharmaceuticals Inc. submitted a New Drug Application (NDA) 218614 for olezarsen with the proposed indication: as an adjunct to diet to reduce triglycerides in adults with familial chylomicronemia syndrome (FCS). This application is under review by the Division of Diabetes, Lipid Disorders and Obesity (DDLO). The Applicant did not submit a proposed REMS or risk management plan with this application.

Results from the clinical trial ISIS 678354-CS3 (Study CS3) showed the difference in percent change in fasting triglycerides from baseline to Month 6 (average of Weeks 23, 25, and 27) was -42.5% (95% CI: -74.1%, -10.9%; $p=0.0084$) in subjects who received olezarsen 80 mg compared to placebo. The treatment effect with olezarsen was seen in adult subjects with fasting triglyceride levels ≥ 880 mg/dL despite low-fat diet (≤ 20 grams fat per day) and optimized lipid lowering therapies. Given the rarity of the condition, the seriousness of the disease, the unmet medical need to treat this disease, the persuasiveness of the results of Study CS3, and the robustness of the confirmatory evidence in subjects with moderate or severe hypertriglyceridemia, DDLO concluded that the Applicant has provided the substantial evidence of effectiveness to support approval.

The most concerning risk determined to be associated with olezarsen is serious hypersensitivity reactions, including symptoms of bronchospasm, diffuse erythema, facial swelling, urticaria, chills, and myalgias. DRM and DDLO agree that a REMS is not necessary to ensure the benefits of olezarsen outweigh its risks. No serious hypersensitivity reactions were observed in the clinical trial setting. Because serious hypersensitivity reactions are a known adverse drug reaction with for this drug class (antisense oligonucleotides), management of the risk through labeling to include signs and symptoms observed is reasonable.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Tryngolza (olezarsen) is necessary to ensure the benefits outweigh its risks.^a Ionis Pharmaceuticals Inc. submitted a New Drug Application (NDA 218614) for olezarsen with the proposed indication: as an adjunct to diet to reduce triglycerides in adults with familial chylomicronemia syndrome (FCS). This application is under review in the Division of Diabetes, Lipid Disorders, and Obesity (DDLO). The Applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

^a Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

2.1. Product Information

Tryngolza (olezarsen), an NME, is a triantennary N-acetyl galactosamine (GalNAc3) conjugated antisense oligonucleotide (ASO) inhibitor of apolipoprotein C-III production. It is proposed as an adjunct to diet to reduce triglycerides in adults with familial chylomicronemia syndrome (FCS).¹ Olezarsen is proposed as an 80 mg/0.8 mL solution for subcutaneous injection administered via a single-dose autoinjector. The recommended dose of olezarsen is 80 mg subcutaneously once monthly (b) (4).^{1, b} Olezarsen will likely be administered in the outpatient setting by the patient or caregiver.

Olezarsen is not currently approved in any jurisdiction. However, volanesorsen (Waylivra), shares the same nucleotide sequence and backbone chemical composition as olezarsen and differs only through its inclusion of GalNAc3.² Volanesorsen is not FDA-approved but was granted conditional approval by the European Medicines Agency on May 3, 2019 and was approved by the Brazilian Regulatory Health Regulatory Agency for FCS on August 23, 2021, and for familial partial lipodystrophy on December 1, 2022.³⁻⁵ Ionis Pharmaceuticals, Inc. is the applicant for both products.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 218614 relevant to this review:

- **04/19/2024:** NDA 218614 submission for olezarsen as an adjunct to diet to reduce triglycerides in adults with FCS received.
- **10/23/2024:** A Post Late-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for olezarsen.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Familial Chylomicronemia Syndrome (FCS), also referred to as familial lipoprotein lipase deficiency, affects approximately 1 to 13 persons per million in the United States and 1 to 19 persons per million in Europe.^{2, c} It is a rare autosomal recessive disease that results from lipoprotein lipase (LPL) deficiency or dysfunction. The LPL deficiency or dysfunction is caused by mutations in the gene encoding LPL, or, less frequently, by genetic mutations encoding other proteins necessary for LPL function.⁶ The lack of functional LPL results in a reduced ability to hydrolyze triglycerides in triglyceride-rich lipoproteins including intestinally derived chylomicrons and hepatically derived very low density lipoproteins (VLDL).² This leads to a buildup of chylomicrons (large particles composed of triglycerides, proteins, cholesterol, and fat-soluble vitamins) and VLDL in the blood stream. Chylomicronemia occurs when plasma triglyceride levels exceed 1,000 mg/dL and patients with FCS range from 1,500 to 15,000 mg/dL (10 to

^b Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

^c Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

100 times normal).^{6,7} In addition to severe hypertriglyceridemia, patients experience recurrent pancreatitis, severe abdominal pain, eruptive xanthomas, arthralgias, neurologic symptoms, lipemia retinalis, and hepatosplenomegaly.⁶ Quality of life is decreased due to frequent hospitalizations for abdominal pain (with or without pancreatitis) and severe pancreatitis (potentially life-threatening).^d

3.2. Description of Current Treatment Options

Currently, there are no pharmacologic treatments indicated for the treatment of FCS in the U.S. The FDA-approved medications indicated for hypertriglyceridemia, fibrates, nicotinic acid, and omega-3 fatty acids, are not effective at significantly lowering triglycerides in this disease state.⁸ For FCS, the mainstay of therapy is nonpharmacologic. Therapeutic lifestyle modifications focused on diet changes include a reduction in dietary saturated fats (< 7% of total calories) and cholesterol intake (< 200 mg/d), alcohol avoidance, and physical activity.⁷ There is an unmet medical need for treatment of FCS.

4. Benefit Assessment

4.1. Study CS3

The efficacy of olezarsen, for the treatment of FCS, was demonstrated in pivotal trial, ISIS 678354-CS3 (Study CS3; NCT NCT04568434). Study CS3 was a randomized, placebo-controlled, double blind clinical trial in adults with genetically diagnosed FCS and fasting TG levels ≥ 880 mg/dL.¹ First, subjects were randomized 1:1 to either Cohort A (50 mg of olezarsen) or Cohort B (80 mg of olezarsen). Then, the subjects were further randomized 2:1 to receive olezarsen or placebo. Overall, 43 subjects received at least one dose of olezarsen: 50 mg (n = 21), 80 mg (n = 22), and placebo (n = 23). Refer to Section 10.2 in the appendices for detailed inclusion and exclusion criteria.

The primary efficacy endpoint was the mean percent change in fasting triglycerides (TG) from baseline to Month 6 for 80 mg of olezarsen compared to placebo. The mean percent change was defined as an average of fasting TG at Weeks 23, 25, and 27.^e

For Cohort B, results showed the difference in percent change in fasting triglycerides from baseline to Month 6 (average of Weeks 23, 25, and 27) was -42.5% (95% CI: -74.1%, -10.9%; p=0.0084) in subjects who received olezarsen 80 mg compared to placebo.¹ For Cohort A, the 6 month percent change for subjects receiving olezarsen 50 mg compared to placebo was -21.5% (95% CI: -48.2%, 5.3%; p=0.1153) and not statistically significant.⁸

The Clinical Team concluded the effect of olezarsen 80 mg monthly on triglyceride levels at 6 months meets criteria for substantial evidence of effectiveness. The magnitude of direct clinical benefit associated with triglyceride-lowering was informed by the pivotal trial, CS3, which showed a reduction in acute pancreatitis events in olezarsen groups compared to placebo.⁸ The triglyceride results were

^d Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

^e Section 505-1 (a) of the FD&C Act: FDAAA factor (C): *The expected benefit of the drug with respect to such disease or condition.*

compelling, the reduction in acute pancreatitis events was reassuring, and the discontinuation rate was acceptable.⁸

Table 1:¹ Mean Baseline (BL) and Mean Percent (%) Changes from Baseline in Lipid/ Lipoprotein Parameters in Patients with FCS at Months 6 in Trial 1

Parameter (mg/dL)	Olezarsen 80 mg N = 22		Placebo N = 23		Olezarsen 80 mg vs. Placebo
	BL	% change Month 6	BL	% change Month 6	Treatment Difference % change (95% CI) at Month 6
Triglycerides	2613.1	-30	2595.7	+12	-42.5 ^a (-74.1, -10.9)
Non-HDL-C	262.9	-18	271.3	+5.7	-23.4 (-45.3, -1.5)
LDL-C	22.8	+64	16.7	+9	+55.0 ^b (0.7, 109.4)
Total ApoB	58.4	+20	59.7	+9	+11.7 (-12.6, 35.9)
ApoB-48	11.6	-51	14.2	+25	-75.9 (-149.8, -2.0)

Abbreviations: apoB = apolipoprotein B; non-HDL-C = non high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.
^a Reached statistical significance (p value < 0.05).
^b Mean LDL-C levels increased but largely remained within normal range.

4.2. Study CS8

Confirmatory evidence was derived from Study ISIS 678354-CS8 (CS8; NCT 05355402). CS8 was a Phase 2b, randomized, double-blind, placebo-controlled trial in adults (n = 154) with hypertriglyceridemia (HTG) and established or increased risk of atherosclerotic cardiovascular disease (ASCVD), or with severe HTG (sHTG). First, randomization was 1:1 for subjects to receive either olezarsen 80 mg (Cohort A) or 50 mg (Cohort B). Each cohort was further randomized 3:1 to either olezarsen or placebo administered every 4 weeks for one year. The primary endpoint was percent change in fasting TG from baseline to Month 6 of olezarsen compared to placebo. For Cohort A, the 6 month percent change in fasting TG for subjects receiving olezarsen 80 mg compared to placebo was -56.5% (95% CI: -67.4%, -45.6%; p<0.0001). For Cohort B, the 6 month percent change in fasting TG for subjects receiving olezarsen 50 mg compared to placebo was -51.7% (95% CI: -62.5%, -41.0%; p<0.0001).⁸

5. Risk Assessment & Safe-Use Conditions

The safety of olezarsen in patients with FCS was evaluated in Study CS3. No serious adverse reactions or risks occurred. Adverse reactions led to discontinuation of treatment in 7% of olezarsen-treated patients

and 0% of placebo-treated patients.¹ The most common adverse reactions occurring in $\geq 5\%$ of patients treated with olezarsen and at $\geq 3\%$ higher frequency than placebo includes: injection site reactions (19%), nasopharyngitis (16%), decreased platelet count (12%), and arthralgia (9%).^f

One death occurred in subjects who received olezarsen 50 mg. The subject had received two doses of olezarsen prior to the fatal adverse event of sudden death (unknown cause). Following review of the narratives and case report forms, it is difficult to discern olezarsen's contribution, if any, to this death given the limited information available.⁸

The Clinical Team determined the most concerning risk for olezarsen is serious hypersensitivity reactions, including symptoms of bronchospasm, diffuse erythema, facial swelling, urticaria, chills, and myalgias. However, the risks associated with olezarsen are clinically monitorable and can be adequately addressed through labeling.⁸

5.1. Hypersensitivity Reactions

Hypersensitivity reactions are a known and labeled adverse drug reaction for several FDA-approved antisense oligonucleotides (ASOs).⁸ Specifically, serious hypersensitivity reactions were noted to occur in the clinical development program for volanesorsen, an ASO with the same nucleotide sequence and backbone chemical composition as olezarsen. One of these serious reactions included an anaphylactic-like reaction in a study subject without FCS within 5 minutes of volanesorsen dosing which required emergency treatment.⁸

Hypersensitivity reactions (including symptoms of bronchospasm, diffuse erythema, facial swelling, urticaria, chills, and myalgias) have been reported in patients treated with olezarsen.¹ In Study CS3, two (9%) subjects who received olezarsen 80 mg discontinued because of hypersensitivity or flu-like reactions compared to none in placebo; however, there were no serious hypersensitivity reactions.⁸ The onset of symptoms can occur within minutes or the same day of the injection. There is a variable length of treatment duration before the event ranging from the first couple of doses to years of exposure. As there were no serious hypersensitivity reactions in the clinical trials, the review team did not elevate hypersensitivity reactions to a Boxed Warning. The Warnings and Precautions section of the label states to advise patients on the signs and symptoms of hypersensitivity reactions and instruct patients to promptly seek medical attention and discontinue use of olezarsen if hypersensitivity reactions occur. The review team concluded that management of the risk through labeling to include signs and symptoms observed is reasonable as hypersensitivity reactions are a known adverse event for this drug class.⁸

^f Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

5.2. Thrombocytopenia

Because the primary safety concerns for volanesorsen (an ASO similar to olezarsen) were thrombocytopenia and the risk of bleeding, the risk of thrombocytopenia and associated bleeding was considered for this review.⁹ Given these concerns, Study CS3 excluded subjects with baseline platelet count < 100 x10⁹/L and instituted platelet monitoring every 2 weeks.

Olezarsen can cause reductions in platelet count.¹ The decrease in platelet count occurs within the first weeks of treatment and is characterized by a gradual decline over time. In Study CS3, at Week 53, the mean percent change in platelet count was -9.5% in subjects who received olezarsen 80 mg compared to 22% in subjects who received placebo. No olezarsen-treated subjects with FCS had a platelet count <50,000/mm³. There were no major bleeding events associated with a low platelet count.¹ Overall, the proportion of subjects experiencing a bleeding adverse event was similar across the olezarsen and placebo treatment groups.¹ The proposed labeling for olezarsen describes the reductions in platelet count in section 6, but does not include recommendations for monitoring for thrombocytopenia or low platelet counts as platelets below the lower limit of normal were not seen in the clinical trial and no associated major bleeding events occurred.

6. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for olezarsen beyond routine pharmacovigilance and labeling.

7. Expected Postmarket Use

Olezarsen will likely be prescribed in the outpatient setting and dispensed by specialty pharmacies for self-administration or caregiver-administration. The likely prescribers include healthcare providers specializing in lipid management (e.g., endocrinologists and lipidologists). These prescribers should be familiar with managing hypersensitivity reactions as they are a common adverse reaction with drug therapy. The proposed label addresses hypersensitivity in the Warnings and Precautions section of the label.

8. Discussion of Need for a REMS

DDLO concluded the Applicant has provided the substantial evidence of effectiveness⁸ to support olezarsen approval as an adjunct to diet to reduce triglycerides in adults with FCS. This is due to the rarity of the condition, the seriousness of the disease, the unmet medical need to treat this disease, the persuasiveness of the results of Study CS3, and the robustness of the confirmatory evidence in patients with moderate or severe hypertriglyceridemia in Study CS8.⁸

⁸ 21 CFR 314.126(a)(b)

FCS is an orphan disease that affects approximately 1 to 13 persons per million in the United States. In addition to severe hypertriglyceridemia, patients experience recurrent pancreatitis, severe abdominal pain, eruptive xanthomas, arthralgias, neurologic symptoms, lipemia retinalis, and hepatosplenomegaly. As there are no FDA-approved drugs to treat FCS, patients rely on dietary restrictions to manage symptoms associated with high triglycerides. There is an unmet clinical need for treatment options in patients with FCS.

The most concerning risk is serious hypersensitivity reactions, including symptoms of bronchospasm, diffuse erythema, chills, and myalgias, though no serious hypersensitivity reactions were seen in the clinical trial. This risk is addressed in the Warnings and Precautions section of the proposed label and is clinically monitorable.⁸ Because serious hypersensitivity reactions are a known adverse drug reaction for this drug class (ASOs), management of the risk through labeling to include signs and symptoms observed is a reasonable mitigation. The likely prescribers (e.g., endocrinologists and lipidologists) should be familiar with managing hypersensitivity reactions as they are a common adverse reaction associated with drug therapy.

For this review, the risk of thrombocytopenia was considered because of its association with a similar ASO, volanesorsen. While olezarsen causes reduction in platelet count and platelet counts tend to be 5% to 15% lower the baseline, no olezarsen-treated subjects with FCS had a platelet count <50,000/mm³.⁸ Additionally, there were no major bleeding events associated with a low platelet count. Low platelet count is addressed under “Laboratory Tests” in the Adverse Reactions section of the proposed label.

All risks associated with olezarsen can be adequately addressed through labeling and none rise to the level of a boxed warning.⁸

DRM recommends that, should olezarsen be approved, a REMS is not necessary to ensure its benefits outweigh its risks as an adjunct to diet to reduce triglycerides in adults with FCS.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for olezarsen to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. Appendices

10.1. References

1. Ionis Pharmaceuticals Inc. Tryngolza (olezarsen). NDA 218614. Labeling (prescribing information), final. December 18, 2024.
2. Stroes ESG, Alexander VJ, Karwatowska-Prokopczuk E, et al. Olezarsen, Acute Pancreatitis, and Familial Chylomicronemia Syndrome. *New England Journal of Medicine*. 2024;390(19):1781-1792. doi:doi:10.1056/NEJMoa2400201

3. PTC Therapeutics. PTC Therapeutics Announces Waylivra™ Approval in Brazil as First Treatment for Familial Chylomicronemia Syndrome. October 4, 2024.
4. PTC Therapeutics. Brazilian Regulatory Authority Grants Approval for Waylivra™ for Familial Partial Lipodystrophy. October 4, 2024.
5. Press Release. Akcea and Ionis announce approval of WAYLIVRA® (volanesorsen) in the European Union. October 4, 2024.
6. Gaudet D, Brisson D, Tremblay K, et al. Targeting APOC3 in the Familial Chylomicronemia Syndrome. *New England Journal of Medicine*. 2014;371(23):2200-2206. doi:10.1056/NEJMoa1400284
7. Leaf DA. Chylomicronemia and the Chylomicronemia Syndrome: A Practical Approach to Management. *The American journal of medicine*. 2008/01/01/ 2008;121(1):10-12.
8. Food and Drug Administration. Division of Diabetes, Lipid Disorders and Obesity (DDLO). Tryngolza (olezarsen). NDA 218614. Integrated Review, draft. December 17, 2024.
9. FDA Briefing Document. Division of Metabolism and Endocrinology Products. Volanesorsen (Waylivra). Endocrinologic and Metabolic Drugs Advisory Committee Meeting. May 10, 2018.

10.2. Inclusion and Exclusion Criteria for Study CS3

Main Inclusion Criteria:⁸

1. A diagnosis of FCS (type 1 Hyperlipoproteinemia) by documentation of confirmed homozygote, compound heterozygote, or double heterozygote for loss-of-function mutations in type 1-causing genes (such as lipoprotein lipase (LPL), glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1), apolipoprotein A5 (APOA5), apolipoprotein C-II (APOC2), glycerol-3 phosphate dehydrogenase 1(GPD1), or lipase maturation factor 1 (LMF1))
2. Fasting TG ≥ 880 mg/dL at screening. If the fasting TG was < 880 mg/dL, up to 2 additional tests may have been performed, with any single test used to qualify
3. Age ≥ 18 years at the time of informed consent
4. History of pancreatitis (defined as a recorded diagnosis of acute pancreatitis or hospitalization or ER visit for severe abdominal pain consistent with acute pancreatitis and for which no alternate diagnosis was made) within 10 years prior to Screening. Patients without a recorded history of pancreatitis, or no recorded history within 10 years prior to Screening, were also eligible but their enrollment was capped at 35% (i.e., ≤ 21) of the 60 planned patients.
5. Willing to follow a diet comprising ≤ 20 g fat per day during the study
6. The following concomitant medications were allowed if on a stable dose for at least 4 weeks prior to Screening:
 - a. Statins, omega-3 fatty acids, prescription and over-the-counter (OTC), fibrates, or other lipid-lowering medications.
 - b. Antidiabetic medications
 - c. Antihypertensive medications
 - d. Oral anticoagulants
 - e. Tamoxifen, estrogens or progestins

Main Exclusion Criteria:⁸

1. Clinically significant abnormalities in medical history (e.g., previous acute coronary syndrome within 6 months of Screening, major surgery within 3 months of Screening) or physical examination
2. Active pancreatitis within 4 weeks prior to Screening
3. Screening laboratory results as follows, or any other clinically significant abnormalities in screening laboratory values that would have rendered a patient unsuitable for inclusion:
 - a. Platelet count $< 100,000/\text{mm}^3$ at Screening or Qualification. If the platelet count was $< 100,000/\text{mm}^3$, up to 2 additional tests may have been performed to qualify at both Screening and Qualification
 - b. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $> 3.0\times$ upper limit of normal (ULN)
 - c. Total bilirubin $> \text{ULN}$ unless due to Gilbert's syndrome
 - d. Estimated glomerular filtration rate (eGFR) $< 45 \text{ mL/min}/1.73 \text{ m}^2$ (as determined by the Chronic Kidney Disease Epidemiology [CKD-EPI] formula for creatinine clearance)
 - e. Urine protein/creatinine ratio (UPCR) $\geq 500 \text{ mg/g}$, or urine albumin/creatinine (UACR) ratio $\geq 300 \text{ mg/g}$
4. Uncontrolled arterial hypertension (blood pressure [BP] $> 160/100 \text{ mm Hg}$)
5. History of bleeding diathesis or coagulopathy or clinically significant abnormality in coagulation parameters at Screening
6. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that had been successfully treated
7. Active infection with human immunodeficiency virus (HIV), hepatitis C or hepatitis B diagnosed by initial serological testing and confirmed with RNA testing, or prior treatment for hepatitis C.
8. Treatment with another investigational drug (non-oligonucleotide), biological agent, or device within 1 month of Screening, or 5 half-lives of investigational agent, whichever was longer

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