



Olezarsen for Reducing Triglycerides and the Risk of Acute Pancreatitis in Adults with sHTG

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sHTG is frequently underdiagnosed with poor follow-up testing¹

- HTG is generally with observed other lipid abnormalities, and triglycerides often go unaddressed¹
- Referrals for sHTG are uncommon; many patients are managed entirely in primary care²

sHTG is more common than you may think^{3,4}



> 3M

US adults living with
TG $\geq$ 500 mg/dL



$\approx$ 1M

High-risk sHTG
(TG $\geq$ 880 mg/dL, or 500 mg/dL
with history of AP or
comorbidities)

AP, acute pancreatitis; HTG, hypertriglyceridemia; sHTG, severe hypertriglyceridemia; TG, triglyceride.

1. Esparza MI et al. *J Endocr Soc.* 2019;3(8):1595-1607. 2. Rashid N, et al. *J Clin Lipidol.* 2016;10(4):880-890. 3. Christian JB, et al. *Am J Cardiol.* 2011;107(6):891-897. 4. Data on file. sHTG prevalence. Ionis Pharmaceuticals; 2024.

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sHTG drives pancreatitis and ASCVD risk¹⁻⁵

≥500 mg/dL

- Defines sHTG^{1,2}

≥880 mg/dL

- Increased risk of AP as TGs approach and exceed 1000 mg/dL^{1-2,4}

≥880 mg/dL, or ≥500 mg/dL with prior AP or comorbidities

- Risk for recurrent, potentially life-threatening acute pancreatitis⁴
- Elevated burden of atherogenic remnant lipoproteins^{1,5}

Risks are elevated as triglyceride levels rise across the sHTG (≥500 mg/dL) continuum³

150-499 mg/dL

≥500 mg/dL

>880 mg/dL

AP risk^{3,4}

ASCVD risk^{3,5}

AP, acute pancreatitis; ASCVD, atherosclerotic cardiovascular disease; sHTG, severe hypertriglyceridemia; TG, triglyceride.

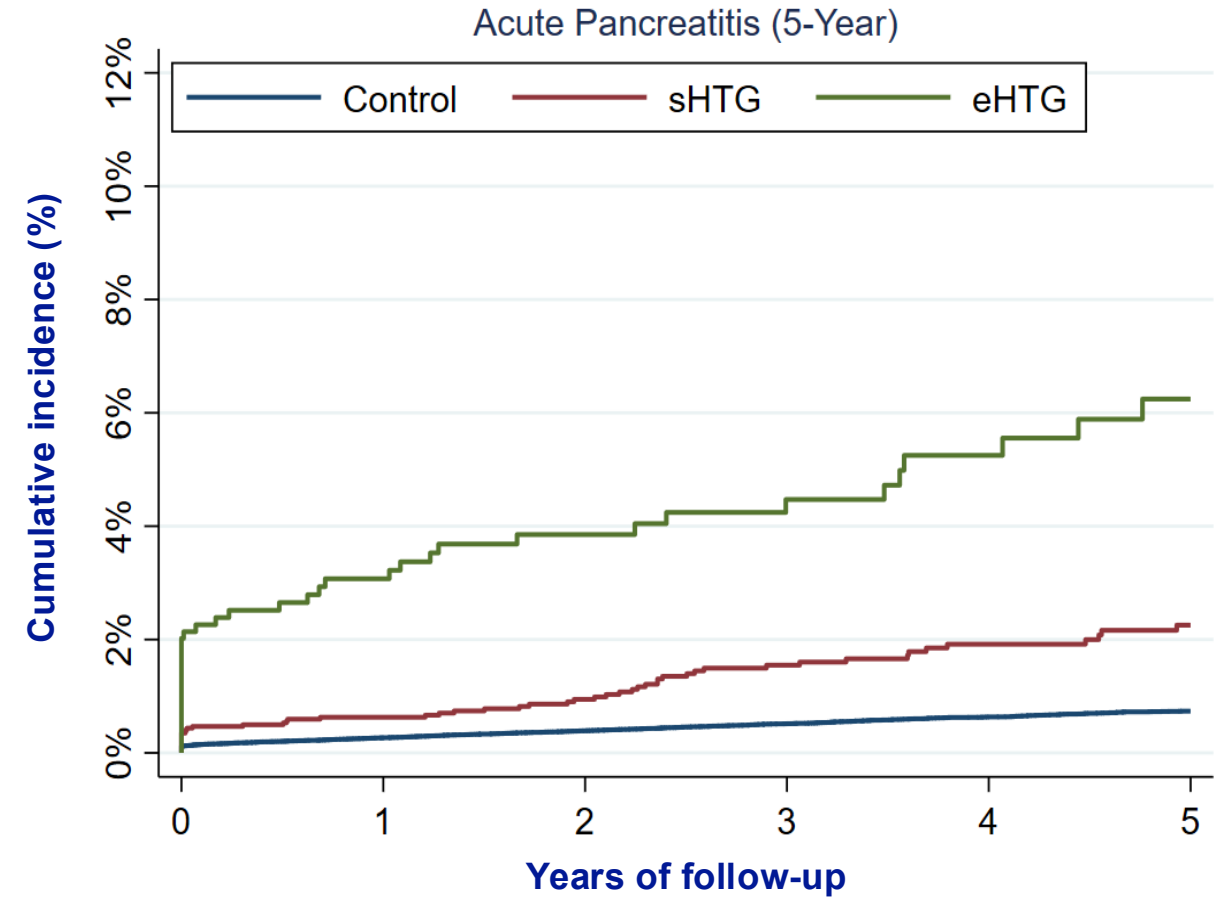
1. Miller M. *Circulation*. 2011;123(20):2292-2333. 2. Jacobson TA, et al. *J Clin Lipidol*. 2015;9(2):129-169. 3. Kessler AS, et al. *Lipids Health Dis*. 2025;24(1):252. 4. Sanchez RJ, et al. *Lipids Health Dis*. 2021;20(1):72. 5. Nordestgaard BG, et al. *Circ Res*. 2016;118(4):547-563.

The risk for initial AP incidents and recurrent events rises with elevated TGs^{1,2}

Preventing initial AP is critical as recurrence burden builds

- Hypertriglyceridemia is the third most common cause of AP¹
- Overall risk of an initial event is low but increases ~15-fold when TG levels are >880 mg/dL²
- An AP event can result in irreversible pancreatic dysfunction or death³
- History of ≥2 events increases risk ~50% if TGs remain severely elevated²

CLEARSHOT AP Event Rate by TG Level^{4,a,b}



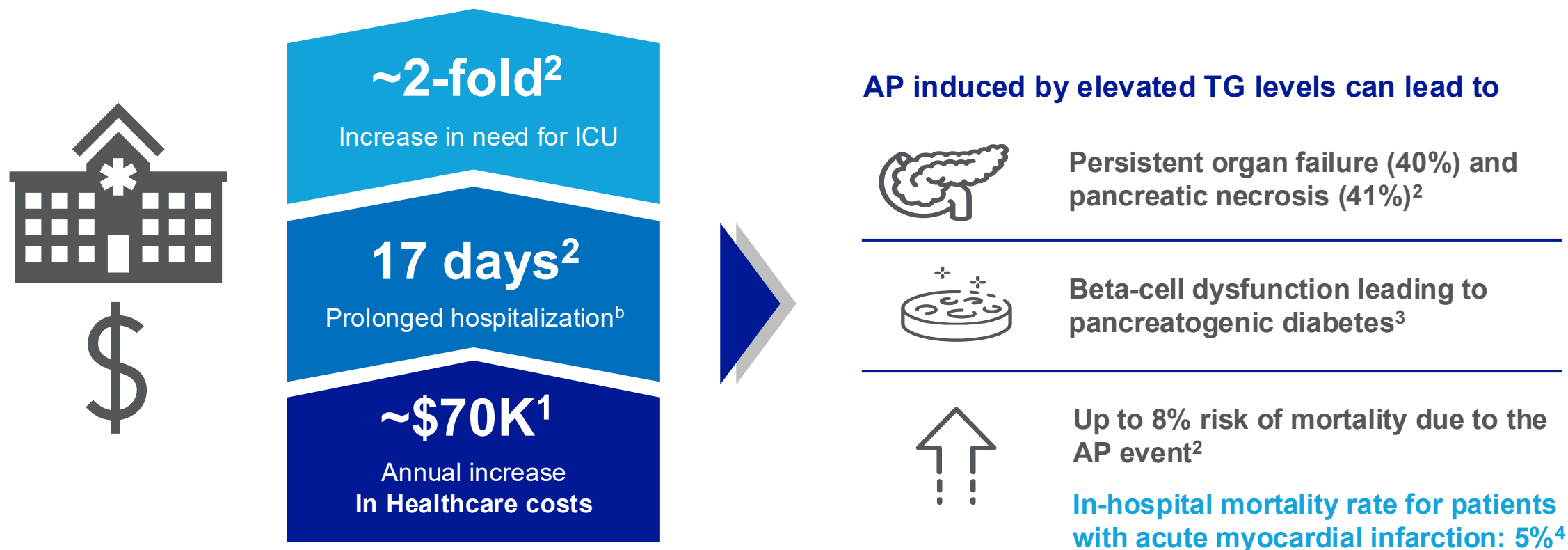
^aRetrospective cohort of 469,979 adults with fasting TG levels followed for a median of 1.6 years for AP and CV events.⁴ ^bExperimental groups were defined by TG level as follows: ≥500 mg/dL for sHTG, ≥880 mg/dL for eHTG, and <500 mg/dL for controls.⁴

AP, acute pancreatitis; CV, cardiovascular; eHTG, extreme hypertriglyceridemia; sHTG, severe hypertriglyceridemia; TG, triglyceride.

1. Fogacci F, Cicero AFG. *Diseases*. 2026;14(2):47. 2. Sanchez RJ, et al. *Lipids Health Dis*. 2021;20(1):72. 3. Symersky T, et al. *JOP*. 2006;7(5):447-453. 4. CLEARSHOT sHTG and eHTG Outcomes Poster ACC 2026.

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Severe hypertriglyceridemia-induced AP has worse outcomes^a and imposes a substantial symptomatic burden¹



^aCompared with non-TG-induced AP. ^bCompared to a median of 7 days in hospital in patients with normal serum TG level.²

AP, acute pancreatitis; ICU, intensive care unit; TG, triglyceride.

1. Kessler AS, et al. *J Clin Lipidol*. 2025;19(4):931-941. 2. Nawaz H, et al. *Am J Gastroenterol*. 2015;110(10):1497-1503. 3. Zhi M, et al. *Front Physiol*. 2019;10:637. 4. Faridi KF, et al. *Circ Cardiovasc Qual Outcomes*. 2025;18(3):e011259.

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Standard of care has limitations

Intervention	Typical TG reduction	Limitations
Diet and lifestyle ¹	Variable	Adherence; may not be sufficient alone
Fibrates ^{1,2}	~30% to 50%	Renal elimination, drug interaction potential, myalgias, elevated hepatic transaminases
Omega-3 FA/icosapent ethyl ¹⁻³	In very high-TG populations, reductions of ~30% from baseline	Pill burden; adherence
Statins ^{1,2}	Minimal TG effect	Myopathy

Other factors to consider¹

Assessment and referral

- Evaluate and manage secondary causes^a
- Refer to dietitian and/or lipid specialist
- Screen for FCS

Monitoring

- Non-HDL and apoB levels
- Ten-year ASCVD risk assessment utilizing the PREVENT-ASCVD equations

No current standard of care therapy has demonstrated a reduction in acute pancreatitis events in sHTG^{2,4}

^aIncluding chronic kidney disease, obesity, uncontrolled diabetes, medications, alcohol excess, or diet high in saturated fat, sugar, or high-glycemic-index foods¹

AP, acute pancreatitis; apoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; FA, fatty acids; FCS, familial chylomicronemia syndrome; HDL, high-density lipoprotein; sHTG, severe hypertriglyceridemia; TG, triglyceride.

1. Blumenthal RS, et al. *J Am Coll Cardiol*. 2026;87(19):2624-2757. 2. Fogacci F, Cicero AFG. *Diseases*. 2026;14(2):47. 3. Wang Z, et al. *Lipids Health Dis*. 2023;22(1):71. 4. Marston NA, et al. *N Engl J Med*. 2026;394(5):429-441.

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Tryngolza[®] (olezarsen)

For the reduction of triglycerides and the risk of acute pancreatitis in adults with severe hypertriglyceridemia, as an adjunct to diet

TRYNGOLZA (olezarsen), a first-in-class GalNAc₃-conjugated apoC-III antisense oligonucleotide



Indication

- 
- TRYNGOLZA is an *ApoC-III*-directed antisense oligonucleotide (ASO) indicated as an adjunct to diet:
- To reduce TG in adults with FCS
 - To reduce TG and the risk of acute pancreatitis in adults with sHTG (TG greater than or equal to 500 mg/dL)

Dosage

- 
- In adults with sHTG,
- The recommended dosage of TRYNGOLZA is 50 mg injected subcutaneously once monthly.
 - Assess TG when clinically appropriate. The TG-lowering effect of TRYNGOLZA may be measured within 3 months after initiation.
 - For patients who tolerate the 50 mg dosage and additional TG reduction is clinically indicated, the dosage may be increased to 80 mg injected subcutaneously once monthly

Administration



TRYNGOLZA is available as a single-dose autoinjector (50 mg/0.8 mL or 80 mg/0.8mL)

Administered into the abdomen, front of the thigh, or back of the upper arm^a

Prior to initiation, train patients and/or caregivers on proper preparation and administration of olezarsen [see Instructions for Use]

^aIf a healthcare provider or caregiver administers the injection.

ApoC-III, apolipoprotein C-III; ASO, antisense oligonucleotide; FCS, familial chylomicronemia syndrome; TG, triglycerides; sHTG, severe hypertriglyceridemia.

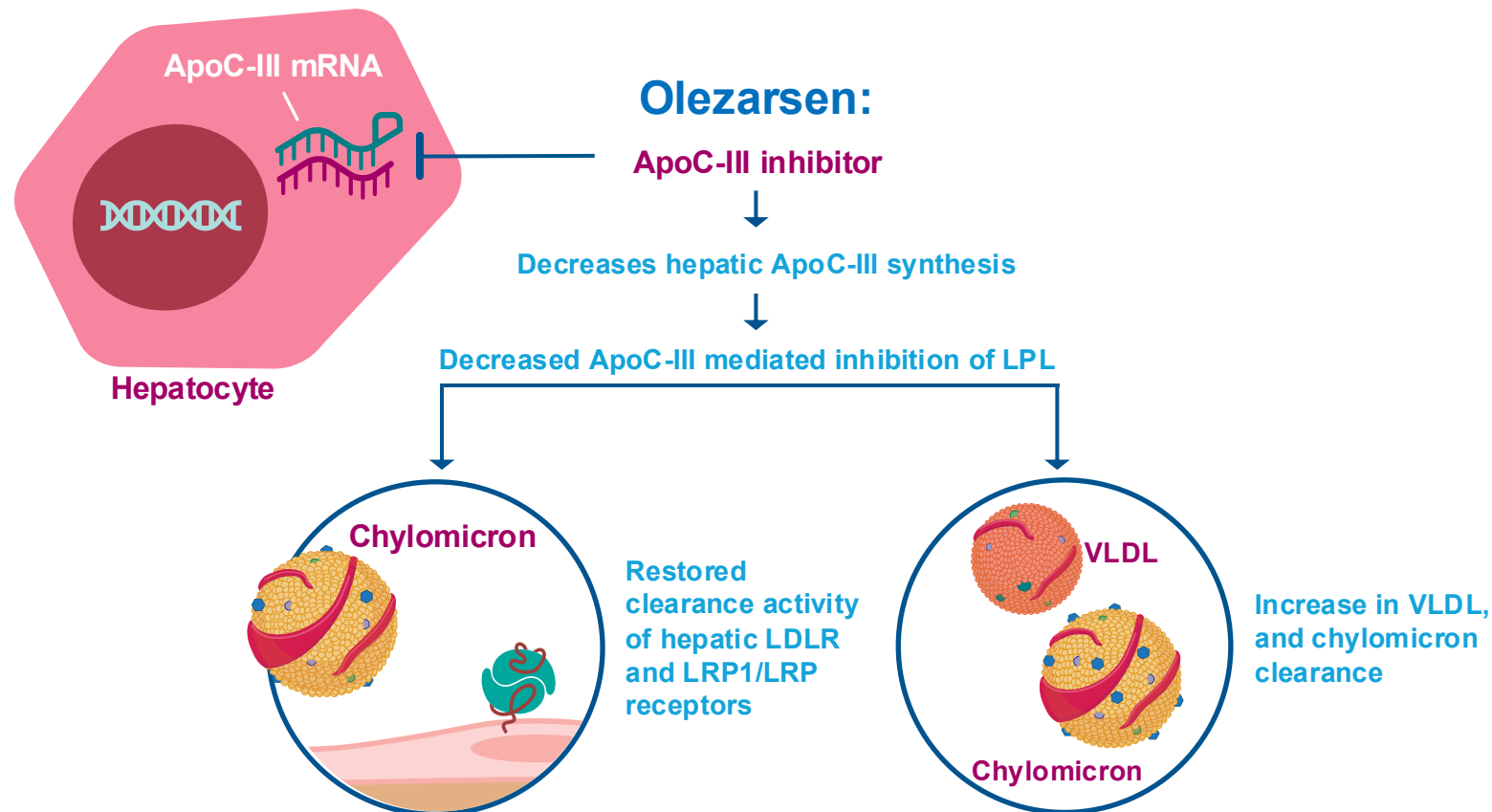
TRYNGOLZA. Prescribing information. Ionis Pharmaceuticals, Inc

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Olezarsen inhibits apoC-III, leading to increased clearance of plasma triglycerides and VLDL¹⁻⁴

ApoC-III

- **Inhibits LPL**
 - Slows intravascular hydrolysis of TGs in chylomicrons and VLDL
- **Blocks TRL clearance**
 - Impairs hepatic uptake of TRL remnants via LDLR/ LRP1 pathways
- **ApoC-III loss-of-function variants in humans are associated with^{4,a}**
 - Plasma triglyceride 39% ↓
 - HDL cholesterol 22% ↑
 - LDL cholesterol 16% ↓
 - Circulating APOC3 46% ↓
 - Risk of coronary heart disease 40% ↓



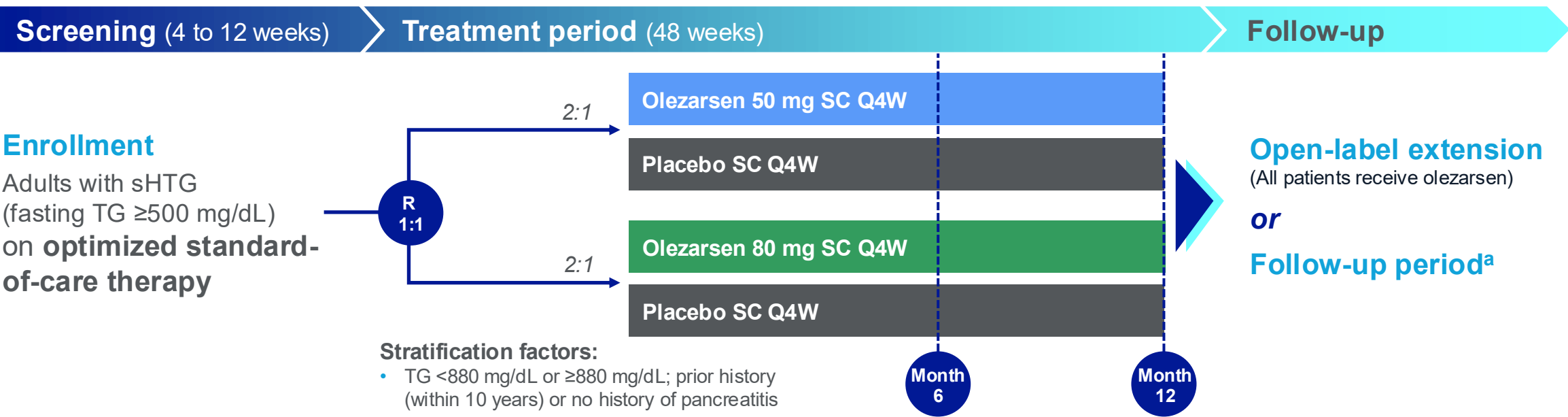
^aCompared to subjects without ApoC-III loss-of-function variants.

ApoC-III, apolipoprotein C-III; HDL-C, high-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; LPL, lipoprotein lipase; LRP1, low-density lipoprotein receptor–related protein 1; mRNA, messenger RNA; TG, triglyceride; TRL, triglyceride rich lipoproteins; VLDL, very low-density lipoprotein.

1. TRYNGOLZA. Prescribing information. Ionis Pharmaceuticals, Inc. 2. Ginsberg HN, et al. *Eur Heart J*. 2021;42(47):4791-4806. 3. Giammanco A, et al. *Curr Atheroscler Rep*. 2023;25(3):67-76. 4. TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute. *N Engl J Med*. 2014;371(1):22-31.

Largest pivotal studies in sHTG ever conducted¹⁻³

CORE and CORE2 were two phase 3, placebo-controlled, randomized clinical trials with the same study design:



	CORE	CORE₂
Olezarsen 50 mg	n=205	n=149
Olezarsen 80 mg	n=204	n=147
Placebo	n=208	n=148

Primary endpoint
% change in fasting TG at 6 months vs placebo

Key secondary endpoints
Adjudicated acute pancreatitis events; safety and tolerability; ApoC-III, remnant-C, non-HDL-C

CORE / CORE₂ (pooled data)

^aParticipants not entering the open-label extension entered the 13-week post-treatment evaluation period. Last dose of study drug is received at week 49⁴.
ApoC-III, apolipoprotein C-III; HDL-C, high-density lipoprotein cholesterol; Q4W, every 4 weeks; R, randomized; remnant-C, remnant cholesterol; SC, subcutaneous; sHTG, severe hypertriglyceridemia; TG, triglyceride.
1. TRYNGOLZA. Prescribing information. Ionis Pharmaceuticals, Inc. 2. Marston NA, et al. *N Engl J Med*. 2026;394(5):429-441. 3. Ionis. Press Release. September 2, 2025. Accessed July 7, 2026. Available from <https://ir.ionis.com/news-releases/news-release-details/olezarsen-significantly-reduces-triglycerides-and-acute>. 4. Marston NA, et al. *Am Heart J* 2025;286:125-135.

Eligibility criteria

Inclusion Criteria

-  Age ≥ 18 years
-  Fasting TG ≥ 500 mg/dL (5.65 mmol/L)
-  Concurrent lipid-lowering therapy adhering to local standard of care, optimized and stabilized for at least 4 weeks prior to screening
-  Agrees to adhere to diet and lifestyle counseling during screening period and throughout the study

Exclusion Criteria

-  Active pancreatitis within 4 weeks
-  Diagnosis of FCS
-  Newly diagnosed, not stabilized, or poorly controlled DM ($\text{HbA}_{1c} \geq 9.5\%$)
-  ACS or stroke/TIA within 6 months; major surgery, peripheral revascularization, or nonurgent PCI within 3 months
-  Uncontrolled comorbidities,^a active infections,^b malignancy,^c laboratory abnormalities,^d or treatment with another investigational drug

^aUncontrolled arterial hypertension (blood pressure $>180/100$ mm Hg) despite antihypertensive therapy; uncontrolled hypothyroidism or thyroid hormone therapy that has not been stable for ≥ 4 weeks. ^bHIV or hepatitis C confirmed with RNA testing, or hepatitis B as evidenced by a positive HbsAg. ^cDiagnosed or treated within 5 years, except for nonmelanoma skin cancers, cervical in situ carcinoma, breast ductal carcinoma in situ, or stage 1 prostate carcinoma that has been successfully treated. ^dALT or AST $>3.0\times$ ULN, total bilirubin $>1.5\times$ ULN, unless due to Gilbert's syndrome, eGFR <30 mL/min/1.73 m², or UPCR ≥ 500 mg/g (56.5 mg/mmol). ACS, acute coronary syndrome; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FCS, familial chylomicronemia syndrome; HbA_{1c} , glycated hemoglobin; HbsAg, hepatitis B surface antigen; HIV, human immunodeficiency virus; PCI, percutaneous coronary intervention; TG, triglyceride; TIA, transient ischemic attack; ULN, upper limit of normal; UPCR, urine protein-to-creatinine ratio.
Marston NA, et al. *N Engl J Med*. 2026;394(5):429-441.

Baseline characteristics were typical of patients with severe hypertriglyceridemia²

CORE **CORE₂**

Baseline characteristics ²	N=617	N=444
Age, median, years ³	54	54
Type 2 Diabetes mellitus, % ¹	59	68
History of AP within prior 10 years, % ¹	19	10
BMI kg/m ² ³	31	31
Lipid-lowering therapies, % ¹	99	99
• Statin ³	72	77
• Fibrate ³	66	60
• Omega-3 fatty acids ³	34	30
• ≥2 therapies ³	67	63

CORE **CORE₂**

	N=617	N=444
Triglycerides, median, mg/dL ³	832	748
ApoC-III, mg/dL ²	34	35
Remnant cholesterol, mg/dL ²	133	121
Non-HDL-C, mg/dL ¹	221	202
ApoB, mg/dL ¹	105	106
LDL-C, mg/dL ¹	64	66
TGs ≥880 mg/dL, % ²	47	37

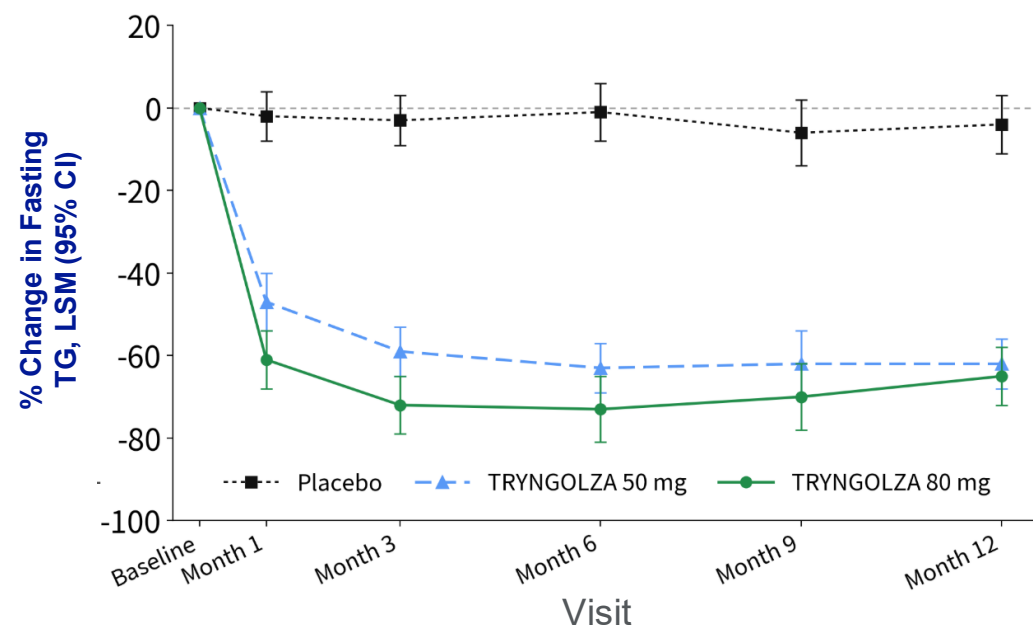
AP, acute pancreatitis; apoB, apolipoprotein B; apoC-III, apolipoprotein C-III; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.

1. TRYNGOLZA. Prescribing information. Ionis Pharmaceuticals, Inc. 2. Marston NA, et al. *N Engl J Med*. 2026;394(5):429-441. 3. Marston NA, et al. presented at American Heart Association (AHA) Scientific Sessions, November 2025, New Orleans, LA.

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Patients treated with olezarsen showed significant reductions in fasting TG levels at 6 and 12 months

CORE

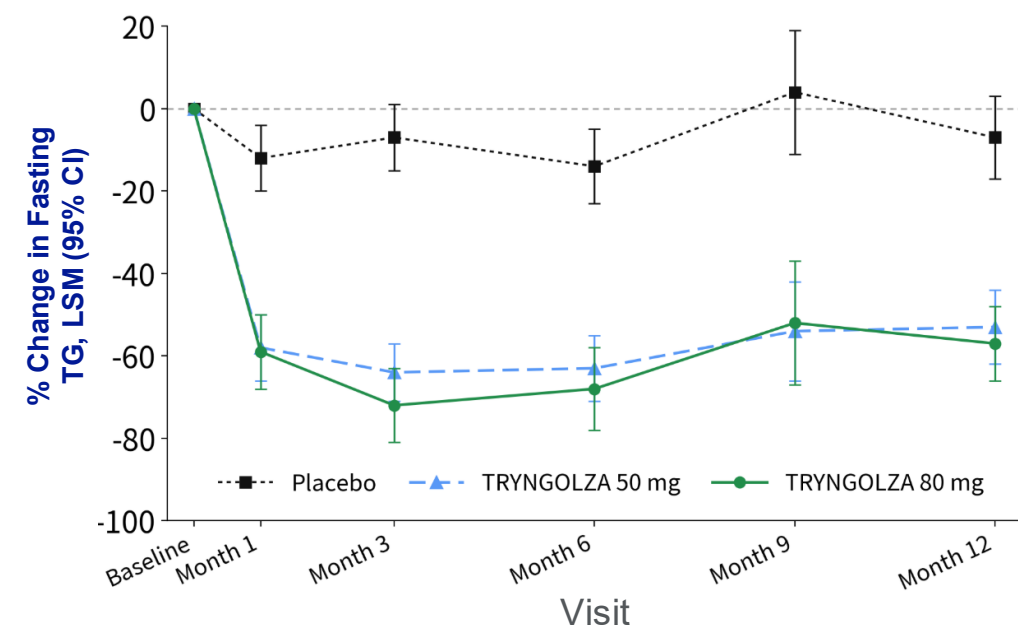


Fasting TG level at 6 months^{a,b}

50 mg
63%
(p < 0.0001)

80 mg
72%
(p < 0.0001)

CORE₂



Fasting TG level at 6 months^{a,b}

50 mg
49%
(p < 0.0001)

80 mg
55%
(p < 0.0001)

^aPercentages shown represent placebo-adjusted reductions. ^bAverage of Weeks 25 and 27.

LSM, least squares mean; TG, triglyceride.

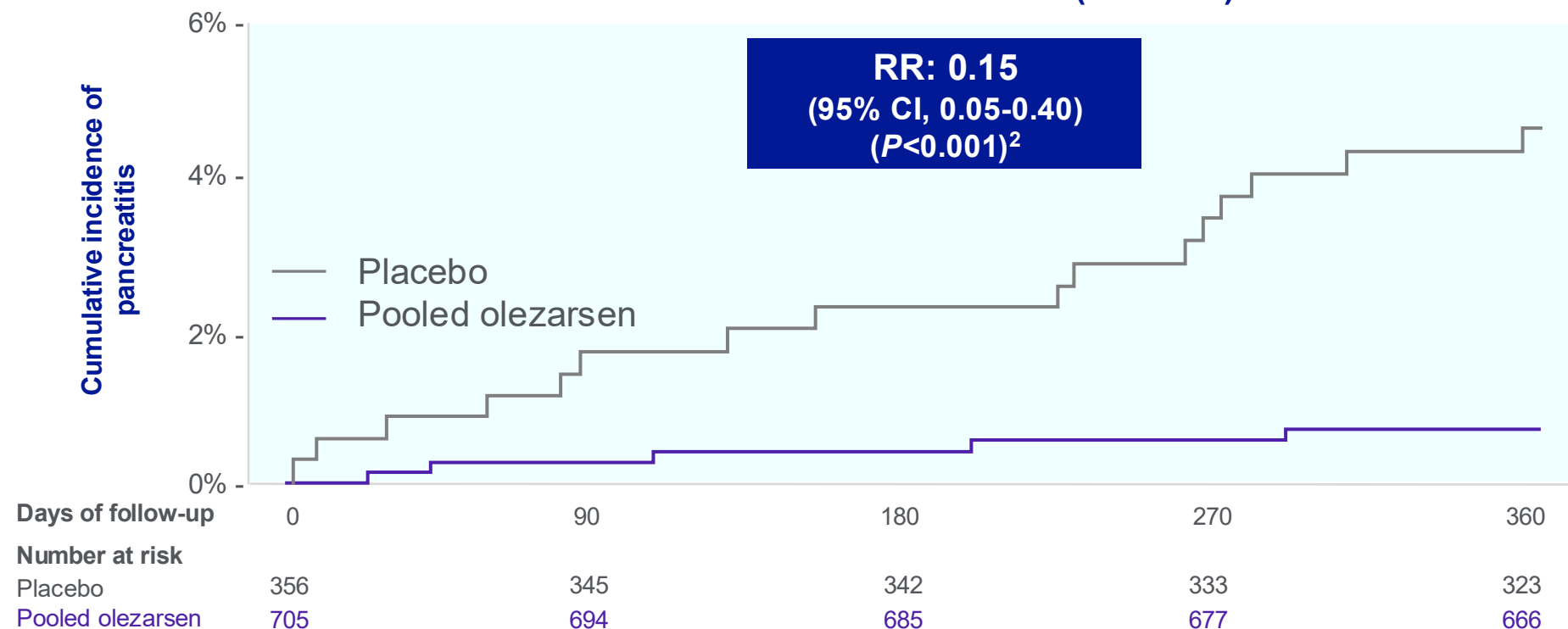
TRYNGOLZA. Prescribing information. Ionis Pharmaceuticals, Inc.

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The 1-year incidence of AP was decreased by 85% in patients treated with olezarsen^{1,2}

CORE/CORE₂ (pooled data)

Overall reduction: 85% ($P < 0.001$)²



TGs ≥ 500 mg/dL²

NNT = 20^a

TGs ≥ 880 mg/dL³

NNT = 9^{a,b}

TGs ≥ 880 mg/dL +
prior AP history²

NNT = 4^{a,b}

Olezarsen is the first therapy to significantly reduce AP events in patients with sHTG^{1,2}

^aNNT represents the number of patients treated with olezarsen over a 1-year period to prevent an acute pancreatitis event. ^bData shown are exploratory and should be interpreted with caution..

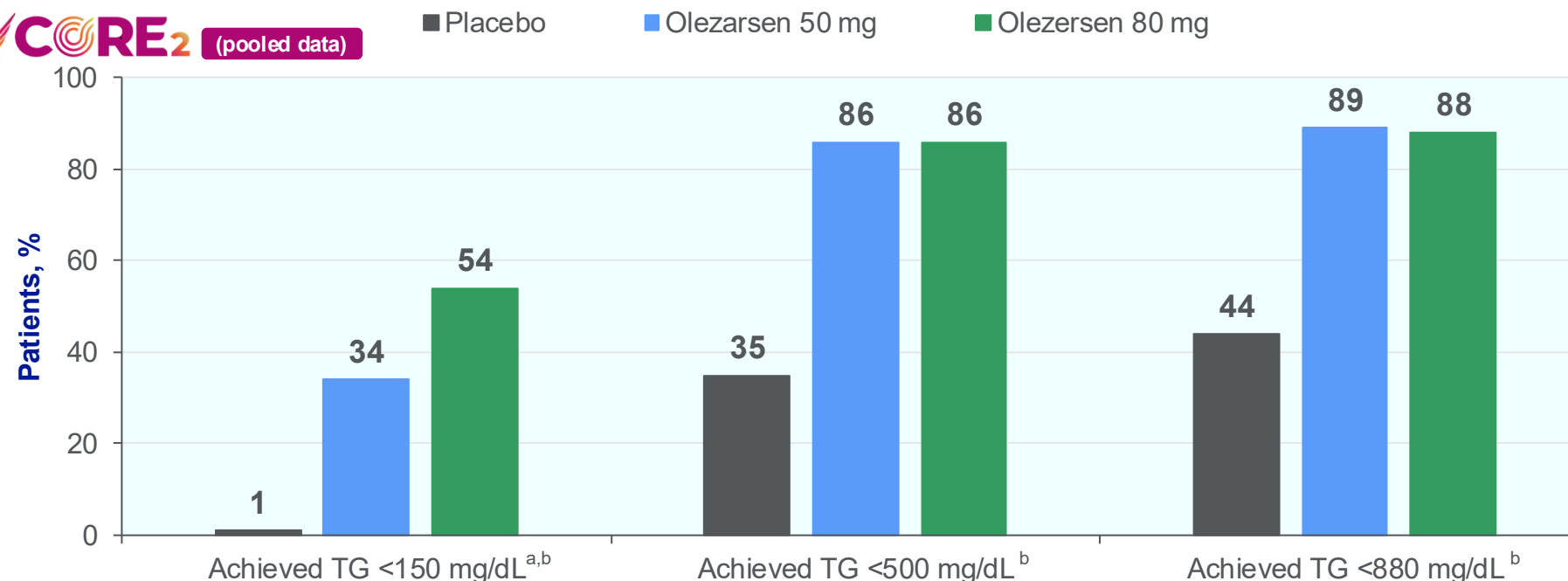
AP, acute pancreatitis; NNT, number needed to treat; RR, rate ratio; sHTG, severe hypertriglyceridemia; TG, triglyceride.

1. TRYNGOLZA. Prescribing information. Ionis Pharmaceuticals, Inc. 2. Marston NA, et al. *N Engl J Med*. 2026;394(5):429-441. 3. Data on file. Ionis Pharmaceuticals.

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Olezarsen reduced TGs below levels known to be high risk for AP by month 12

CORE/CORE2 (pooled data)



Compared with placebo, more than twice as many patients treated with olezarsen achieved TG levels below known AP risk thresholds, with approximately 90% achieving <500 mg/dL by month 12^c

- 54% of patients on olezarsen 80 mg achieved normal TG levels^a

^aData shown are exploratory and should be interpreted with caution. ^bAmong patients with baseline levels above these thresholds and available TG levels at Month 12. ^cBased on pooled analyses of CORE and CORE2 results.

AP, acute pancreatitis; TG, triglyceride.

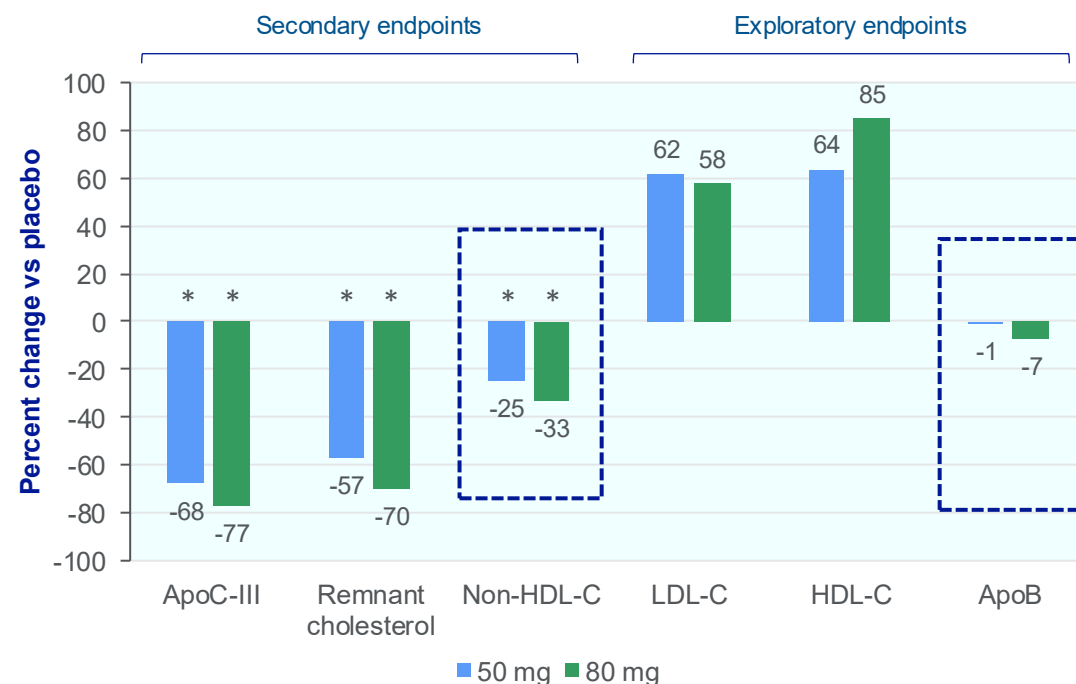
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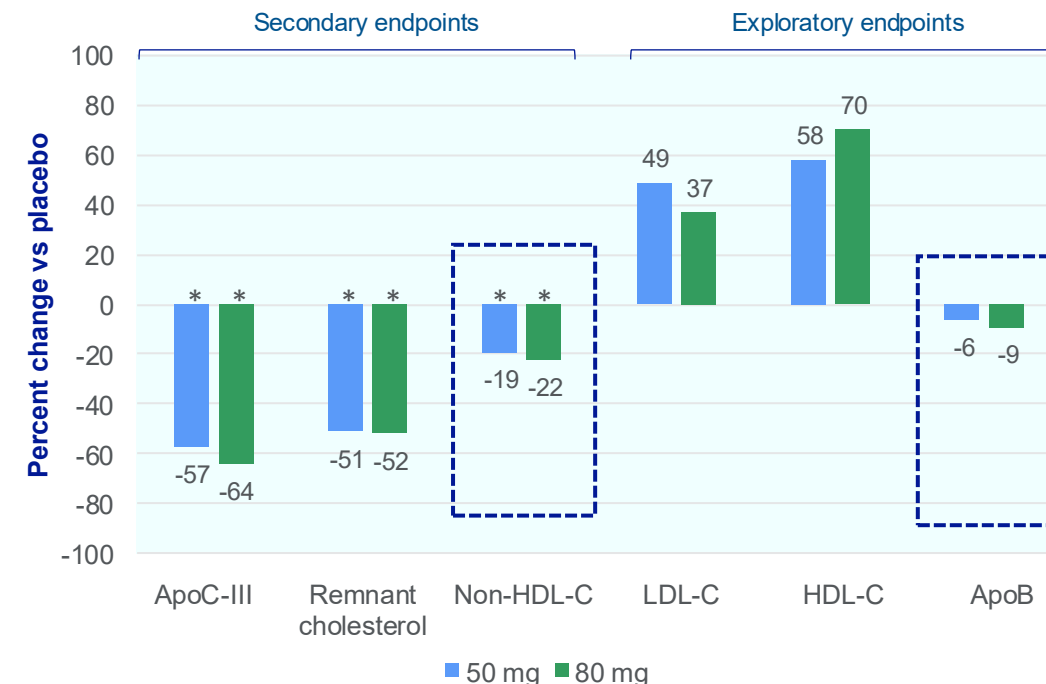
Olezarsen showed sustained net reduction in remodeled atherogenic particles^{1,2}

In patients with elevated TGs, non-HDL-C and apoB more accurately assess patients' CV risk compared with LDL-C³

CORE lipoprotein 6-month outcomes



CORE2 lipoprotein 6-month outcomes



In patients treated with olezarsen, **significant reductions in non-HDL-C and remnant cholesterol** were sustained through 12 months²

*P<0.001.

ApoB, apolipoprotein B; apoC-III, apolipoprotein C-III; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.

1. TRYNGOLZA. Prescribing information. Ionis Pharmaceuticals, Inc. 2. Marston NA, et al. *N Engl J Med*. 2026;394(5):429-441. 3. Blumenthal RS, et al. *Circulation*. 2026;153(17):e1154-e1276.

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Safety and tolerability in patients with sHTG



Warnings and precautions

- Hypersensitivity Reactions:* Have been reported in patients treated with TRYNGOLZA. TRYNGOLZA is contraindicated in patients with a history of serious hypersensitivity to olezarsen or any of the excipients in TRYNGOLZA.
- Liver Enzyme Abnormalities:* Increases in liver enzymes and hepatic fat have occurred in adults. Consider liver enzyme testing before TRYNGOLZA initiation or an increase in dosage and when clinically indicated thereafter.

sHTG, severe hypertriglyceridemia.
TRYNGOLZA. Prescribing information. Ionis Pharmaceuticals, Inc

Adverse reactions

- The most common adverse reactions in patients with sHTG (incidence $\geq 2\%$ higher than placebo) were injection site reactions and liver enzyme increases.

Event category	Olezarsen 50 mg	Olezarsen 80 mg	Placebo
Injection-site reactions	43 (12%)	64 (18%)	8 (2%)
Transaminases increased	11 (3%)	14 (4%)	2 (1%)

- In patients with sHTG, increases in liver enzymes $\geq 3x$ the upper limit of normal were reported more frequently with TRYNGOLZA 80 mg (7%) compared to TRYNGOLZA 50 mg (3%) and placebo (3%).
- Adverse reactions led to discontinuation of treatment in 5% of TRYNGOLZA-treated patients and 2% of placebo-treated patients.
- The most common adverse reaction for TRYNGOLZA treatment discontinuation was injection site reactions.

Laboratory findings in sHTG

Decrease in platelet count

TRYNGOLZA can cause reductions in platelet count. Across CORE AND CORE2, mean decreases from baseline through week 53 ranging from 6% (50mg) to 10% (80 mg) were observed in TRYNGOLZA-treated patients, whereas placebo-treated patients showed no change. The proportion of patients experiencing a bleeding adverse event was similar between the TRYNGOLZA and placebo groups and there were no major bleeding events associated with low platelet counts.

Increase in glucose

In CORE and CORE2, increases in average values in fasting glucose (≤ 9 mg/dL) and HbA1c (< 0.3 percentage points) were observed over time in the sHTG population treated with TRYNGOLZA. These increases were more pronounced in patients with a history of diabetes at baseline; however, increases in fasting glucose and HbA1c were also observed more frequently with TRYNGOLZA compared with placebo in patients without a history of diabetes at baseline.

Increase in liver enzymes

When evaluating any liver enzyme increase in patients with sHTG, increases in liver enzymes greater than or equal to 3 times the upper limit of normal were reported more frequently with TRYNGOLZA 80 mg (7%) compared with TRYNGOLZA 50 mg (3%) and placebo (3%). Liver enzymes returned toward baseline with discontinuation of TRYNGOLZA.

Increase in hepatic fat fraction

HFF was assessed in patients with sHTG in a substudy within CORE and CORE2. Mean HFFs were elevated at baseline (17% TRYNGOLZA 50 mg, 14% TRYNGOLZA 80 mg, 14% placebo). Dose-dependent changes in HFF at 12 months of treatment were a mean increase of 2 percentage points in the TRYNGOLZA 50 mg group and 4 percentage points in the TRYNGOLZA 80 mg group vs 0 percentage points in the placebo group. The clinical meaningfulness of these findings remains uncertain.

HbA_{1c}, hemoglobin A_{1c}; HFF, hepatic fat fraction; sHTG, severe hypertriglyceridemia.

1. TRYNGOLZA. Prescribing information. Ionis Pharmaceuticals, Inc.

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Efficacy and tolerability in sHTG



Up to
72% reduction of
triglycerides

In the largest clinical trials of an FDA-approved treatment for sHTG, olezarsen **reduced triglycerides by 63% to 72% at 6 months on top of standard of care**^{1,2}

- 86% of patients who received olezarsen achieved triglyceride levels below 500 mg/dL at 12 months
- 54% achieved levels below 150 mg/dL at 12 months on the 80-mg dose^a

91% decrease in
AP risk

Olezarsen **reduced the rate of acute pancreatitis by up to 91%**^b in patients with sHTG¹

- Only 4 patients at highest risk for acute pancreatitis^c need to be treated for 1 year to prevent another event (**NNT = 4**)²

5% discontinued
due to
adverse
reactions

Adverse reactions led to discontinuation of treatment in **5%** of olezarsen-treated patients and **2%** of placebo-treated patients

- The most common adverse reaction for olezarsen treatment discontinuation was injection site reactions

^aExploratory endpoint. Interpret with caution. ^bThis outcome is with the 50 mg dose. ^cPatients in the highest risk population defined as TG ≥880 mg/dL with a history of acute pancreatitis.

ApoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NNT, number needed to treat; sHTG, severe hypertriglyceridemia.

1. TRYNGOLZA. Prescribing information. Ionis Pharmaceuticals, Inc. 2. Marston NA, et al. *N Engl J Med*. 2026;394(5):429-441.



Thank you

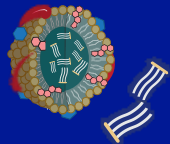
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Appendix

Interpreting LDL findings in the context of olezarsen treatment

HTG¹► VLDL overproduction¹► CETP-mediated exchange of TG to LDL¹► Hydrolysis of LDL by hepatic lipase¹► sdLDL formation¹

Increasing atherogenicity²



Elevated TGs are associated with proatherogenic lipoprotein changes^{3,4}

- Lower HDL-C/small HDL-particles
- Increased TRLs
- Increased remnant cholesterol lipoproteins
- Shift towards small dense LDL-P (diameter <25.5 nm)



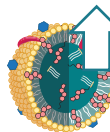
Olezarsen 50 mg Q4W in 22 patients with moderately elevated TGs (200-500 mg/dL) was associated with favorable changes in lipoprotein particle size and concentration, consistent with a less atherogenic lipoprotein profile^{4,a,b}



Increased total and small HDL-P



Reduced TRLs by 51%



LDL particle shifted to larger LDL-P

- Large LDL-P increased by 186%
- Small LDL-P decreased by 39%
- Total LDL-P: minimal effect
 - Average diameter at baseline: 20 nm

^a Patients with or at risk for ASCVD and fasting triglycerides ≥ 200 and < 500 mg/dL (N=114) received olezarsen (10 or 50 mg every 4 weeks, 15 mg every 2 weeks, or 10 mg every week) or saline placebo subcutaneously for 6-12 months. NMR LipoProfile® analysis was performed in frozen EDTA plasma samples collected at baseline and at the primary analysis timepoint (PAT) at 6 months.

^b Compared with placebo

CETP, cholesterol ester transfer protein; LDL, low-density lipoprotein; sdLDL, small dense low-density lipoprotein; sHTG, severe hypertriglyceridemia; TG, triglyceride; VLDL, very low-density lipoprotein.

1. Quispe R, et al. *Arch Med Sci*. 2019;15(5):1195-1202. 2. Packard CJ, Shepherd J. *Arterioscler Thromb Vasc Biol*. 1997;17(12):3542-3556. 3. Akyol O, et al. *Front Cardiovasc Med*. 2025;12:1649759. 4.. Karwatowska-Prokopczuk E, et al. *J Clin Lipidol*. 2022;16(5):617-625.