The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 29, 2026 VOL. 394 NO. 5

Olezarsen for Managing Severe Hypertriglyceridemia and Pancreatitis Risk

N.A. Marston,[1,2] B.A. Bergmark,[1,2] V.J. Alexander,[3] T.A. Prohaska,[3] Y.M. Kang,[1,4] F.A. Moura,[1,5,6] A. Zimerman,[1,7] E. Waldman,[3] J. Weinland,[3] S.A. Murphy,[1,2] E.L. Goodrich,[1,2] S. Zhang,[1,2] S. Xia,[3] D. Li,[3] A.C. Goldberg,[8] A. Goudev,[9] L. Badimon,[10-12] R.G. Kiss,[13,14] M. Vrablik,[15] D. Gaudet,[16,17] P. Moulin,[18] E.S.G. Stroes,[19] M. Banach,[20] H. Cohen,[21] D. Blom,[22] M.-J. Charng,[23] B.G. Nordestgaard,[24] S.J. Nicholls,[25] S. Tsimikas,[3,26] R.P. Giugliano,[1,2] and M.S. Sabatine,[1,2] for the CORE-TIMI 72a and CORE2-TIMI 72b Investigators

ABSTRACT

BACKGROUND

Patients with severe hypertriglyceridemia have an increased risk of acute pancreatitis. The efficacy and safety of olezarsen, an antisense oligonucleotide targeting apolipoprotein C-III messenger RNA, have not been established in this population.

METHODS

We conducted two double-blind, randomized, placebo-controlled trials (CORE-TIMI 72a and CORE2-TIMI 72b). Patients with severe hypertriglyceridemia were assigned in a 1:1:1 ratio to receive olezarsen at a dose of 50 mg, olezarsen at a dose of 80 mg, or placebo monthly for 12 months. The primary outcome was the percent change in the triglyceride level at 6 months, reported as the difference between each olezarsen dose group and the placebo group (placebo-adjusted change). Secondary lipid outcomes included the percent change in the triglyceride level at 12 months and in apolipoprotein C-III, remnant cholesterol, and non–high-density lipoprotein (non-HDL) cholesterol at 6 months and 12 months. Acute pancreatitis events were assessed across both trials.

RESULTS

A total of 1061 patients were included in the primary analysis (617 in the CORE-TIMI 72a trial and 444 in the CORE2-TIMI 72b trial). At 6 months, the placebo-adjusted least-squares mean change from baseline in the triglyceride level was −62.9 percentage points in the olezarsen 50-mg group and −72.2 percentage points in the olezarsen 80-mg group in the CORE-TIMI 72a trial and was −49.2 percentage points in the olezarsen 50-mg group and −54.5 percentage points in the olezarsen 80-mg group in the CORE2-TIMI 72b trial (P<0.001 for all comparisons of olezarsen with placebo). Decreases in the levels of triglycerides, apolipoprotein C-III, remnant cholesterol, and non-HDL cholesterol were greater with olezarsen than with placebo (P<0.001 for all comparisons). The incidence of acute pancreatitis was lower with olezarsen than with placebo (mean rate ratio, 0.15; 95% confidence interval, 0.05 to 0.40; P<0.001). The incidence of any adverse events appeared to be similar across trial groups. Elevations in liver-enzyme levels and thrombocytopenia (platelet count, <100,000 per microliter) were more common with the 80-mg dose of olezarsen, and a dose-dependent increase in the hepatic fat fraction was noted.

CONCLUSIONS

Among patients with severe hypertriglyceridemia, treatment with olezarsen led to a significantly greater reduction in the triglyceride level at 6 months and in the incidence of acute pancreatitis than placebo. (Funded by Ionis Pharmaceuticals; CORE-TIMI 72a and CORE2-TIMI 72b ClinicalTrials.gov numbers, NCT05079919 and NCT05552326.)

The authors' full names, academic degrees, and affiliations are listed at the end of the article. Nicholas A. Marston can be contacted at nmarston@bwh.harvard.edu or at the TIMI Study Group, Hale Building for Transformative Medicine, 7th Fl., 60 Fenwood Rd., Boston, MA 02115.

Nicholas A. Marston and Brian A. Bergmark contributed equally to this article.

This article was published on November 8, 2025, and last updated on November 19, 2025, at NEJM.org.

N Engl J Med 2026;394:429-41.
DOI: 10.1056/NEJMoa2512761

CME

A Quick Take is available at NEJM.org

Severe hypertriglyceridemia, defined as a serum triglyceride level of 500 mg per deciliter or higher (≥5.65 mmol per liter), affects approximately 1 in 100 persons and can have clinical consequences, including an increased risk of life-threatening acute pancreatitis.[1,2] Conventional triglyceride-lowering therapies, such as fibrates and n–3 fatty acids, often have modest effects on the triglyceride level and have not been shown to reduce the risk of acute pancreatitis.[3]

Olezarsen targets apolipoprotein C-III messenger RNA, leading to a reduction in the plasma apolipoprotein C-III level and thereby facilitating triglyceride clearance through derepression of lipoprotein lipase and increased hepatic uptake of triglyceride-rich lipoprotein remnants.[4] The CORE-TIMI 72a and CORE2-TIMI 72b trials were designed to evaluate the efficacy and safety of olezarsen in patients with severe hypertriglyceridemia.

Methods

Trial Design and Oversight

We conducted two phase 3, international, multicenter, double-blind, randomized, placebo-controlled clinical trials in accordance with regulatory guidance. The trial designs were identical and have been described previously[5]; the trial protocols are available with the full text of this article at NEJM.org. The trials were designed in a collaboration between the Thrombolysis in Myocardial Infarction (TIMI) Study Group and Ionis Pharmaceuticals, the trial sponsor. Data were collected at each participating site and stored by Medpace, a contract research organization. The protocols were approved by all the relevant institutional ethical review boards, and an independent data and safety monitoring board oversaw trial safety. All the participants provided written informed consent.

The first and subsequent drafts of the manuscript were written by the first author, and all the authors agreed with the decision to submit the manuscript for publication. The authors vouch for the completeness and accuracy of the data and for the fidelity of each trial to the protocol.

Trial Population

Patients were eligible for the trials if they were at least 18 years of age and had severe hypertriglyceridemia, defined as a fasting triglyceride level of at least 500 mg per deciliter obtained on two occasions while they were receiving stable lipid-lowering therapy according to the local standard of care. Patients were excluded if they had genetically confirmed familial chylomicronemia syndrome, acute pancreatitis at the time of screening or in the 4 weeks before screening, poorly controlled diabetes mellitus (glycated hemoglobin level, ≥9.5%), or an estimated glomerular filtration rate of less than 30 ml per minute per 1.73 m^2. Additional information about inclusion and exclusion criteria is provided in the Supplementary Appendix, available at NEJM.org.

Randomization and Treatment

In each trial, eligible patients were randomly assigned in a 1:1 ratio to either the 50-mg or the 80-mg dose cohort. Within each cohort, patients were then randomly assigned in a 2:1 ratio to receive either subcutaneous olezarsen or matching placebo every 4 weeks for a total of 48 weeks. In effect, patients in both trials were randomly assigned in a 1:1:1 ratio to receive olezarsen at a dose of 50 mg, olezarsen at a dose of 80 mg, or placebo monthly for a 12-month treatment period. Randomization was stratified according to the triglyceride level at baseline (≥880 mg per deciliter [9.94 mmol per liter] or <880 mg per deciliter) and the presence or absence of a history of pancreatitis within 10 years before screening.

Outcomes

The primary outcome was the percent change from baseline in the fasting triglyceride level at 6 months, reported for each trial individually as the difference between each olezarsen dose group and the placebo group (placebo-adjusted change). Prespecified secondary outcomes for each trial individually were the percent change from baseline in the fasting triglyceride level at 12 months, as well as the percent change from baseline in the apolipoprotein C-III level, the remnant cholesterol level (measured directly[6]), and the non–high-density lipoprotein (non-HDL) cholesterol level at 6 months and 12 months. Prespecified secondary outcomes for both trials combined were triglyceride levels below certain thresholds (500 mg per deciliter and 880 mg per deciliter) at 12 months among patients with baseline levels above those thresholds, acute pancreatitis events, and the change from baseline in the hepatic fat fraction on magnetic resonance imaging

(MRI) at 12 months (specifically the MRI proton density fat fraction [MRI-PDFF]) among the patients in the imaging substudy.

Exploratory outcomes included the high-density lipoprotein (HDL) cholesterol level, the low-density lipoprotein (LDL) cholesterol level, the apolipoprotein B level, and major adverse cardiovascular events, defined as a composite of death from cardiovascular causes, myocardial infarction, ischemic stroke, or arterial revascularization. Acute pancreatitis events and major adverse cardiovascular events were adjudicated by a central committee in a blinded manner; acute pancreatitis events were defined according to the revised Atlanta classification.[7] Key safety outcomes included the results of liver-function tests and kidney-function tests, as well as platelet counts.

STATISTICAL ANALYSIS

We planned for the sample sizes to have sufficient power for the primary efficacy analysis and to satisfy regulatory requirements for the safety evaluation. We calculated that a sample size of at least 540 patients in the CORE-TIMI 72a trial and 390 patients in the CORE2-TIMI 72b trial would provide each trial with more than 90% power to show a 60 percentage-point difference in the reduction of the triglyceride level between each olezarsen dose group and the placebo group, assuming a two-sided alpha level of 0.05, a standard deviation of 73%, and 20% discontinuation. The primary efficacy analysis was performed with an analysis of covariance (ANCOVA) model in the modified intention-to-treat population, which included all the patients who had received at least one dose of olezarsen or placebo. The same patients were included in the safety population. No interim analysis was performed.

A multiple-imputation approach was used to address missing lipid levels; details are provided in the statistical analysis plan, available with the protocol. Secondary outcomes were tested in hierarchical order for control of the overall type I error from multiple comparisons. Analyses of continuous lipid levels were performed with an ANCOVA model, and analyses of categorical triglyceride levels were performed with a logistic-regression model. Acute pancreatitis events were assessed in pooled olezarsen and placebo groups. Details regarding statistical analysis are provided in the Supplementary Appendix. All analyses were conducted by the TIMI Study Group on a complete, independently held dataset with the use of commercially available software (SAS software, version 9.4).

RESULTS

PATIENTS

In the CORE-TIMI 72a trial, 617 patients were enrolled at 157 sites across 23 countries from December 2021 through April 2024. Of these patients, 205 were randomly assigned to the olezarsen 50-mg group, 204 to the olezarsen 80-mg group, and 208 to the placebo group (Fig. S1A in the Supplementary Appendix). Early discontinuation of the trial regimen occurred in 17 patients (8.3%) in the olezarsen 50-mg group, 19 (9.3%) in the olezarsen 80-mg group, and 19 (9.1%) in the placebo group.

In the CORE2-TIMI 72b trial, 446 patients were enrolled at 142 sites across 23 countries from November 2022 through June 2024. Of these patients, 149 were randomly assigned to the olezarsen 50-mg group, 147 to the olezarsen 80-mg group, and 150 to the placebo group (Fig. S1B). All but 2 patients (both in the placebo group) received at least one dose of olezarsen or placebo, with 444 patients included in the primary efficacy analysis. Early discontinuation of the trial regimen occurred in 20 patients (13.4%) in the olezarsen 50-mg group, 18 (12.2%) in the olezarsen 80-mg group, and 15 (10.1%) in the placebo group.

Baseline demographic and clinical characteristics of the patients in each trial are summarized in Table 1. Across both trials, the median age of the patients was 54 years (interquartile range, 45 to 61), and 23.6% were women (Table S1). A total of 88.4% of the patients were White, 5.4% were Asian, and 2.1% were Black; 12.3% identified as Hispanic or Latino. Diabetes mellitus was present in 63.4% of the patients, and almost all the patients were receiving at least one lipid-lowering medication, with 63.5% receiving a fibrate. The median triglyceride level at baseline was 793.0 mg per deciliter (8.96 mmol per liter; interquartile range, 593.3 to 1248.0 mg per deciliter [6.71 to 14.11 mmol per liter]) across both trials, 832.0 mg per deciliter (9.40 mmol per liter; interquartile range, 601.5 to 1382.3 mg per deciliter [6.80 to 15.62 mmol per liter]) in the CORE-TIMI 72a trial, and 747.8 mg per deciliter (8.45 mmol per liter; interquartile range, 584.0 to 1135.5 [6.60 to 12.83 mmol per liter]) in the

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	CORE-TIMI 72a			CORE2-TIMI 72b		
	Placebo (N=208)	Olezarsen, 50 mg (N=205)	Olezarsen, 80 mg (N=204)	Placebo (N=148)	Olezarsen, 50 mg (N=149)	Olezarsen, 80 mg (N=147)
Median age (IQR) — yr	54 (45–62)	54 (45–61)	54 (45–61)	54 (44–62)	55 (48–62)	55 (48–62)
Female sex — no. (%)	42 (20.2)	52 (25.4)	53 (26.0)	27 (18.2)	39 (26.2)	37 (25.2)
Race — no. (%)†						
White	195 (93.8)	191 (93.2)	189 (92.6)	124 (83.8)	125 (83.9)	114 (77.6)
Black	7 (3.4)	2 (1.0)	4 (2.0)	1 (0.7)	3 (2.0)	5 (3.4)
Asian	5 (2.4)	3 (1.5)	4 (2.0)	17 (11.5)	15 (10.1)	13 (8.8)
Hispanic or Latino — no./total no. (%)†	10/202 (5.0)	7/195 (3.6)	12/200 (6.0)	31/148 (20.9)	33/149 (22.1)	35/147 (23.8)
Median BMI (IQR)‡	30.9 (28.2–34.6)	31.2 (28.4–35.2)	31.2 (28.1–34.7)	32.2 (28.3–36.1)	30.9 (27.9–34.8)	30.7 (27.7–33.5)
Atherosclerotic cardiovascular disease — no. (%)	54 (26.0)	37 (18.0)	50 (24.5)	45 (30.4)	41 (27.5)	45 (30.6)
Diabetes mellitus — no. (%)	113 (54.3)	128 (62.4)	127 (62.3)	102 (68.9)	102 (68.5)	101 (68.7)
Chronic kidney disease — no. (%)	10 (4.8)	11 (5.4)	18 (8.8)	13 (8.8)	25 (16.8)	12 (8.2)
History of pancreatitis — no. (%)	48 (23.1)	51 (24.9)	43 (21.1)	21 (14.2)	17 (11.4)	20 (13.6)
Median triglyceride level (IQR) — mg/dl	838.2 (606.2–1233.0)	845.5 (630.0–1427.0)	810.0 (579.8–1396.0)	729.8 (577.0–1097.2)	762.0 (600.5–1114.5)	750.5 (572.0–1145.5)
Triglyceride level ≥880 mg/dl — no. (%)	95 (45.7)	101 (49.3)	96 (47.1)	57 (38.5)	49 (32.9)	57 (38.8)
Median apolipoprotein C-III level (IQR) — mg/dl	34.1 (26.1–43.0)	34.6 (28.4–50.9)	33.8 (25.5–45.3)	34.8 (27.1–44.0)	34.9 (28.0–44.1)	34.1 (26.0–43.9)
Median remnant cholesterol level (IQR) — mg/dl§	130.4 (92.7–187.5)	137.6 (97.3–197.3)	130.4 (82.2–180.1)	109.6 (76.8–165.8)	127.9 (87.0–164.0)	125.0 (79.5–199.2)
Median non-HDL cholesterol level (IQR) — mg/dl	199.2 (161.0–242.0)	197.5 (160.5–252.0)	203.2 (160.8–258.4)	181.0 (147.0–217.0)	197.5 (159.0–240.0)	186.0 (149.5–241.0)
Median apolipoprotein B level (IQR) — mg/dl	101.6 (87.1–121.8)	105.0 (88.2–125.0)	101.8 (81.0–122.2)	103.5 (81.7–118.8)	109.2 (93.9–129.5)	101.5 (85.8–120.3)
Median LDL cholesterol level (IQR) — mg/dl	58.5 (41.0–80.5)	59.0 (41.8–83.3)	57.5 (37.2–84.8)	57.8 (39.2–81.5)	66.6 (44.8–90.0)	60.0 (40.5–81.0)
Median glycated hemoglobin level (IQR) — %	6.3 (5.5–7.5)	6.5 (5.6–7.5)	6.1 (5.5–7.6)	6.8 (5.8–7.8)	6.6 (5.8–7.8)	6.6 (5.7–7.9)
Median creatinine level (IQR) — mg/dl	0.9 (0.8–1.1)	0.9 (0.8–1.1)	0.9 (0.8–1.0)	0.9 (0.8–1.1)	0.9 (0.8–1.1)	0.9 (0.7–1.0)
Median platelet count (IQR) — cells/μl	226,167 (191,167–265,833)	233,000 (192,000–282,500)	228,000 (190,125–264,367)	238,500 (201,000–273,292)	236,333 (201,000–279,667)	236,667 (182,667–272,667)
Median INR (IQR)	1.0 (1.0–1.1)	1.0 (1.0–1.1)	1.0 (1.0–1.1)	1.0 (1.0–1.1)	1.0 (1.0–1.1)	1.0 (1.0–1.1)
Lipid-lowering therapy — no. (%)	203 (97.6)	200 (97.6)	203 (99.5)	147 (99.3)	149 (100.0)	146 (99.3)
Statin	147 (70.7)	144 (70.2)	153 (75.0)	114 (77.0)	111 (74.5)	115 (78.2)
Ezetimibe	53 (25.5)	46 (22.4)	43 (21.1)	31 (20.9)	29 (19.5)	37 (25.2)

Fibrate	146 (70.2)	133 (64.9)	130 (63.7)	90 (60.8)	87 (58.4)	88 (59.9)
n–3 Fatty acid	70 (33.7)	68 (33.2)	70 (34.3)	48 (32.4)	46 (30.9)	38 (25.9)
Niacin	1 (0.5)	2 (1.0)	2 (1.0)	4 (2.7)	6 (4.0)	5 (3.4)
PCSK9 inhibitor	3 (1.4)	4 (2.0)	11 (5.4)	3 (2.0)	3 (2.0)	2 (1.4)
Two or more therapies	144 (69.2)	129 (62.9)	138 (67.6)	90 (60.8)	95 (63.8)	96 (65.3)
Median MRI-PDFF — %¶	14.5 (7.6–19.1)	15.0 (10.2–23.9)	13.2 (9.8–19.0)	13.4 (9.0–20.2)	15.6 (9.7–24.8)	13.3 (6.7–18.3)

* To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for creatinine to micromoles per liter, multiply by 88.4. HDL denotes high-density lipoprotein, INR international normalized ratio, IQR interquartile range, LDL low-density lipoprotein, and PCSK9 proprotein convertase subtilisin kexin type 9.
† Race and ethnic group were reported by the patients.
‡ The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.
§ Remnant cholesterol was directly measured.
¶ The hepatic fat fraction on magnetic resonance imaging (MRI), specifically the MRI proton density fat fraction (MRI-PDFF), is shown for the patients with measurements at both baseline and 12 months: in CORE-TIMI 72a, 35 patients in the placebo group, 34 in the olezarsen 50-mg group, and 28 in the olezarsen 80-mg group; in CORE-TIMI 72b, 45 patients in the placebo group, 46 in the olezarsen 50-mg group, and 64 in the olezarsen 80-mg group.

CORE2-TIMI 72b trial. Overall, 455 patients (42.9%) had fasting triglyceride levels at baseline of 880 mg per deciliter or higher, and 200 (18.9%) had a history of pancreatitis.

TRIGLYCERIDE LEVELS

In the CORE-TIMI 72a trial, the placebo-adjusted least-squares mean (LSM) change from baseline in the triglyceride level at 6 months was −62.9 percentage points (95% confidence interval [CI], −72.2 to −53.6; P<0.001) in the olezarsen 50-mg group and −72.2 percentage points (95% CI, −81.4 to −63.1; P<0.001) in the olezarsen 80-mg group (Table 2). In the CORE2-TIMI 72b trial, the placebo-adjusted LSM change from baseline in the triglyceride level was −49.2 percentage points (95% CI, −59.7 to −38.8; P<0.001) in the olezarsen 50-mg group and −54.5 percentage points (95% CI, −65.1 to −44.0; P<0.001) in the olezarsen 80-mg group. The results of the primary efficacy analysis for both olezarsen doses in both trials were largely consistent across key prespecified clinical subgroups (Fig. S2). The results of a prespecified on-treatment analysis are provided in Table S2.

The reduction in triglyceride levels that had been attained at 6 months remained stable through the 12-month treatment period (Fig. 1A and 1B). Across both trials, among the patients with measurements at baseline and 12 months, triglyceride levels of less than 500 mg per deciliter at 12 months occurred in 260 of 303 patients (85.8%) receiving the 50-mg dose of olezarsen and 246 of 287 patients (85.7%) receiving the 80-mg dose of olezarsen, as compared with 104 of 295 patients (35.3%) receiving placebo (P<0.001 for each comparison of olezarsen with placebo) (Fig. S3). Among the 409 patients with baseline triglyceride levels of 880 mg per deciliter or higher, triglyceride levels of less than 880 mg per deciliter at 12 months occurred in 118 of 132 patients (89.4%) receiving the 50-mg dose of olezarsen and 125 of 142 patients (88.0%) receiving the 80-mg dose of olezarsen, as compared with 60 of 135 patients (44.4%) receiving placebo (P<0.001 for each comparison).

ADDITIONAL SECONDARY AND EXPLORATORY OUTCOMES

The effects of treatment with olezarsen on additional lipid outcomes are shown in Table 2 and Table S3. The placebo-adjusted change in the apolipoprotein C-III level at 6 months was −77.4 and

Table 2. Lipid Outcomes at 6 Months.*

Variable	CORE-TIMI 72a			CORE2-TIMI 72b		
	Placebo (N=208)	Olezarsen, 50 mg (N=205)	Olezarsen, 80 mg (N=204)	Placebo (N=148)	Olezarsen, 50 mg (N=149)	Olezarsen, 80 mg (N=147)
Triglycerides						
Level at baseline — mg/dl	1208.0±1295.4	1168.8±825.8	1168.5±973.7	1018.6±1053.7	967.8±599.9	1088.4±964.5
Level at 6 mo — mg/dl	1083.7±1105.1	389.9±581.6	267.1±300.5	809.6±935.4	315.3±383.8	289.6±349.0
LSM change (95% CI) — %	−0.4 (−7.8 to 6.9)	−63.4 (−70.6 to −56.1)	−72.7 (−80.0 to −65.4)	−13.6 (−22.9 to −4.3)	−62.8 (−72.1 to −53.5)	−68.1 (−77.6 to −58.7)
Placebo-adjusted LSM change (95% CI) — percentage points	—	−62.9 (−72.2 to −53.6)	−72.2 (−81.4 to −63.1)	—	−49.2 (−59.7 to −38.8)	−54.5 (−65.1 to −44.0)
P value vs. placebo	—	<0.001	<0.001	—	<0.001	<0.001
Apolipoprotein C-III						
Level at baseline — mg/dl	37.4±15.9	39.4±16.0	36.9±15.0	36.5±13.6	38.0±15.6	36.9±14.8
Level at 6 mo — mg/dl	35.3±18.1	10.8±10.9	6.9±7.4	31.5±17.0	11.7±13.2	8.3±9.4
LSM change (95% CI) — %	−3.6 (−7.9 to 0.7)	−72.0 (−76.3 to −67.6)	−81.0 (−85.5 to −76.6)	−13.5 (−20.1 to −7.0)	−70.1 (−76.7 to −63.4)	−77.0 (−83.6 to −70.4)
Placebo-adjusted LSM change (95% CI) — percentage points	—	−68.3 (−73.9 to −62.8)	−77.4 (−83.0 to −71.9)	—	−56.5 (−63.9 to −49.2)	−63.5 (−70.9 to −56.0)
P value vs. placebo	—	<0.001	<0.001	—	<0.001	<0.001
Remnant cholesterol						
Level at baseline — mg/dl	150.9±83.1	157.5±85.5	145.4±81.3	127.8±74.3	140.3±83.6	144.2±83.7
Level at 6 mo — mg/dl	148.9±96.6	65.1±57.4	46.3±39.3	118.1±98.2	57.1±54.6	49.0±51.0
LSM change (95% CI) — %	4.7 (−1.7 to 11.0)	−52.6 (−58.8 to −46.3)	−65.4 (−71.4 to −59.3)	0.8 (−9.8 to 11.5)	−49.8 (−60.4 to −39.2)	−51.4 (−62.2 to −40.6)
Placebo-adjusted LSM change (95% CI) — percentage points	—	−57.2 (−65.3 to −49.2)	−70.1 (−77.9 to −62.2)	—	−50.6 (−62.4 to −38.7)	−52.2 (−64.2 to −40.1)
P value vs. placebo	—	<0.001	<0.001	—	<0.001	<0.001
Non-HDL cholesterol						
Level at baseline — mg/dl	221.0±109.8	224.2±94.9	218.7±102.3	191.1±91.0	210.6±73.5	205.2±82.2
Level at 6 mo — mg/dl	208.7±96.2	155.7±76.0	133.1±53.2	171.5±93.2	147.6±63.2	134.4±55.8
LSM change (95% CI) — %	−2.8 (−7.0 to 1.3)	−27.6 (−31.9 to −23.4)	−35.5 (−39.7 to −31.2)	−7.4 (−12.7 to −2.0)	−26.7 (−32.1 to −21.3)	−29.6 (−35.1 to −24.2)

Placebo-adjusted LSM change (95% CI) — percentage points	—	–24.8 (–30.3 to –19.3)	–32.6 (–38.0 to –27.3)	—	–19.3 (–25.3 to –13.3)	–22.3 (–28.4 to –16.1)
P value vs. placebo	—	<0.001	<0.001	—	<0.001	<0.001
HDL cholesterol						
Level at baseline — mg/dl	26.1±12.1	25.6±8.2	25.6±8.1	26.7±9.3	28.7±8.6	27.7±8.9
Level at 6 mo — mg/dl	27.7±13.6	42.4±16.3	48.6±18.7	29.3±12.5	47.0±17.6	48.8±18.4
LSM change (95% CI) — %	9.1 (1.5 to 16.8)	73.4 (65.6 to 81.1)	94.5 (86.7 to 102.3)	13.4 (4.4 to 22.3)	71.6 (62.8 to 80.4)	83.1 (74.4 to 91.9)
Placebo-adjusted LSM change (95% CI) — percentage points	—	64.2 (54.4 to 74.1)	85.4 (75.5 to 95.2)	—	58.3 (48.5 to 68.1)	69.8 (60.0 to 79.6)
Apolipoprotein B						
Level at baseline — mg/dl	104.4±26.8	109.1±34.9	103.2±30.7	101.2±27.4	113.1±26.6	104.8±30.7
Level at 6 mo — mg/dl	102.1±27.6	102.8±34.7	92.2±31.4	97.3±25.0	100.3±30.0	91.6±30.0
LSM change (95% CI) — %	–2.3 (–5.6 to 1.1)	–3.5 (–6.9 to –0.1)	–9.5 (–13.0 to –6.1)	–2.4 (–6.8 to 1.9)	–8.2 (–12.5 to –3.9)	–11.2 (–15.5 to –6.9)
Placebo-adjusted LSM change (95% CI) — percentage points	—	–1.2 (–5.6 to 3.1)	–7.3 (–11.6 to –3.0)	—	–5.8 (–10.6 to –0.9)	–8.7 (–13.6 to –3.9)
LDL cholesterol						
Level at baseline — mg/dl	63.1±33.9	65.6±36.3	64.2±37.0	62.4±33.0	70.8±35.0	64.8±34.3
Level at 6 mo — mg/dl	66.7±37.2	94.9±46.6	88.8±43.1	67.2±34.7	95.4±45.2	88.3±43.8
LSM change (95% CI) — %	7.2 (–5.1 to 19.5)	69.1 (56.8 to 81.5)	65.1 (52.6 to 77.7)	36.0 (17.9 to 54.2)	85.2 (67.3 to 103.0)	72.7 (54.9 to 90.5)
Placebo-adjusted LSM change (95% CI) — percentage points	—	62.0 (46.2 to 77.8)	57.9 (42.2 to 73.7)	—	49.2 (29.1 to 69.3)	36.7 (17.0 to 56.4)

* Plus–minus values are means ±SD. LSM denotes least-squares mean.

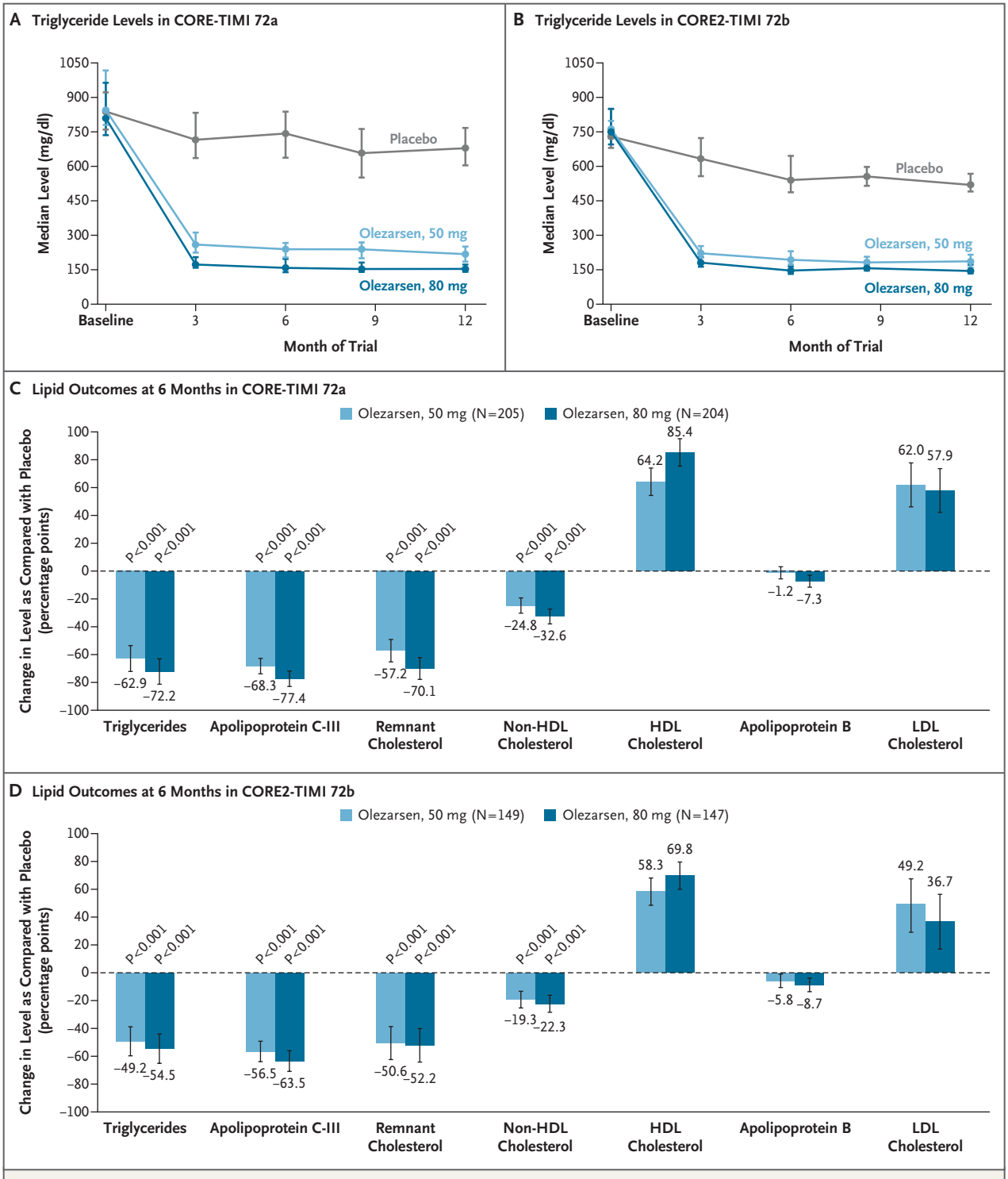

Figure 1. Triglyceride Levels through 12 Months and Lipid Outcomes at 6 Months.

Panels A and B show the median triglyceride levels in the CORE-TIMI 72a trial and the CORE2-TIMI 72b trial, respectively. Panels C and D show the results for the primary outcome (the percent change from baseline in the triglyceride level at 6 months) as well as secondary and exploratory lipid outcomes in the CORE-TIMI 72a trial and the CORE2-TIMI 72b trial, respectively. I bars indicate 95% confidence intervals. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. HDL denotes high-density lipoprotein and LDL low-density lipoprotein.

–63.5 percentage points with the 80-mg dose of olezarsen in the CORE-TIMI 72a and CORE2-TIMI 72b trials, respectively (P<0.001 for each comparison of olezarsen with placebo) (Fig. 1C and 1D). The placebo-adjusted change in the remnant cholesterol level at 6 months was –70.1 and –52.2 percentage points with the 80-mg dose of olezarsen in the CORE-TIMI 72a and CORE2-TIMI 72b trials, respectively (P<0.001 for each comparison); these results corresponded to an absolute change of –100.7 and –75.7 mg per deciliter (–2.61 and –1.96 mmol per liter). For the LDL cholesterol level, the placebo-adjusted change was 57.9 and 36.7 percentage points with the 80-mg dose of olezarsen in the two trials, corresponding to an absolute change of 21.3 and 19.1 mg per deciliter (0.55 and 0.49 mmol per liter). The placebo-adjusted change in the non-HDL cholesterol level was –32.6 and –22.3 percentage points with the 80-mg dose of olezarsen in the two trials (P<0.001 for each comparison), corresponding to an absolute change of –74.6 and –43.9 mg per deciliter (–1.93 and –1.14 mmol per liter). For the apolipoprotein B level, the placebo-adjusted change was –7.3 and –8.7 percentage points with the 80-mg dose of olezarsen in the CORE-TIMI 72a and CORE2-TIMI 72b trials, respectively. Across both trials, major adverse cardiovascular events occurred in 23 patients, including 14 in the pooled olezarsen group (2.0%) and 9 in the pooled placebo group (2.5%) (Table S4).

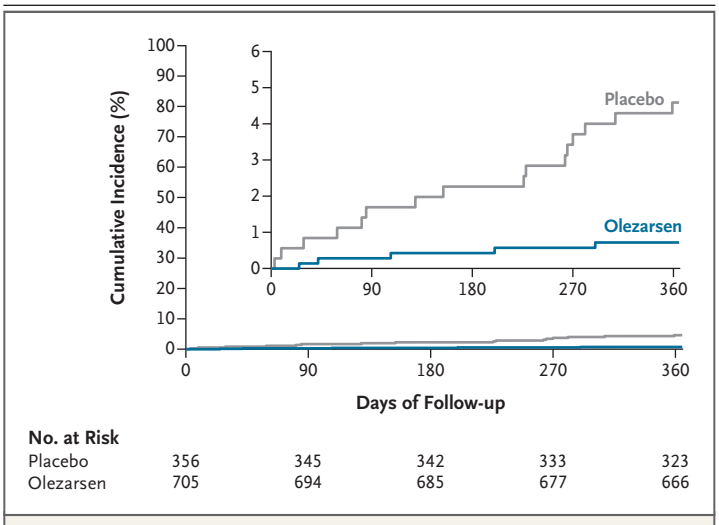

Figure 2. Cumulative Incidence of Acute Pancreatitis Events.
Shown are the results of a time-to-first-event analysis of acute pancreatitis events in the pooled olezarsen group and the pooled placebo group across both the CORE-TIMI 72a trial and the CORE2-TIMI 72b trial. The inset shows the same data on an enlarged y axis.

ACUTE PANCREATITIS

A total of 29 acute pancreatitis events occurred in 22 patients across both trials. During 696.1 patient-years in the pooled olezarsen group, 7 acute pancreatitis events occurred in 5 of 705 patients (observed incidence rate, 1.01 events per 100 patient-years; 95% CI, 0.40 to 2.07). During 352.9 patient-years in the pooled placebo group, 22 acute pancreatitis events occurred in 17 of 356 patients (observed incidence rate, 6.23 events per 100 patient-years; 95% CI, 3.91 to 9.44). The mean rate ratio for acute pancreatitis with olezarsen as compared with placebo was 0.15 (95% CI, 0.05 to 0.40; P<0.001) (Fig. 2); the number needed to treat in a 1-year period to prevent one episode of pancreatitis was 20. Of the 29 acute pancreatitis events, 25 (86%) occurred among the 141 patients who had baseline triglyceride levels of 880 mg per deciliter or higher and had a history of pancreatitis. In this high-risk subgroup, the observed incidence rate was 6.55 events per 100 patient-years (95% CI, 2.40 to 14.25) with olezarsen and 39.09 events per 100 patient-years (95% CI, 23.53 to 61.04) with placebo (mean rate ratio, 0.17; 95% CI, 0.06 to 0.47), corresponding to a number needed to treat of 4 (Table S5).

HEPATIC FAT FRACTION

A total of 252 patients (97 in the CORE-TIMI 72a trial and 155 in the CORE2-TIMI 72b trial) participated in the imaging substudy and underwent hepatic MRI at both baseline and 12 months. At baseline, the median hepatic fat fraction (normal value, <5%) on MRI was elevated at 13.9% (interquartile range, 8.6 to 20.5). At 12 months, a dose-dependent increase in the hepatic fat fraction on MRI was observed with olezarsen, with a LSM absolute increase of 2.28 percentage points in the olezarsen 50-mg group and 4.18 percentage points in the olezarsen 80-mg group, as compared with 0.14 percentage points in the placebo group. An absolute increase of 5 percentage points or more occurred in 27.5% of the patients in the olezarsen 50-mg group and in 40.2% of those in the olezarsen 80-mg group, as compared with 12.5% of those in the placebo group (Table S6). The incidence of site-reported adverse events related to hepatic steatosis is shown in Table 3.

Table 3. Adverse Events and Laboratory Measures (CORE-TIMI 72a and CORE2-TIMI 72b Pooled Safety Population).*

Event or Measure	Placebo (N=356)	Olezarsen, 50 mg (N=354)	P Value vs. Placebo	Olezarsen, 80 mg (N=351)	P Value vs. Placebo
Adverse events — no. (%)					
Any adverse event	267 (75.0)	264 (74.6)	0.86	267 (76.1)	0.64
Adverse event leading to discontinuation of olezarsen or placebo	7 (2.0)	12 (3.4)	0.25	15 (4.3)	0.09
Any serious adverse event	49 (13.8)	31 (8.8)	0.04	38 (10.8)	0.24
Serious adverse event leading to discontinuation of olezarsen or placebo	1 (0.3)	4 (1.1)	0.22	2 (0.6)	0.57
Injection-site reaction					
Any	3 (0.8)	36 (10.2)	<0.001	58 (16.5)	<0.001
Mild	3 (0.8)	34 (9.6)	<0.001	52 (14.8)	<0.001
Moderate†	0	4 (1.1)	0.06	10 (2.8)	<0.001
Severe	0	0	—	0	—
Possible hypersensitivity event‡					
Any	11 (3.1)	25 (7.1)	0.02	24 (6.8)	0.03
Mild	10 (2.8)	21 (5.9)	0.05	17 (4.8)	0.16
Moderate	1 (0.3)	4 (1.1)	0.21	9 (2.6)	0.04
Severe	0	0	—	0	—
Hepatic steatosis adverse event — no. (%)‖	4 (1.1)	9 (2.5)	0.17	8 (2.3)	0.24
Laboratory measures					
Hepatic measures					
ALT or AST ≥3× ULN — no./total no. (%)	7/351 (2.0)	9/347 (2.6)	0.60	24/346 (6.9)	0.003
ALT or AST ≥5× ULN — no./total no. (%)	3/351 (0.9)	3/347 (0.9)	0.99	5/346 (1.4)	0.47
Total bilirubin ≥2× ULN — no./total no. (%)	1/351 (0.3)	1/347 (0.3)	0.99	2/346 (0.6)	0.56
LSM absolute change in INR from baseline to highest value (95% CI)§	0.1 (0.1 to 0.1)	0.1 (0.1 to 0.1)	0.89	0.1 (0.1 to 0.1)	0.13
LSM absolute change in MRI-PDFF from baseline to 12 mo (95% CI)¶	0.14 (–1.50 to 1.79)	2.28 (0.59 to 3.96)	0.05	4.18 (2.52 to 5.85)	<0.001
Renal measures — no./total no. (%)					
eGFR decrease ≥30%	47/351 (13.4)	31/347 (8.9)	0.06	35/346 (10.1)	0.18
eGFR decrease ≥50%	7/351 (2.0)	3/347 (0.9)	0.22	10/346 (2.9)	0.45

UPCR ≥500***	50/352 (14.2)	42/347 (12.1)	0.41	47/346 (13.6)	0.81
UPCR ≥1000***	16/352 (4.5)	18/347 (5.2)	0.70	14/346 (4.0)	0.74
Platelet-count thresholds — no./total no. (%)					
<100,000 cells/μl	12/352 (3.4)	7/347 (2.0)	0.26	25/347 (7.2)	0.03
<75,000 cells/μl	6/352 (1.7)	2/347 (0.6)	0.18	7/347 (2.0)	0.76

* The events shown occurred or worsened during treatment or within 28 days after treatment. ALT denotes alanine aminotransferase, AST aspartate aminotransferase, eGFR estimated glomerular filtration rate, and ULN upper limit of the normal range.

† P values for moderate injection-site reactions were calculated with Fisher's exact test because of the absence of events in the placebo group.

‡ No possible hypersensitivity events met the algorithmic Food and Drug Administration Medical Query definition.

§ P values are for the placebo-adjusted LSM change. Data were available for 345 patients in the placebo group, 336 patients in the olezarsen 50-mg group, and 333 patients in the olezarsen 80-mg group.

¶ The MRI-PDFF measurements were obtained at baseline and 12 months as part of the imaging substudy. P values are for the placebo-adjusted LSM change. Data were available for 80 patients in the placebo group, 80 patients in the olezarsen 50-mg group, and 92 patients in the olezarsen 80-mg group.

‖ Hepatic steatosis adverse events are defined as site-reported adverse events related to hepatic steatosis or fatty liver.

** The urinary protein-to-creatinine ratio (UPCR) was calculated with protein measured in milligrams and creatinine measured in grams.

SAFETY

During the 12-month treatment period, the incidence of adverse events, serious adverse events, and serious adverse events leading to discontinuation of the trial regimen appeared to be similar across the olezarsen dose groups and the placebo group. The incidences of injection-site reactions and possible hypersensitivity events are shown in Table 3.

Levels of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) that were above the upper limit of the normal range occurred in 49.3% of the patients in the olezarsen 50-mg group, 54.9% of those in the olezarsen 80-mg group, and 29.6% of those in the placebo group ($P<0.001$ for each comparison of olezarsen with placebo). Levels of ALT or AST that were at least 3 times the upper limit of the normal range occurred in 2.6% of the patients in the olezarsen 50-mg group, 6.9% of those in the olezarsen 80-mg group, and 2.0% of those in the placebo group ($P=0.60$ for the 50-mg dose vs. placebo; $P=0.003$ for the 80-mg dose vs. placebo). Levels of ALT or AST that were at least 5 times the upper limit of the normal range appeared to occur in a similar percentage of patients across trial groups, and no cases met the criteria for Hy's law. Elevations in levels of ALT or AST did not appear to be correlated with increases in the hepatic fat fraction.

Platelet counts of less than 100,000 per microliter occurred in a higher percentage of patients in the olezarsen 80-mg group than in the olezarsen 50-mg group or the placebo group ($P=0.03$ for the 80-mg dose vs. placebo); platelet counts of less than 75,000 per microliter appeared to occur in a similar percentage of patients across trial groups. The increase in the glycated hemoglobin level at 12 months was greater in the olezarsen 50-mg and olezarsen 80-mg groups than in the placebo group; this greater increase occurred only among patients with diabetes (Table S7). No consistent pattern of changes was observed with olezarsen in the homeostatic model assessment for insulin resistance or beta-cell function (Table S8A and S8B).

DISCUSSION

In these two phase 3 trials, the addition of olezarsen to standard lipid-lowering therapy led to a greater reduction in the triglyceride level at

6 months than placebo among patients with severe hypertriglyceridemia. Treatment with olezarsen in this population also led to a greater reduction in the triglyceride level at 12 months and in the levels of apolipoprotein C-III, remnant cholesterol, and non-HDL cholesterol at 6 months and 12 months. The incidence of acute pancreatitis was lower with olezarsen than with placebo. The incidence of serious adverse events appeared to be similar across trial groups; however, elevations in the ALT or AST level and thrombocytopenia (platelet count, <100,000 per microliter) were more common with the 80-mg dose of olezarsen, increases in the glycated hemoglobin level were seen with both doses, and a dose-dependent increase in the hepatic fat fraction was noted.

The placebo-adjusted reduction in the triglyceride level seen with the addition of olezarsen to standard care in these trials was greater than the effect seen with conventional therapies used for patients with severe hypertriglyceridemia. Among patients treated with olezarsen who had baseline and follow-up data, 86% in each dose group had triglyceride levels below 500 mg per deciliter at 12 months, and 34% and 54% receiving the 50-mg and 80-mg doses, respectively, had levels below 150 mg per deciliter (1.69 mmol per liter). Olezarsen treatment also appeared to reduce the risk of chylomicronemia, a condition in which triglyceride levels are typically in excess of 880 mg per deciliter; chylomicronemia is the primary driver of pancreatitis, and current therapies have had modest effects on triglyceride levels in affected patients. Among patients with baseline triglyceride levels of 880 mg per deciliter or higher, the percentage in whom triglyceride levels were below this clinically relevant threshold after treatment with olezarsen was 2 times that seen with placebo.

The primary purpose of triglyceride lowering in patients with severe hypertriglyceridemia is to reduce the risk of acute pancreatitis, which can be life-threatening. Current therapies have more modest triglyceride-lowering effects in patients with severe hypertriglyceridemia and have not been shown to reduce the incidence of pancreatitis in this population. Our trials showed that olezarsen reduced the incidence of acute pancreatitis by 85% among patients with severe hypertriglyceridemia. The number needed to treat in a 1-year period to prevent one episode of acute pancreatitis was 20 in the overall cohort and 4 in the high-risk subgroup of patients with baseline triglyceride levels of 880 mg per deciliter or higher and a history of pancreatitis.

The effect of olezarsen on levels of atherogenic lipoproteins appeared to be favorable, with reduced levels of remnant cholesterol, non-HDL cholesterol, and apolipoprotein B; the latter two are established and comprehensive measures of overall lipid-mediated atherogenic risk.[8,9] Although the use of olezarsen led to increases in the LDL cholesterol level, it led to greater decreases in the remnant cholesterol level and thus decreases in the non-HDL cholesterol level. Increases in the glycated hemoglobin level were observed among patients with diabetes, without changes in the homeostatic model assessment for insulin resistance or beta-cell function. This finding has also been observed with plozasiran, which suggests that it may be a mechanism-related class effect of apolipoprotein C-III inhibitors.[10] Longer-term follow-up in an open-label extension study may help in determining whether the increased glycated hemoglobin levels are transient.[5]

Increases in the hepatic fat fraction were observed and appeared to be dose-dependent, with an increase of 2.28 percentage points in the olezarsen 50-mg group and 4.18 percentage points in the olezarsen 80-mg group. The clinical relevance of this imaging finding is unclear, especially in a population with an increased hepatic fat fraction at baseline; the absence of an association with elevated levels of ALT or AST is reassuring. Whether this effect of olezarsen is a pathway-specific finding (related to increased uptake of remnant cholesterol and reduced secretion of very-low-density lipoprotein cholesterol from the liver) or a drug-specific finding warrants further study. Earlier data regarding the parent compound volanesorsen, an apolipoprotein C-III inhibitor that lacks the N-acetylgalactosamine moiety that is responsible for directing olezarsen to hepatocytes, showed a trend toward reducing the hepatic fat fraction in three different populations of patients with hypertriglyceridemia.[11] In a small phase 2 study, a numerical increase in the hepatic fat fraction was observed among patients with severe hypertriglyceridemia who had been treated with another N-acetylgalactosamine–conjugated apolipoprotein C-III inhibitor, plozasiran.[10] The underlying mechanisms related to this observation are not known; the change may re-

flect the rapid movement of circulating triglycerides to the liver, which then needs time to adapt and process them.

These trials have limitations. Women made up only one quarter of the overall trial population, although this proportion is consistent with that seen in the population of patients with severe hypertriglyceridemia.[2] In addition, the trial duration was only 1 year, which precludes assessment of longer-term efficacy and safety. However, olezarsen use beyond 1 year is being assessed in the open-label extension study (ClinicalTrials.gov number, NCT05681351).

In these two phase 3 trials, olezarsen led to a significantly greater reduction in the triglyceride level at 6 months and in the incidence of pancreatitis than placebo among patients with severe hypertriglyceridemia.

Supported by Ionis Pharmaceuticals.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank Julia F. Kuder for providing statistical programming and analysis expertise.

AUTHOR INFORMATION

Nicholas A. Marston, M.D., M.P.H.,[1,2] Brian A. Bergmark, M.D.,[1,2] Veronica J. Alexander, Ph.D.,[3] Thomas A. Prohaska, M.D., Ph.D.,[3] Yu Mi Kang, M.D., Ph.D.,[1,4] Filipe A. Moura, M.D., Ph.D.,[1,5,6] Andre Zimerman, M.D., Ph.D.,[1,7] Elaine Waldman, M.B.A.,[3] Julia Weinland, B.S.N.,[3] Sabina A. Murphy, M.P.H.,[1,2] Erica L. Goodrich, M.S.,[1,2] Shuanglu Zhang, M.P.H.,[1,2] Shuting Xia, M.S.,[3] Dan Li, Ph.D.,[3] Anne C. Goldberg, M.D.,[8] Assen Goudev, M.D., D.Sc.,[9] Lina Badimon, Ph.D.,[10-12] Robert Gabor Kiss, M.D., Ph.D.,[13,14] Michal Vrablik, M.D., Ph.D.,[15] Daniel Gaudet, M.D., Ph.D.,[16,17] Philippe Moulin, M.D., Ph.D.,[18] Erik S.G. Stroes, M.D., Ph.D.,[19] Maciej Banach, M.D., Ph.D.,[20] Hofit Cohen, M.D.,[21] Dirk Blom, M.B., Ch.B., Ph.D.,[22] Min-Ji Charng, M.D., Ph.D.,[23] Børge G. Nordestgaard, M.D., Ph.D.,[24] Stephen J. Nicholls, M.D.,[25] Sotirios Tsimikas, M.D.,[3,26] Robert P. Giugliano, M.D.,[1,2] and Marc S. Sabatine, M.D., M.P.H.[1,2]

[1] TIMI Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston; [2] Harvard Medical School, Boston; [3] Ionis Pharmaceuticals, Carlsbad, CA; [4] Division of Endocrinology, Diabetes, and Hypertension, Brigham and Women's Hospital, Boston; [5] Section of Cardiovascular Medicine, Yale School of Medicine, New Haven, CT; [6] Veterans Affairs Connecticut Healthcare System, West Haven; [7] MOVE Academic Research Organization, Hospital Moinhos de Vento, Porto Alegre, Brazil; [8] Division of Endocrinology, Metabolism, and Lipid Research, Washington University, St. Louis; [9] Division of Cardiology, University Hospital Tsaritsa Yoanna, Sofia, Bulgaria; [10] University of Vic–Central University of Catalonia Medical School and the Institute for Research and Innovation in Life Sciences and Health in Central Catalonia, Barcelona; [11] Centro de Investigación Biomédica en Red Cardiovascular, Instituto de Salud Carlos III, Madrid; [12] Cardiovascular Research Foundation for Health and Innovation, Barcelona; [13] Department of Cardiology, Central Hospital of Northern Pest-Military Hospital, Budapest, Hungary; [14] Cardiovascular Center, Semmelweis University, Budapest, Hungary; [15] Charles University of Prague, Prague, Czech Republic; [16] Université de Montréal, Montreal; [17] ECOGENE-21, Chicoutimi, QC, Canada; [18] Centre Hospitalier Universitaire de Lyon, Lyon, France; [19] Academic Medical Center, Amsterdam; [20] Medical University of Lodz, Lodz, Poland; [21] Sheba Medical Center, Gray Faculty of Medical and Health Sciences, Tel Aviv University, Tel Aviv, Israel; [22] University of Cape Town, Cape Town, South Africa; [23] Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan; [24] Copenhagen University Hospital, Copenhagen; [25] Monash Victorian Heart Institute, Clayton, VIC, Australia; [26] Division of Cardiovascular Medicine, University of California, San Diego, La Jolla.

REFERENCES

1. Christian JB, Bourgeois N, Snipes R, Lowe KA. Prevalence of severe (500 to 2,000 mg/dl) hypertriglyceridemia in United States adults. Am J Cardiol 2011;107:891-7.
2. Gurevitz C, Chen L, Muntner P, Rosenson RS. Hypertriglyceridemia and multiorgan disease among U.S. adults. JACC Adv 2024;3:100932.
3. Filtz A, Parihar S, Greenberg GS, et al. New approaches to triglyceride reduction: is there any hope left? Am J Prev Cardiol 2024;18:100648.
4. Packard CJ, Pirillo A, Tsimikas S, Ference BA, Catapano AL. Exploring apolipoprotein C-III: pathophysiological and pharmacological relevance. Cardiovasc Res 2024;119:2843-57.
5. Marston NA, Bergmark BA, Alexander VJ, et al. Design and rationale of the CORE-TIMI 72a and CORE2-TIMI 72b trials of olezarsen in patients with severe hypertriglyceridemia. Am Heart J 2025;286:125-35.
6. Varbo A, Nordestgaard BG. Directly measured vs. calculated remnant cholesterol identifies additional overlooked individuals in the general population at higher risk of myocardial infarction. Eur Heart J 2021;42:4833-43.
7. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis — 2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013;62:102-11.
8. Soffer DE, Marston NA, Maki KC, et al. Role of apolipoprotein B in the clinical management of cardiovascular risk in adults: an expert clinical consensus from the National Lipid Association. J Clin Lipidol 2024;18(5):e647-e663.
9. Ramjee V, Sperling LS, Jacobson TA. Non-high-density lipoprotein cholesterol versus apolipoprotein B in cardiovascular risk stratification: do the math. J Am Coll Cardiol 2011;58:457-63.
10. Gaudet D, Pall D, Watts GF, et al. Plozasiran (ARO-APOC3) for severe hypertriglyceridemia: the SHASTA-2 randomized clinical trial. JAMA Cardiol 2024;9:620-30.
11. Prohaska TA, Alexander VJ, Karwatowska-Prokopczuk E, et al. APOC3 inhibition with volanesorsen reduces hepatic steatosis in patients with severe hypertriglyceridemia. J Clin Lipidol 2023;17:406-11.