ORIGINAL ARTICLE

Olezarsen, Acute Pancreatitis, and Familial Chylomicronemia Syndrome

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ABSTRACT

BACKGROUND

Familial chylomicronemia syndrome is a genetic disorder associated with severe hypertriglyceridemia and severe acute pancreatitis. Olezarsen reduces the plasma triglyceride level by reducing hepatic synthesis of apolipoprotein C-III.

METHODS

In a phase 3, double-blind, placebo-controlled trial, we randomly assigned patients with genetically identified familial chylomicronemia syndrome to receive olezarsen at a dose of 80 mg or 50 mg or placebo subcutaneously every 4 weeks for 53 weeks. There were two primary end points: the difference between the 80-mg olezarsen group and the placebo group in the percent change in the fasting triglyceride level from baseline to 6 months, and (to be assessed if the first was significant) the difference between the 50-mg olezarsen group and the placebo group. Secondary end points included the mean percent change from baseline in the apolipoprotein C-III level and an independently adjudicated episode of acute pancreatitis.

RESULTS

A total of 66 patients underwent randomization; 22 were assigned to the 80-mg olezarsen group, 21 to the 50-mg olezarsen group, and 23 to the placebo group. At baseline, the mean (±SD) triglyceride level among the patients was 2630±1315 mg per deciliter, and 71% had a history of acute pancreatitis within the previous 10 years. Triglyceride levels at 6 months were significantly reduced with the 80-mg dose of olezarsen (−43.5%; 95% confidence interval [CI], −69.1 to −17.9; P<0.001) but not with the 50-mg dose (−22.4%; 95% CI, −47.2 to 2.5; P=0.08). The difference in the mean percent change in the apolipoprotein C-III level from baseline to 6 months in the 80-mg group as compared with the placebo group was −73.7% (95% CI, −94.6 to −52.8) and between the 50-mg group as compared with the placebo group was −65.5% (95% CI, −82.6 to −48.3). By 53 weeks, 11 episodes of acute pancreatitis had occurred in the placebo group, and 1 episode had occurred in each olezarsen group (rate ratio [pooled olezarsen groups vs. placebo], 0.12; 95% CI, 0.02 to 0.66). Adverse events of moderate severity that were considered by a trial investigator at the site to be related to the trial drug or placebo occurred in 4 patients in the 80-mg olezarsen group.

CONCLUSIONS

In patients with familial chylomicronemia syndrome, olezarsen may represent a new therapy to reduce plasma triglyceride levels. (Funded by Ionis Pharmaceuticals; Balance ClinicalTrials.gov number, NCT04568434.)

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Familial chylomicronemia syndrome is a rare inherited form of severe hypertriglyceridemia and is estimated to affect 1 to 13 persons per 1,000,000 in the United States[1-6] and 1 to 19 persons per 1,000,000[7-9] in Europe. The condition is caused by biallelic loss-of-function variants in *LPL* (encoding lipoprotein lipase) or in related genes needed for LPL activity.[10-12] Loss of LPL activity results in a reduced ability to hydrolyze triglycerides in triglyceride-rich lipoproteins, such as intestinally derived chylomicrons and hepatically derived very-low-density lipoproteins, leading to their accumulation in plasma and subsequent severe hypertriglyceridemia.[10-12] Acute and recurrent episodes of pancreatitis are the major complications of familial chylomicronemia syndrome and have been documented to occur in infancy as early as 30 days after birth.[13] Approximately 85% of patients with familial chylomicronemia syndrome report at least one episode of acute pancreatitis, and 40% have multiple recurrences during their lifetime.[14] Hypertriglyceridemia-induced acute pancreatitis is a highly morbid condition that can lead to multiorgan failure, admission to an intensive care unit, and prolonged hospitalization, with an in-hospital mortality up to 8%.[15] Patients with familial chylomicronemia syndrome have a minimal response to conventional triglyceride- and lipid-lowering therapies, such as fibrates, omega-3 fatty acids, or statins.[10] Severely fat-restricted diets may be useful to reduce chylomicronemia and hypertriglyceridemia but are difficult to maintain in the long term.[16]

Apolipoprotein C-III, a small glycoprotein produced by the liver and to a lesser extent by the intestine, is present in multiple copies on the surface of all triglyceride-rich lipoproteins and is particularly enriched in chylomicrons. Rare loss-of-function variants in *APOC3* are associated with lifelong low plasma triglyceride levels and a reduced risk of cardiovascular disease.[17-20] In contrast, elevated levels of apolipoprotein C-III lead to chylomicronemia and severe hypertriglyceridemia by inhibiting LPL activity,[21] inhibiting hepatic uptake of triglyceride-rich lipoproteins,[22] and increasing hepatic secretion of triglyceride-rich lipoproteins.[21] Patients with familial chylomicronemia syndrome lack LPL activity and are dependent on the less efficient hepatic pathways of clearing triglyceride-rich lipoproteins; they cannot adequately regulate plasma chylomicron and triglyceride levels. Volanesorsen is an antisense oligonucleotide that targets *APOC3* messenger RNA (mRNA) and reduces plasma apolipoprotein C-III levels, as well as the degree of chylomicronemia and plasma triglyceride levels. The agent has been approved in the European Union and the United Kingdom for the treatment of familial chylomicronemia syndrome and in Brazil for the treatment of familial chylomicronemia syndrome and familial partial lipodystrophy.[23-25] Volanesorsen has not been approved in the United States because of concerns about thrombocytopenia, which has been associated with its use.

Triantennary N-acetylgalactosamine ($GalNAc_3$) is a carbohydrate ligand for asialoglycoprotein receptors that are abundant on the surface of hepatocytes. Conjugation of $GalNAc_3$ to the antisense oligonucleotide facilitates its entry into the hepatocyte nucleus, where *APOC3* mRNA is generated.[26,27] Olezarsen is an investigational $GalNAc_3$-conjugated antisense oligonucleotide that reduces apolipoprotein C-III production by binding to *APOC3* mRNA and inducing its degradation through ribonuclease H1–mediated cleavage of the sense strand.[26,28,29] Olezarsen has the same nucleotide sequence and backbone chemical composition as volanesorsen and differs from it only through its inclusion of $GalNAc_3$, which should permit lower dosing and injection volume than with volanesorsen. Here, we report the primary results of the Balance trial of olezarsen in the treatment of familial chylomicronemia syndrome.

METHODS

TRIAL DESIGN AND OVERSIGHT

In this phase 3, double-blind, randomized trial, we evaluated the efficacy and safety of olezarsen, as compared with placebo, among patients who had familial chylomicronemia syndrome and were 18 years of age or older (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The trial was conducted from November 2020 through October 2023 at 29 centers in 11 countries. The protocol, available at NEJM.org, was approved by the institutional review board at each participating center, and the trial was performed in accordance with the guidelines of the International Council for Harmonisation and the principles of the Declaration of Helsinki. All the patients provided written informed consent before enrollment.

An independent data and safety monitoring board reviewed data on safety and side effects. All the authors, including those employed by the sponsor (Ionis Pharmaceuticals), participated in the interpretation of the data, the preparation of the manuscript, and the decision to submit the manuscript for publication. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol and statistical analysis plan. Additional details on the methods are provided in the Supplementary Appendix.

PATIENTS

Patients who had fasting triglyceride levels of 880 mg per deciliter (9.9 mmol per liter) or higher and suspected familial chylomicronemia syndrome underwent screening and genetic testing (for homozygosity, compound heterozygosity, or double heterozygosity) to identify loss-of-function variants in *LPL*, *APOC2*, *APOA5*, *GPIHBP1*, or *LMF1*; genetic testing was performed by PreventionGenetics. The results were corroborated by the fourth author by means of an established bioinformatic variant classification and annotation pipeline (details are provided in the Supplementary Appendix).[30]

Once a genotype was established for a patient, it was determined whether the patient has been maintaining a stable diet (which was known to the investigator who followed the patient at the site); if not, the patient was enrolled in a 2-week dietary run-in period. All the patients were instructed to consume no more than 20 g of total fat per day, and alcohol use was discouraged during the trial. Dietary counseling began at the start of the diet-stabilization period and was reinforced at intervals throughout the trial. Dietary questions included whether a patient had fasted in the previous 24 hours and how a patient would describe their dietary fat intake in the previous 24 hours.

RANDOMIZATION AND TREATMENT

After the screening period, patients were randomly assigned in a 1:1 ratio to receive 80 mg or 50 mg of olezarsen, and then within each dose cohort, they underwent randomization again, in a 2:1 ratio, to receive olezarsen at the assigned dose or placebo; those assigned to receive placebo in each dose cohort composed the placebo group. Patients who had previously received volanesorsen were eligible to be enrolled in the trial; all the patients included in the trial had not received volanesorsen for at least 1 year before randomization. Randomization was stratified according to history of pancreatitis and previous treatment with volanesorsen. Olezarsen or a matching volume of placebo was administered subcutaneously once every 4 weeks for 49 weeks.

ASSESSMENTS

Blood samples for blood chemical and lipid analyses were taken after the patients had fasted for at least 10 hours and preferably not more than 12 hours. Episodes of acute pancreatitis were adjudicated by an independent committee in a blinded manner using the Atlanta classification of acute pancreatitis.[31] Safety regarding the incidence and severity of adverse events and changes in laboratory measurements was assessed, and prespecified measures were monitored against their respective rules for dose modification or treatment discontinuation. Additional details regarding the assessments are provided in the Supplementary Appendix.

END POINTS

The two primary efficacy end points in order of hierarchy were the difference in the percent change in the fasting triglyceride level from baseline to 6 months in the 80-mg olezarsen group as compared with the placebo group and in the 50-mg olezarsen group as compared with the placebo group. Secondary end points are listed in order of hierarchy in the Supplementary Appendix and included the percent change in the fasting triglyceride level from baseline to month 12; the percent changes in fasting levels of apolipoprotein C-III, apolipoprotein B-48, and non–high-density lipoprotein cholesterol from baseline to month 6 and to month 12; a reduction in the fasting triglyceride level of at least 40% and at least 70% at 6 months; an independently adjudicated episode of acute pancreatitis during weeks 1 to 53 and during weeks 13 to 53 among patients with a history of pancreatitis within 10 years before screening, among all patients, and among patients with 2 or more events within 5 years before enrollment; and a fasting triglyceride level of 880 mg per deciliter or lower and of 500 mg per deciliter (5.6 mmol per liter) or lower at 6 months.

STATISTICAL ANALYSIS

On the basis of previous clinical trial experience with familial chylomicronemia syndrome, we anticipated a standard deviation of approximately 46% in the percent change from baseline in the triglyceride level. We estimated that a sample of 14 patients in each olezarsen group and 14 patients in the placebo group would provide the trial with 90% power to detect a relative difference of 60% in the percent change between each olezarsen group and the placebo group at a two-sided alpha level of 0.05, assuming a percent change from baseline of 60% among the patients who received olezarsen and no change among the patients who received placebo.

The primary efficacy analysis was conducted in the full analysis set, and all the safety analyses were performed in the safety analysis set. The full and safety analysis sets were identical and included all the patients who had undergone randomization and received at least one dose of olezarsen or placebo.

With respect to the two primary end points, the percent change in the fasting triglyceride level from baseline (defined as the mean of the predose measurement on day 1 and the last predose measurement closest to day 1) at 6 months (the mean of outcome values at assessment weeks 23, 25, and 27) was evaluated with the use of an analysis of covariance model, with two randomization stratification factors (presence or absence of a history of pancreatitis and previous treatment with volanesorsen) and trial group as fixed effects, the natural log-transformed fasting triglyceride level at baseline as a covariate, and a two-sided alpha level of 0.05. Data were considered to be missing only if predose data were not available at baseline or all three measurements were absent at month 6. Missing data were handled with the use of multiple imputation.

To control the type I error at 0.05 across the primary and secondary end points, the primary and secondary efficacy end points were tested hierarchically. First, the 80-mg olezarsen group was compared with the placebo group to determine the difference in the percent change in the fasting triglyceride level from baseline to 6 months (the first primary end point). If the result was significant ($P<0.05$), the 50-mg olezarsen group was compared with the placebo group to determine the same (the second primary end point). If the result for the second primary end point was significant, the ranked secondary end points could then be tested (see the Supplementary Appendix).

RESULTS

PATIENT CHARACTERISTICS

A total of 144 patients underwent screening, and 66 were randomly assigned to a trial group; 60 patients (91%) completed the assigned trial regimen (Fig. S2). Among the patients who underwent randomization, the majority were female, were White, and had a normal body-mass index, and the mean (±SD) triglyceride level was 2630±1315 mg per deciliter (29.7±14.9 mmol per liter). Of the 66 patients, 55 (83%) had biallelic pathogenic variants in *LPL*, and the remaining 11 (17%) had other causative genotypes (Table 1 and Table S1). The patients were generally representative of the population of patients with this rare disease in the United States, Canada, and Europe (Table S2). At screening, 47 patients (71%) had a recorded history of acute pancreatitis within the previous 10 years, and 26 (39%) had previously received volanesorsen. The mean number of previous episodes of acute pancreatitis across the trial groups ranged from 4.1 to 6.6 during the previous 10 years, with a maximum of 79 episodes in one patient.

PRIMARY EFFICACY END POINTS

In the analysis of the first primary end point, the difference between the 80-mg olezarsen group and the placebo group in the percent change in the fasting triglyceride level from baseline to 6 months was significant, with a least-squares mean reduction of 43.5% (95% confidence interval [CI], −69.1 to −17.9; $P<0.001$) (Fig. 1A; absolute values are provided in Fig. S3A, and sensitivity analyses in Table S3). In the analysis of the second primary end point, the result was not significant in the 50-mg olezarsen group as compared with the placebo group (least-squares mean change, −22.4% [95% CI, −47.2 to 2.5]; $P=0.08$) (Fig. 1A). A waterfall plot of individual results for both doses is shown in Figure S4A.

In a nonprespecified exploratory analysis, the observed differences in the mean percent change from baseline to week 53 in triglyceride levels suggest that there are differences between each olezarsen group and the placebo group. A prespecified subgroup analysis of the primary end

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Olezarsen, 80 mg (N=22)	Olezarsen, 50 mg (N=21)	Placebo (N=23)
Age — yr	47.7±13.3	43.2±12.1	44.0±14.7
Sex — no. (%)			
Female	11 (50)	15 (71)	12 (52)
Male	11 (50)	6 (29)	11 (48)
Race and ethnic group — no. (%)†			
White	17 (77)	17 (81)	22 (96)
Hispanic or Latino	1 (5)	3 (14)	3 (13)
Asian	3 (14)	3 (14)	0
Native Hawaiian or Pacific Islander	0	1 (5)	0
Other	2 (9)	0	1 (4)
Weight — kg	68.4±16.7	61.2±11.6	67.8±16.1
Body-mass index‡	25.1±6.0	22.4±3.5	24.2±4.1
History of acute pancreatitis in the previous 10 years — no. (%)	17 (77)	15 (71)	15 (65)
No. of episodes of acute pancreatitis per patient in the previous 10 years§	4.8±7.5	4.1±4.4	6.6±16.5
Type 1 or 2 diabetes mellitus — no. (%)	7 (32)	3 (14)	6 (26)
Hypertension — no. (%)	4 (18)	3 (14)	6 (26)
Tobacco user — no. (%)	2 (9)	3 (14)	0
Current thrombocytopenia — no. (%)¶	2 (9)	4 (19)	4 (17)
Laboratory measures — mg/dl			
Triglyceride level			
Mean	2613±1499	2684±1235	2596±1256
Median (range)	2086 (683–6898)	2679 (779–5965)	2493 (334–5436)
Apolipoprotein C-III level	27.5±11.6	27.7±10.5	27.7±11.7
Total cholesterol level	277.4±99.3	323.4±100.5	286.0±113.9
LDL cholesterol level	22.8±14.1	17.6±8.5	16.7±8.4
HDL cholesterol level	14.5±4.5	15.7±4.0	14.7±3.8
Total apolipoprotein B level	58.4±17.2	65.2±13.5	59.7±18.9
Apolipoprotein B-48 level	11.6±8.1	18.5±15.3	14.2±14.2
Chylomicron triglyceride level	2477±2123	2302±1265‖	2269±1237
Chylomicron-C level plus VLDL cholesterol level**	245.7±110.9	293.2±103.1	255.3±114.4
Non-HDL cholesterol level	262.9±100.4	307.6±101.8	271.3±113.3
Previous treatment with volanesorsen — no. (%)	8 (36)	8 (38)	10 (43)
Concomitant medications — no. (%)			
Statin	5 (23)	4 (19)	7 (30)
Omega-3 fatty acid	12 (55)	6 (29)	7 (30)
Fibrate	11 (50)	8 (38)	11 (48)
Other lipid-lowering agent	3 (14)	0	3 (13)

* Plus–minus values are means ±SD. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. HDL denotes high-density lipoprotein, LDL low-density lipoprotein, VLDL very-low-density lipoprotein. Additional characteristics are shown in Table S1 in the Supplementary Appendix.

† Race and ethnic group were reported by the patients. Patients could report both a race and an ethnic group.

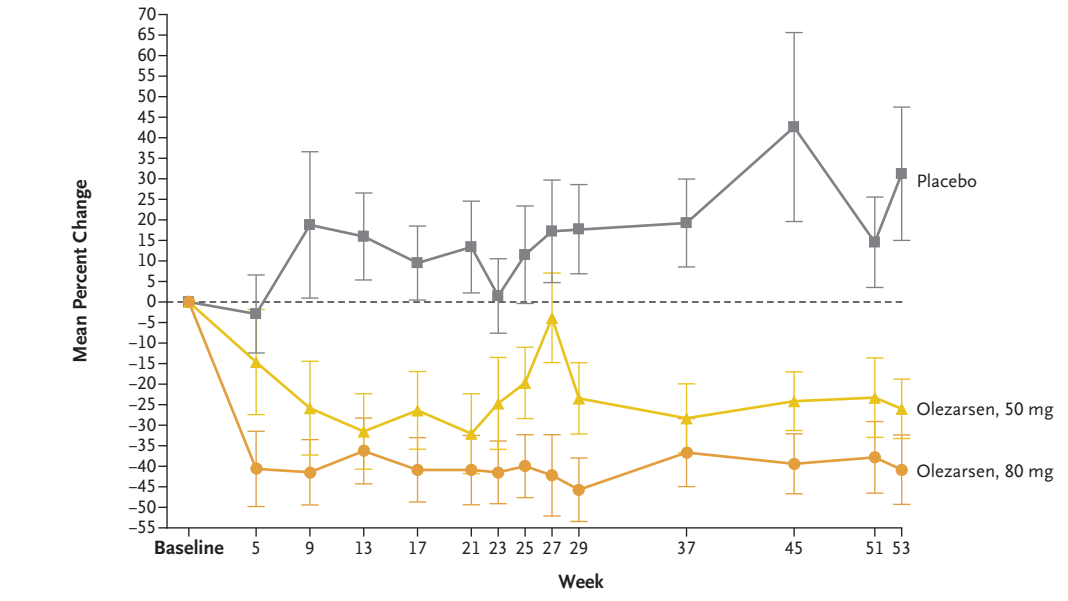
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ The numbers of previous episodes of pancreatitis were obtained from the medical records; episodes were not adjudicated for patients older than 5 years of age. One patient in the placebo group had a history of 79 episodes of acute pancreatitis. Without this patient, the mean number of acute pancreatitis episodes in the previous 10 years in the placebo group is 3.3±4.9.

¶ Thrombocytopenia was defined as a platelet count lower than 140,000 per cubic millimeter.

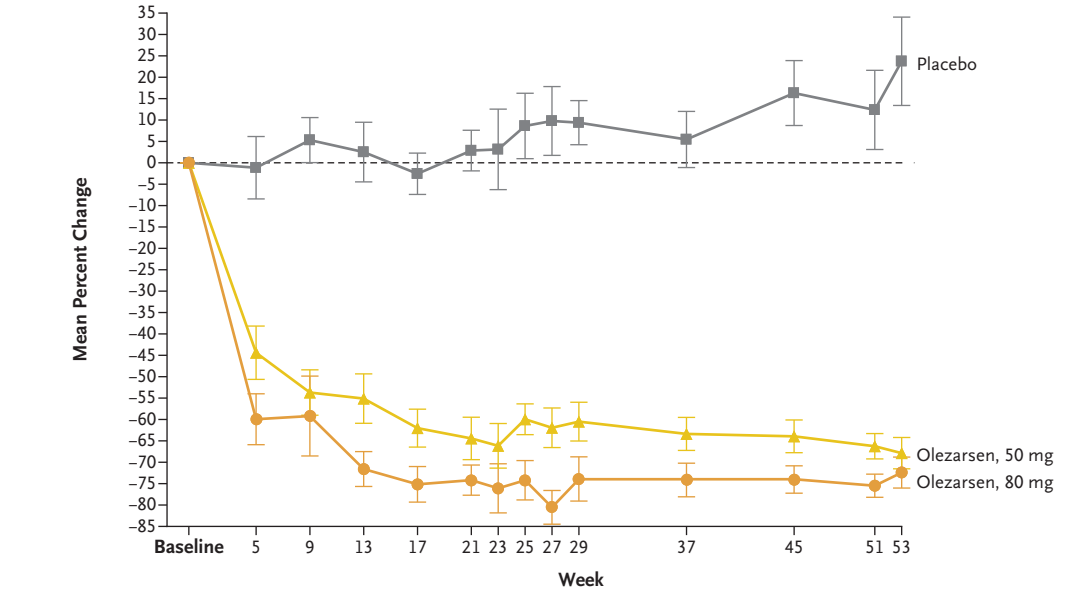
‖ Data on the chylomicron triglyceride level were available for 20 patients in the 50-mg olezarsen group.

** This variable represents the cholesterol content in the density fraction of less than 1.006 g per milliliter and represents the combined cholesterol content of the chylomicron and VLDL fractions.



No. of Patients

Placebo	23	23	21	21	22	22	19	21	19	21	22	20	19	20
Olezarsen, 50 mg	21	19	18	20	19	15	17	19	18	18	18	19	18	19
Olezarsen, 80 mg	22	21	20	21	20	20	15	19	16	20	18	19	15	17



No. of Patients

Placebo	23	23	21	21	22	22	19	21	19	21	22	20	19	20
Olezarsen, 50 mg	21	19	18	20	19	15	17	19	18	18	18	19	18	19
Olezarsen, 80 mg	22	21	20	21	20	20	15	19	16	20	18	19	15	17

Figure 1. Mean Percent Change from Baseline in Fasting Plasma Levels of Triglycerides and Apolipoprotein C-III Over Time.

Shown are the mean percent changes from baseline in fasting plasma levels of triglycerides (Panel A) and apolipoprotein C-III (Panel B) over time in the full analysis set. I bars denote standard errors.

point did not support an effect of previous exposure to volanesorsen (Table S5).

SECONDARY END POINTS

Because the second primary end point was not significant, the secondary end points are presented as least-squares mean changes with the 95% confidence intervals, mean rate ratios with the 95% confidence intervals, or percentages. The 95% confidence intervals for the secondary end points were not adjusted for multiplicity, and the results should not be interpreted as hypothesis tests.

The difference in the least-squares mean change in the fasting triglyceride level from baseline to 12 months in the 80-mg olezarsen group as compared with the placebo group was −59.4% (95% CI, −90.7 to −28.1) and between the 50-mg olezarsen group and the placebo group was −43.8 (95% CI, −73.9 to −13.7) (Fig. 1A and Fig. S4B). The difference in the least-squares mean change in the fasting apolipoprotein C-III level from baseline to 6 months in the 80-mg olezarsen group as compared with the placebo group was −73.7% (95% CI, −94.6 to −52.8) (Fig. 1B and Figs. S3B and S5A), and from baseline to 12 months, the difference between these groups was −81.3% (95% CI, −104.7 to −57.9) (Fig. 1B and Fig. S5B); the corresponding values in the 50-mg olezarsen group as compared with the placebo group were −65.5% (95% CI, −82.6 to −48.3) from baseline to 6 months and −77.1% (95% CI, −98.9 to −55.2) from baseline to 12 months. The results for the other secondary end points are provided in Table S4.

By 53 weeks, 1 episode of acute pancreatitis occurred among 22 patients in the 80-mg olezarsen group, 1 episode occurred among 21 patients in the 50-mg olezarsen group, and 11 episodes (in 7 patients) occurred among 23 patients in the placebo group (mean rate ratio [pooled olezarsen groups vs. placebo], 0.12; 95% CI, 0.02 to 0.66). Kaplan–Meier curves for the time to the first episode of acute pancreatitis are shown in Figure 2. All 9 patients who had an episode of acute pancreatitis had had two or more previous episodes before the trial.

It was noted that the placebo group had larger fluctuations in triglyceride and apolipoprotein C-III levels than the two olezarsen groups, with fluctuations of greater than 50% above baseline (Fig. S6). Individual-level data on adjudicated episodes of acute pancreatitis are provided in Table S6. The lowest baseline triglyceride level was 1651 mg per deciliter (18.6 mmol per liter) among the patients in the two olezarsen groups and 1355 mg per deciliter (15.3 mmol per liter) among those in the placebo group, and the highest baseline levels were 6116 mg per deciliter (69.1 mmol per liter) and 4421 mg per deciliter (49.9 mmol per liter), respectively. The first episode of pancreatitis occurred on day 357 in the 80-mg olezarsen group, day 102 in the 50-mg olezarsen group, and day 9 in the placebo group. The lowest plasma triglyceride level before an event was 1806 mg per deciliter (20.4 mmol per liter) in the 80-mg olezarsen group, 1876 mg per deciliter (21.2 mmol per liter) in the 50-mg olezarsen group, and 1784 mg per deciliter (20.1 mmol per liter) in the placebo group.

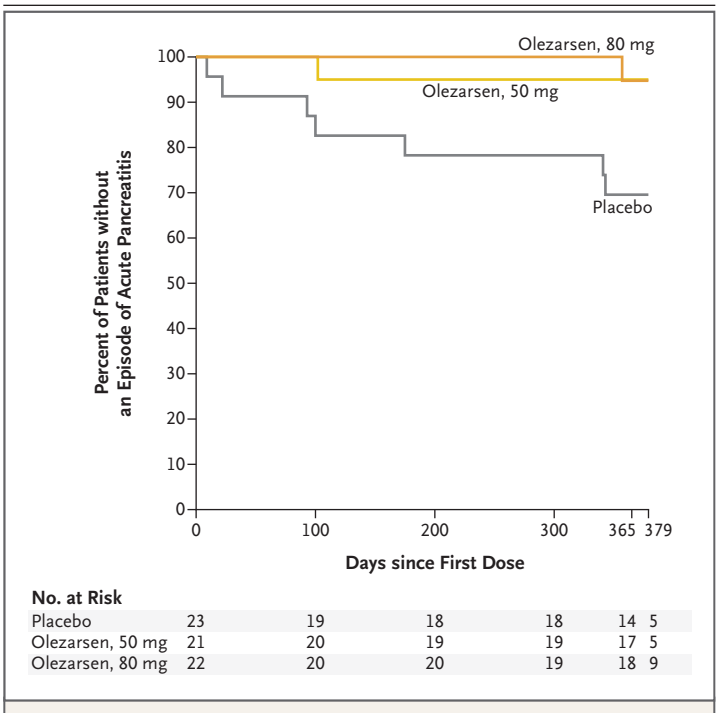


Figure 2. Kaplan–Meier Curves for the Time to the First Episode of Acute Pancreatitis.

The last observation at week 53 (day 365) included a visit window up to day 379.

PRESPECIFIED EXPLORATORY END POINTS

Changes from baseline to 6 months in the mean low-density lipoprotein (LDL) cholesterol level and the total apolipoprotein B level were assessed in a prespecified exploratory analysis. In the 80-mg olezarsen group, the mean LDL cholesterol level changed from 22.8±14.1 mg per deciliter to

37.6±36.3 mg per deciliter (0.59±0.37 mmol per liter to 0.97±0.94 mmol per liter), and the total apolipoprotein B level changed from 58.4±17.2 mg per deciliter to 69.0±33.5 mg per deciliter. In the 50-mg olezarsen group, the changes were from 17.6±8.5 mg per deciliter to 23.7±14.2 mg per deciliter (0.46±0.22 mmol per liter to 0.61±0.37 mmol per liter) for LDL cholesterol and from 65.2±13.5 mg per deciliter to 66.8±19.8 mg per deciliter for total apolipoprotein B, and in the placebo group, from 16.7±8.4 mg per deciliter to 18.1±9.7 mg per deciliter (0.43±0.22 mmol per liter to 0.47±0.25 mmol per liter) and from 59.7±18.9 mg per deciliter to 65.0±22.7 mg per deciliter, respectively.

SAFETY

Adverse events that occurred during the treatment period are shown in Table 2. The most common adverse events were coronavirus disease 2019, abdominal pain, and diarrhea, none of which occurred more frequently among the patients who received either dose of olezarsen than among those who received placebo. Serious adverse events occurred in 14% of the patients in the 80-mg olezarsen group, in 19% of those in the 50-mg olezarsen group, and in 39% of those in the placebo group.

Adverse events of moderate severity that were considered to be related to the trial drug or placebo occurred in 4 patients (18%) in the 80-mg olezarsen group: 1 patient had chills, myalgia, and trismus; 1 had chest discomfort, diarrhea, flushing, and vomiting; 1 had a transient decrease in the platelet count; and 1 had alopecia. Three patients (2 in the 80-mg olezarsen group and 1 in the 50-mg olezarsen group) reported adverse events (diarrhea, vomiting, chest discomfort, chills, myalgia, trismus, and flushing) that led to treatment discontinuation. One death occurred in the 50-mg olezarsen group, and this death was assessed by the investigator as being unrelated to the trial treatment. Injection-site reactions were reported in 14% of the patients in the 80-mg olezarsen group, 14% of those in the 50-mg olezarsen group, and 9% of those in the placebo group; all of these injection-site reactions were mild.

There were no imbalances among the three trial groups with respect to liver, renal, or clinically meaningful platelet laboratory variables. In an exploratory safety end-point analysis, no major changes in the glycated hemoglobin level from baseline to week 53 were noted in any of the three trial groups. No differences in safety were identified in the patients that were or were not previously treated with volanesorsen. Additional data on safety and side effects are provided in Tables S7 and S8.

DISCUSSION

Among patients with familial chylomicronemia syndrome, olezarsen, administered at a dose of 80 mg every 4 weeks, reduced triglyceride levels significantly more than placebo; the lower dose of 50 mg did not. These findings, together with the safety data, support further clinical research of olezarsen as a pharmacologic treatment for familial chylomicronemia syndrome. Moreover, the findings showed an advantage of olezarsen over the parent drug volanesorsen, which was administered weekly in a previous trial and was associated with a risk of reversible thrombocytopenia.[25]

The approvals by various regulatory authorities of fibrates, omega-3 fatty acids, and niacin for patients with triglyceride levels above 500 mg per deciliter were based on their triglyceride-lowering properties in the context of historical data that support a correlation between the incidence of pancreatitis and severity of hypertriglyceridemia.[32] These drugs, however, have not been tested for their effectiveness in reducing the incidence of acute pancreatitis.[33] Moreover, the reduction in apolipoprotein C-III levels by the conventional triglyceride-lowering agents, such as fibrates and omega-3 fatty acids, is modest (10 to 40%), and these agents have not been effective in lowering triglyceride levels in patients with familial chylomicronemia syndrome.[21,34]

Our findings are consistent with the results of a meta-analysis of three randomized, placebo-controlled trials of volanesorsen, which showed an association between treatment and a reduction in the incidence of acute pancreatitis.[35] An urgent clinical issue now is to determine whether lowering the triglyceride level by reducing the synthesis of apolipoprotein C-III in patients with severe hypertriglyceridemia (a triglyceride level of ≥500 mg per deciliter) — a much larger population that is estimated to comprise approximately 3.5 million persons in the United

Table 2. Adverse Events That Occurred during the Treatment Period.*

Event	Olezarsen, 80 mg (N=22)	Olezarsen, 50 mg (N=21)	Placebo (N=23)
Adverse event — no. of patients/no. of events (% of patients)			
Any adverse event	19/110 (86)	18/133 (86)	22/141 (96)
Adverse event related to the trial drug or placebo			
Any severity	7/25 (32)	6/29 (29)	5/7 (22)
Mild	3/16 (14)	6/29 (29)	3/5 (13)
Moderate	4/9 (18)	0	0
Severe	0	0	2/2 (9)
Any adverse event leading to discontinuation of the trial drug or placebo	2/7 (9)	1/1 (5)	0
Any serious adverse event	3/3 (14)	4/4 (19)	9/21 (39)
Any serious adverse event related to trial drug	0	0	0
Any adverse event leading to death	0	1/1 (5)	0
Most frequent adverse event†			
Coronavirus disease 2019	3/3 (14)	6/6 (29)	8/8 (35)
Abdominal pain	4/5 (18)	3/5 (14)	8/14 (35)
Diarrhea	2/2 (9)	1/1 (5)	6/12 (26)
Headache	1/3 (5)	4/7 (19)	3/4 (13)
Pancreatitis	1/1 (5)	2/2 (10)	4/5 (17)
Fatigue	1/1 (5)	1/3 (5)	4/4 (17)
Adverse event of interest — no. of patients (%)			
Reduction in platelet count‡	0	0	0
≥1 Injection-site reaction in a patient	3 (14)	3 (14)	2 (9)
≥1 Influenza-like illness in a patient§	1 (5)	1 (5)	0
≥1 Hypersensitivity adverse event in a patient	0	1 (5)	3 (13)
Narrow FMQ for anaphylactic reaction	0	0	0
Narrow FMQ for hepatic failure	0	0	0
Abnormal hepatic laboratory value			
ALT level ≥3×ULN	0	0	2 (9)
AST level ≥3×ULN	1 (5)	0	1 (4)
Total bilirubin level ≥2×ULN	0	0	0
GGT level ≥2×ULN	2 (9)	6 (29)	6 (26)
ALP level ≥2×ULN	0	0	1 (4)
INR ≥1.5×ULN	2 (9)	0	1 (4)
Patients with ≥1 renal impairment–related adverse event according to narrow or broad SMQ for acute renal failure	0	0	2 (9)

* ALP denotes alkaline phosphatase, ALT alanine aminotransferase, AST aspartate aminotransferase, FMQ Food and Drug Administration medical query, GGT γ-glutamyltransferase, INR international normalized ratio, SMQ standardized *Medical Dictionary for Regulatory Activities* (MedDRA) query, and ULN upper limit of the normal range.
† The most frequent adverse events were those that occurred in at least 15% of patients.
‡ A reduction in platelet count was defined as a reduction to levels below 50,000 per cubic millimeter accompanied by a major bleeding event or clinically relevant nonmajor bleeding event or a reduction in platelet count to levels below 25,000 per cubic millimeter, irrespective of bleeding status.
§ Adverse events with preferred terms in MedDRA, version 26.0, include influenza-like illness, pyrexia, feeling hot, body temperature increased, chills, myalgia, or arthralgia, starting on the day of injection or the next day.

States[36] — will also reduce the incidence of acute pancreatitis. A phase 2b trial by Bergmark et al.,[37] the results of which are now reported in the *Journal*, tested the effect of olezarsen on severe hypertriglyceridemia, but the trial was not powered to detect changes in the incidence of pancreatitis.

Because the result for the second primary end point was not significant, we cannot make definitive statements about differences between olezarsen and placebo in the results for the secondary end points. However, we would note that observed differences in the mean percent change from baseline to week 53 in triglyceride levels and fluctuations in fasting levels of triglycerides, apolipoprotein C-III, and apolipoprotein B-48 between the olezarsen groups and the placebo group warrant further study as potential end points in future trials. Furthermore, the fasting triglyceride thresholds used to define risk may not fully reflect the risk of pancreatitis in familial chylomicronemia syndrome. Postprandial fluctuations are not easily quantified, but they almost always occur with each meal that contains fat and are a potent risk factor for pancreatitis.[38] Our data indicate marked variability in fasting triglyceride levels with fluctuations of up to 2.5 times as high as the mean baseline level of 2630 mg per deciliter. We did not measure postprandial fluctuations in this trial.

The data on the reduction in apolipoprotein C-III levels that were obtained in the Balance trial are consistent with those of studies in which healthy participants or patients with coronary artery disease with normal LPL activity had reductions of 74.0 to 85.5% with olezarsen doses between 50 and 60 mg every 4 weeks.[28,29] However, only patients with familial chylomicronemia syndrome with a genetically caused deficit of LPL activity were enrolled in the Balance trial. These patients are entirely dependent on LPL-independent hepatic removal of triglyceride-rich particles and therefore may not have as favorable a response as patients with partial LPL activity. In a recent phase 1 trial involving heathy volunteers and patients with chylomicronemia that was not genetically defined as familial chylomicronemia syndrome, a short interfering RNA inhibiting *APOC3* (called plozasiran) given twice over a 1-month period showed reductions of 68.1 to 94.2% in the apolipoprotein C-III level and of 48.7 to 69.3% in the triglyceride level.[39] In a previous trial involving patients with familial chylomicronemia syndrome, the administration of volanesorsen at a weekly dose of 300 mg per deciliter over a 3-month period was accompanied by reductions in apolipoprotein C-III and triglyceride levels of 84% and 77%, respectively,[25] but the patients could have a clinical diagnosis of familial chylomicronemia syndrome or residual LPL activity (or both), which perhaps accounts for the relatively robust reductions in triglyceride levels. In a phase 2 trial involving patients with triglyceride levels above 500 mg per deciliter, the administration of plozasiran at doses of 10 mg, 25 mg, and 50 mg resulted in reductions from baseline in apolipoprotein C-III levels that were 67, 71, and 77 percentage points greater, respectively, than with placebo, as well as reductions from baseline in triglyceride levels that were 49, 53, and 57 percentage points greater, respectively, than with placebo.[40] However, it is difficult to compare results across trials owing to differences in patient populations, doses, and dosing intervals.

Our findings are consistent with the observations that LDL cholesterol levels are typically very low (<20 mg per deciliter [0.52 mmol per liter]) and total apolipoprotein B levels are within the low-to-normal range in persons with familial chylomicronemia syndrome.[25] These findings are probably due to the reduced uptake of chylomicrons and chylomicron remnants by the liver and insufficient LPL activity to permit the remodeling of very-low-density lipoprotein particles to LDL particles, which leads to extremely low LDL cholesterol levels but low-to-normal numbers of apolipoprotein B particles. We surmise that this process is partially corrected (through enhancing hepatic uptake of triglyceride-rich lipoproteins) by olezarsen, which would explain apparent, albeit nonsignificant, increases in the levels of LDL cholesterol and, to a lesser extent, total apolipoprotein B.

The safety analysis showed no imbalance among the three trial groups with respect to liver, renal, or platelet laboratory variables; mild injection-site reactions were more common with olezarsen than with placebo. More adverse events were reported in the placebo group than in either olezarsen dose group, primarily on account of a higher incidence of abdominal symptoms with placebo.

Limitations of this trial include the small size

of the trial cohort and uncertainty about adherence to dietary restrictions, which could have affected the degree of triglyceride lowering and incidence of acute pancreatitis. The trial included mostly White patients, partially owing to genetic founder effects in European populations. Additional trials in larger and more diverse populations are needed to confirm our findings.

The efficacy and safety results of the Balance trial support further clinical testing of olezarsen to prevent the clinical sequelae of familial chylomicronemia syndrome.

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

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APPENDIX

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