ORIGINAL ARTICLE

Plozasiran for Managing Persistent Chylomicronemia and Pancreatitis Risk

Gerald F. Watts, D.Sc., M.D., Ph.D., Robert S. Rosenson, M.D.,
Robert A. Hegele, M.D., Ira J. Goldberg, M.D., Antonio Gallo, M.D., Ph.D.,
Ann Mertens, M.D., Ph.D., Alexis Baass, M.D., Rong Zhou, Ph.D.,
Ma'an Muhsin, M.D., Jennifer Hellawell, M.D., Nicholas J. Leeper, M.D.,
and Daniel Gaudet, M.D., Ph.D., for the PALISADE Study Group*

ABSTRACT

BACKGROUND

Persistent chylomicronemia is a genetic recessive disorder that is classically caused by familial chylomicronemia syndrome (FCS), but it also has multifactorial causes. The disorder is associated with the risk of recurrent acute pancreatitis. Plozasiran is a small interfering RNA that reduces hepatic production of apolipoprotein C-III and circulating triglycerides.

METHODS

In a phase 3 trial, we randomly assigned 75 patients with persistent chylomicronemia (with or without a genetic diagnosis) to receive subcutaneous plozasiran (25 mg or 50 mg) or placebo every 3 months for 12 months. The primary end point was the median percent change from baseline in the fasting triglyceride level at 10 months. Key secondary end points were the percent change in the fasting triglyceride level from baseline to the mean of values at 10 months and 12 months, changes in the fasting apolipoprotein C-III level from baseline to 10 months and 12 months, and the incidence of acute pancreatitis.

RESULTS

At baseline, the median triglyceride level was 2044 mg per deciliter. At 10 months, the median change from baseline in the fasting triglyceride level (the primary end point) was −80% in the 25-mg plozasiran group, −78% in the 50-mg plozasiran group, and −17% in the placebo group (P<0.001). The key secondary end points showed better results in the plozasiran groups than in the placebo group, including the incidence of acute pancreatitis (odds ratio, 0.17; 95% confidence interval, 0.03 to 0.94; P=0.03). The risk of adverse events was similar across groups; the most common adverse events were abdominal pain, nasopharyngitis, headache, and nausea. Severe and serious adverse events were less common with plozasiran than with placebo. Hyperglycemia with plozasiran occurred in some patients with prediabetes or diabetes at baseline.

CONCLUSIONS

Patients with persistent chylomicronemia who received plozasiran had significantly lower triglyceride levels and a lower incidence of pancreatitis than those who received placebo. (Funded by Arrowhead Pharmaceuticals; PALISADE ClinicalTrials .gov number, NCT05089084.)

From the School of Medicine, University of Western Australia, and the Department of Cardiology, Royal Perth Hospital — both in Perth, Australia (G.F.W.); the Metabolism and Lipids Program, Mount Sinai Fuster Heart Hospital, Icahn School of Medicine at Mount Sinai (R.S.R.), and New York University (NYU) Grossman School of Medicine, NYU Langone Health (I.J.G) — both in New York; Robarts Research Institute, London, ON (R.A.H.), and the Department of Medicine, McGill University, and the Genetic Dyslipidemia Clinic, Montreal Clinical Research Institute (A.B.) and Université de Montréal and ECOGENE-21 (D.G.), Montreal — all in Canada; Sorbonne University, INSERM UMR1166, Lipidology and Cardiovascular Prevention Unit, Department of Nutrition, Pitié–Salpêtrière Hospital, Assistance Publique–Hôpitaux de Paris, Paris (A.G.); the Department of Endocrinology, University Hospitals Leuven–KU Leuven, Leuven, Belgium (A.M.); and Arrowhead Pharmaceuticals, Pasadena (R.Z., M.M., J.H.), and Stanford University, Palo Alto (N.J.L.) — both in California. Dr. Watts can be contacted at gerald.watts@uwa.edu.au or at the School of Medicine, University of Western Australia, Level 4, Medical Research Foundation Bldg., Royal Perth Hospital Campus, 50 Murray St., Perth WA 6001, Australia.

*The PALISADE Study Group investigators are listed in the Supplementary Appendix, available at NEJM.org.

PATIENTS WITH CHYLOMICRONEMIA ARE identified through a combination of symptoms and clinical signs, such as fatty deposits under the skin and possibly in the retina, and by extremely high levels of triglycerides, which are collectively caused by the buildup of large lipoprotein particles (chylomicrons) that are crucial in the transport of dietary fats in the circulation. Persistent chylomicronemia is characterized by extremely high fasting triglyceride levels of more than 880 mg per deciliter, values that reflect the marked accumulation of chylomicron particles owing to impaired lipolytic clearance.[1] This condition substantially increases the risk of recurrent acute pancreatitis and associated long-term sequelae, including a poor quality of life.[2-4]

The classic cause of this disorder is familial chylomicronemia syndrome (FCS), an ultra-rare autosomal recessive disorder with a worldwide prevalence of 1 per 100,000 persons to 1 per 1 million persons.[2] Some patients with the more common multifactorial chylomicronemia syndrome are phenotypically similar to those with FCS.[1,5,6] FCS is characterized by biallelic pathogenic variants in genes encoding lipoprotein lipase or one of four interacting cofactors leading to impaired clearance of chylomicrons and very-low-density lipoproteins (VLDLs).[7] Clinical manifestations of FCS, including pancreatitis, can also occur in patients with persistent chylomicronemia because of a multifactorial, polygenic cause.[5,7] Currently approved triglyceride-lowering medications (e.g., statins, fibrates, and fish oils) provide minimal benefit for such patients, and none of these treatments have been shown to lower the risk of acute pancreatitis.[8-10] Strict dietary modifications, including reducing fat to less than 10 to 20% of total calories, can partially lower chylomicronemia and triglyceride levels.[11] However, dietary adherence can be challenging, with many patients remaining at risk for the consequences of severe and persistent hypertriglyceridemia.[4,12]

Apolipoprotein C-III is a small glycoprotein, predominantly synthesized by the liver, that is a major determinant of triglyceride levels.[13] Apolipoprotein C-III circulates on the surface of triglyceride-rich lipoproteins such as chylomicrons and VLDLs and increases triglyceride levels by three main processes. First, apolipoprotein C-III inhibits lipoprotein lipase activity, which prevents the lipolysis of chylomicrons. Second, it inhibits receptor-mediated uptake and hepatic clearance of triglyceride-rich lipoprotein remnants.[13] And third, it stimulates hepatic secretion of VLDLs, which compete with chylomicrons for lipoprotein lipase–mediated clearance.[12,14]

Plozasiran is a hepatically targeted small interfering RNA that reduces the production and secretion of hepatic apolipoprotein C-III.[15] In a phase 1 study involving 20 patients with persistent chylomicronemia (4 with FCS), we found that plozasiran substantially reduced apolipoprotein C-III levels, with a median reduction in triglyceride levels of −86%.[16] These preliminary results led us to conduct the PALISADE trial of plozasiran to treat patients with extreme and persistent chylomicronemia, including those with genetically defined disease.

METHODS

OVERSIGHT

The trial was conducted from January 2022 through April 2024 at 58 centers in 21 countries. The protocol (which is available with the full text of this article at NEJM.org) was approved by the institutional review board or ethics committee at each center. The trial was performed according to 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 monitoring committee reviewed safety and adverse effects. The manufacturer of plozasiran, Arrowhead Pharmaceuticals, funded the trial; representatives of the sponsor were involved in the design and conduct of the trial and participated in the collection and analysis of the data. All the authors had unrestricted access to the trial data and 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 regarding the methods are provided in the Supplementary Appendix, available at NEJM.org.

TRIAL DESIGN AND PATIENTS

In this phase 3, double-blind, randomized trial, we evaluated the efficacy and safety of plozasiran, as compared with placebo, among adults with

genetically confirmed FCS or symptomatic persistent chylomicronemia (Fig. S1 in the Supplementary Appendix). The original protocol was designed to evaluate only patients who had FCS with an established genetic diagnosis, but at the request of a regulatory authority, we amended the protocol to include patients with symptomatic, persistent chylomicronemia suggestive of FCS.[17-20]

Key inclusion criteria were an age of at least 18 years and a diagnosis of severe hypertriglyceridemia that was resistant to standard lipid-lowering therapy, a documented history of a fasting triglyceride level of more than 1000 mg per deciliter on at least three occasions, and at least one of the following criteria: a previous genetic diagnosis of FCS, absent or low postheparin lipoprotein lipase activity (<20% of normal value), a history of acute pancreatitis not caused by alcohol or cholelithiasis,[18-20] recurrent hospitalizations for severe abdominal pain without another identified cause, childhood pancreatitis, or a family history of hypertriglyceridemia-induced pancreatitis.[4,17,19] Exclusion criteria included uncontrolled diabetes, use of corticosteroids or anabolic steroids, and chronic kidney disease.[17,19-21]

Dietary counseling began with initiation of the diet and treatment stabilization period (Table S1). Patients who had not undergone previous genotyping were genetically tested during the trial.

RANDOMIZATION AND TREATMENT

After screening and dietary stabilization, 75 eligible patients were randomly assigned in a 2:1:2:1 ratio to receive 25 mg of plozasiran or volume-matched placebo or to receive 50 mg of plozasiran or volume-matched placebo subcutaneously every 3 months for 12 months. The goal of this randomization plan was to achieve a 1:1 assignment for the comparison of each plozasiran dose with pooled placebo (Fig. S1). Randomization was stratified according to the triglyceride level (<2000 mg or ≥2000 mg per deciliter). Patients who completed the blinded phase of the trial could enter an ongoing extension phase of open-label plozasiran.

ASSESSMENTS

We obtained blood samples for safety assessments and lipid analyses immediately before the administration of the first dose of plozasiran or placebo and monthly thereafter after a minimum 10-hour fasting period. Episodes of acute pancreatitis were adjudicated in a blinded manner by an indepen-

dent committee using the Atlanta classification, with at least two of the three criteria used to define an event.[22] At the request of the data monitoring committee after trial initiation, the protocol was amended to stipulate that patients who had a new episode of clinically suspected acute pancreatitis would be transitioned to the open-label plozasiran group, regardless of subsequent adjudication of the event. (Details regarding the assessments and protocol amendments are provided in the Supplementary Appendix.)

END POINTS

The primary end point was the median percent change from baseline in the fasting triglyceride level at 10 months. The primary estimand was the median difference between plozasiran and placebo in the percent change in the fasting triglyceride level from baseline to 10 months. Key secondary end points were the percent change in the fasting triglyceride level from baseline to a mean of the levels at 10 months and 12 months and the percent change from baseline in fasting levels of apolipoprotein C-III at 10 months and 12 months. The final key secondary end point was the incidence of positively adjudicated events of acute pancreatitis. Exploratory end points are described in the Supplementary Appendix.

STATISTICAL ANALYSIS

We determined that the enrollment of 72 patients who underwent the planned randomization would provide the trial with approximately 99% power to detect a statistically significant between-group difference in the percent change from baseline in the fasting triglyceride level (the primary end point). For this comparison, we used a two-sided test and Holm's step-down multiple-comparison procedure, with a 2.5% level of significance for each test. On the basis of the change from baseline to 10 months in the fasting triglyceride level, this power calculation assumed a mean (±SD) of 75±40% reduction in the 25-mg plozasiran group, a 80±40% reduction in the 50-mg plozasiran group, and a 5% reduction in the placebo group. We used the Wilcoxon (Mann–Whitney) rank-sum test with the assumption that the null hypothesis was correct. We determined that there was a 10.8% chance that the observed difference between the groups was due to random variation alone. The withdrawal rate from the trial was predicted to be 10 to 15%.

In the primary efficacy analysis, we used the Hodges–Lehmann method to estimate the median difference and its corresponding 95% confidence interval for the percent change from baseline in each plozasiran dose group as compared with placebo. To account for missing data, we used multiple imputation with a pattern-mixture model for the primary analysis. The results that are presented in the text and tables include the imputed data. Details regarding the imputation method are provided in the Supplementary Appendix.

To control for the family-wise type I error at a 0.05 level, we used a fixed-sequence hierarchical step-down procedure for the hypothesis testing. In this procedure, we tested the key secondary end points in a step-down manner only if the efficacy analysis of the primary end point and alpha-controlled secondary end points for both plozasiran doses proved to significantly favor the active treatment (Table S2). For the analysis of incident pancreatitis, the plozasiran doses were combined, as prespecified, for comparison with pooled placebo. Additional details regarding the measurements of the primary and key secondary end points and of the hierarchical testing procedure are provided in the trial protocol.

RESULTS

CHARACTERISTICS OF THE PATIENTS

A total of 123 patients underwent screening. Of these patients, 75 underwent randomization: 26 were assigned to the 25-mg plozasiran group, 24 to the 50-mg plozasiran group, and 25 to the placebo group; 64 patients (85%) completed the blinded treatment phase of the trial (Fig. S2). At baseline, 51% of the patients were women, and 73% were White; the median body-mass index (the weight in kilograms divided by the square of the height in meters) was approximately 25.

The median triglyceride level was 2044 mg per deciliter (interquartile range, 1333 to 2955). Biallelic or digenic pathogenic variants in the five genes that encode proteins regulating lipoprotein lipase activity (the definition of genetically confirmed FCS) were confirmed in 44 patients (59%). The remaining 31 patients (41%) had clinically diagnosed persistent chylomicronemia and not genetically confirmed FCS (Table 1 and Table S3).

The patients were generally representative of the population with persistent chylomicronemia in the United States, Canada, and Europe (Table S4). Of the 75 patients, 37 (49%) were enrolled on the basis of a previous genetic confirmation. Of the patients with a clinical diagnosis but no FCS genotype at the time of randomization, 34 (45%) qualified on the basis of a history of acute pancreatitis, which was recurrent in 76%; 2 patients had evidence of low lipoprotein lipase activity (<20% of normal value) on the basis of source-verifiable documentation. One patient met the criterion of having a documented history of recurrent hospitalizations for severe abdominal pain without other documented cause, and 1 patient met the criterion of a family history of hypertriglyceridemia-induced acute pancreatitis. At 10 months, data regarding triglyceride measurements were missing for 10 patients (2 in each plozasiran group and 6 in the placebo group), so these data were imputed, as described in the Statistical Analysis section.

CHANGES IN FASTING TRIGLYCERIDE LEVELS

At 10 months, the median relative reduction from baseline in the fasting triglyceride level (the primary end point) was −80% in the 25-mg plozasiran group, −78% in the 50-mg plozasiran group, and −17% in the placebo group (Fig. 1A). Absolute values are provided in Table 2 and in Figures S3 and S4. The median percent change in the fasting triglyceride level in the plozasiran group as compared with placebo was −59 percentage points (95% confidence interval [CI], −90 to −28; P<0.001) in the 25-mg group and −53 percentage points (95% CI, −83 to −22; P<0.001) in the 50-mg group.

The first key secondary end point — the triglyceride level at a mean of months 10 and 12 in the plozasiran groups — was a change of −60 percentage points (95% CI, −92 to −28; P<0.001) in the 25-mg group and −51 percentage points (95% CI, −84 to −18; P<0.001) in the 50-mg group, as compared with placebo (Table 2 and Fig. S4). Marked reductions in the median triglyceride level were present as early as 1 month after trial initiation and showed modest variation throughout the 12-month blinded treatment period (Fig. 1A). The mean percent change in the triglyceride level was similar to median values and is shown as an absolute value in Figures S3, S4, and S5. Corresponding waterfall plots for 10-month values (Fig. S6) showed that the majority (approximately 80%) of patients who received plozasiran had a reduction of 50% or more in the fasting triglyceride level.

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

Characteristic	Plozasiran, 25 mg (N=26)	Plozasiran, 50 mg (N=24)	Placebo (N=25)
Age — yr	47.9±14.4	42.6±10.9	47.4±13.9
Sex — no. (%)			
Female	14 (54)	13 (54)	11 (44)
Male	12 (46)	11 (46)	14 (56)
White race — no. (%)†	19 (73)	17 (71)	19 (76)
Body-mass index	26.1±3.9	25.4±4.8	25.0±4.1
Apolipoprotein C-III — mg/dl	38.5±17.1	32.5±19.8	39.9±17.6
Triglycerides			
Median (IQR) — mg/dl	2008.0 (1204.2–3360.5)	1902.4 (1434.4–2948.1)	2052.6 (1435.1–2755.2)
Mean — mg/dl	2349.5±1374.5	2491.5±1523.2	2271.9±1141.4
Medications — no. (%)			
Statin	11 (42)	12 (50)	11 (44)
Fibrate	19 (73)	15 (63)	16 (64)
N–3 fatty acids	9 (35)	7 (29)	6 (24)
Diabetes or prediabetes — no./total no. (%)‡	10/26 (38)	7/24 (29)	11/25 (44)
Receipt of metformin or related therapy	3/10 (30)	5/7 (71)	7/11 (64)
Receipt of insulin	4/10 (40)	4/7 (57)	5/11 (45)
Genetic confirmation of familial chylomicronemia syndrome — no. (%)	14 (54)	16 (67)	14 (56)
Previous episode of pancreatitis — no. (%)	23 (89)	22 (92)	22 (88)

* Plus–minus values are means ±SD. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. IQR denotes interquartile range.
† Race was reported by the patients.
‡ Diabetes was defined by a glycated hemoglobin level of 6.5% or more, a fasting glucose level of at least 126 mg per deciliter, or a medical history of a diabetes diagnosis or receipt of a diabetic medication at baseline. Prediabetes was defined by a glycated hemoglobin range of 5.7 to less than 6.5%.

OTHER KEY SECONDARY END POINTS

The level of apolipoprotein C-III at 10 months and 12 months changed minimally with placebo, with a relative median reduction of −1% (interquartile range, −17 to 27) at 10 months and an increase of 8% (interquartile range, −34 to 31) at 12 months. In comparison, the level of apolipoprotein C-III was substantially reduced with the 25-mg dose of plozasiran, with values of −93% (interquartile range, −98 to −88) at 10 months and −89% (interquartile range, −94 to −80) at 12 months, an absolute reduction of −91 percentage points (95% CI, −108 to −73) and −87 percentage points (95% CI, −113 to −61), respectively, as compared with placebo (P<0.001 for both comparisons). Apolipoprotein C-III levels were also reduced with the 50-mg dose of plozasiran, with values of −96% (interquartile range,

−98 to −90) at 10 months and −88% (interquartile range, −93 to −79) at 12 months (P<0.001 for both time points) (Table 2). Apolipoprotein C-III levels at serial time points are shown in Figure 1B.

The final alpha-controlled secondary efficacy end point was the incidence of positively adjudicated acute pancreatitis. Among the 38 suspected cases of acute pancreatitis that were referred for adjudication, 9 episodes in 7 patients were positively adjudicated. A total of 2 incident cases occurred in 2 of 50 patients (4%) receiving plozasiran, and 7 incident cases occurred in 5 of 25 patients (20%) receiving placebo (odds ratio, 0.17; 95% CI, 0.03 to 0.94; P=0.03) (Fig. 2 and Table S5). Of the 7 patients with incident cases of pancreatitis, 3 were reported in the patients with genetically defined FCS.
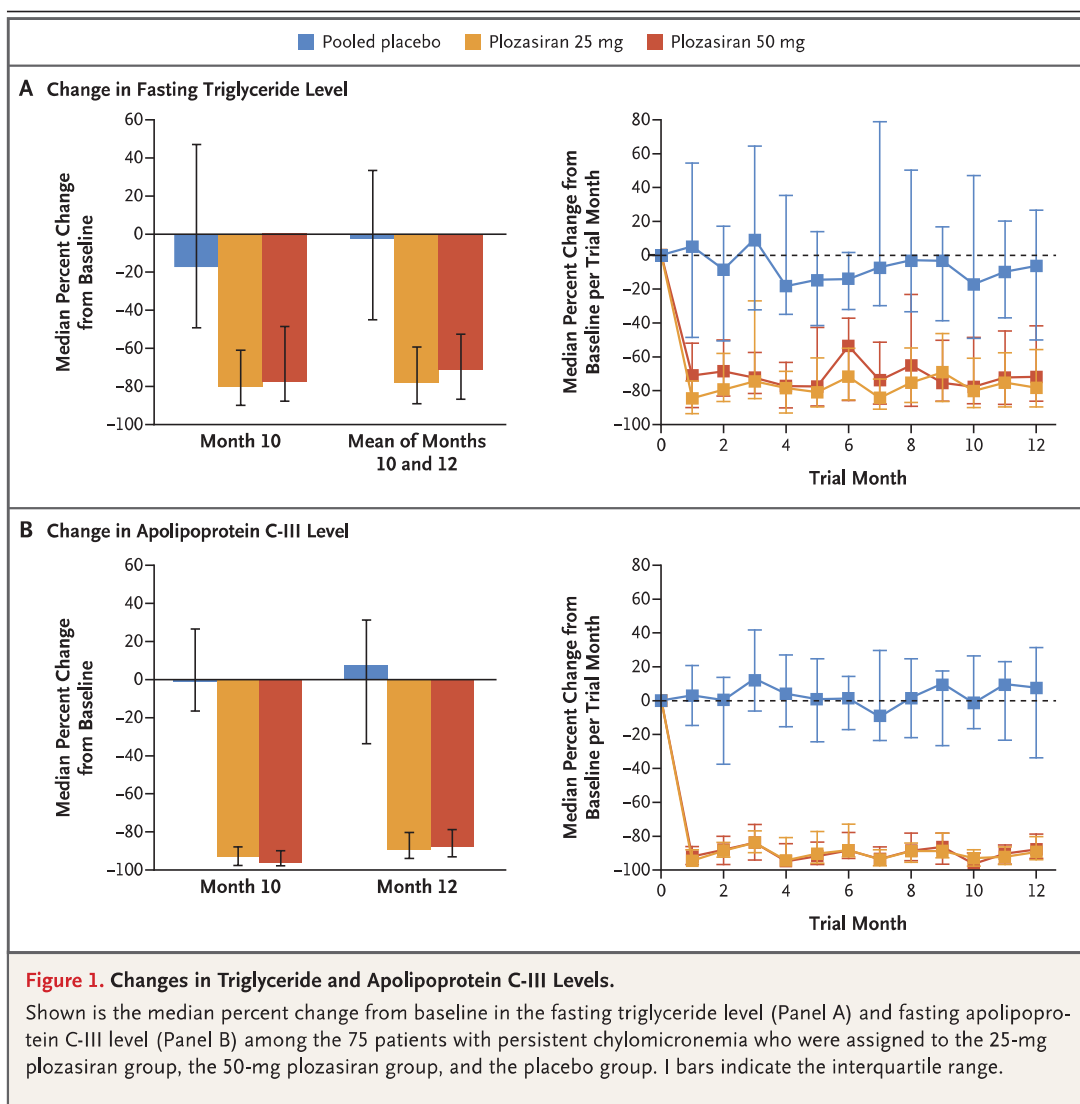
OTHER SECONDARY AND EXPLORATORY OUTCOMES

Levels of non–high-density lipoprotein (non-HDL) cholesterol were high at baseline (approximately 270 mg per deciliter) and were lower (approximately 150 mg per deciliter) at 10 months and 12 months among the patients in the plozasiran groups (Table S6). HDL cholesterol levels were low at baseline (approximately 18 mg per deciliter) and were approximately 27 mg per deciliter in the two plozasiran dose groups at months 10 and 12. Levels of low-density lipoprotein (LDL) cholesterol were low at baseline (approximately 25 mg per deciliter) and were higher at months 10 and 12 (approximately

49 mg per deciliter) but were below the target level of 55 mg per deciliter for LDL cholesterol. Apolipoprotein B levels generally remained within the normal range in all three groups (Table S6).

SUBGROUP ANALYSIS ACCORDING TO GENETIC CHARACTERISTICS OR SEX

Patients with genetically defined FCS may have a response to plozasiran that differs from the response in patients without a genetic defect, so we performed a prespecified subgroup analysis in which we found that the trial patients had a similar response to plozasiran independent of their confirmed genetic characteristics (Fig. S7).

Figure 1. Changes in Triglyceride and Apolipoprotein C-III Levels.

Shown is the median percent change from baseline in the fasting triglyceride level (Panel A) and fasting apolipoprotein C-III level (Panel B) among the 75 patients with persistent chylomicronemia who were assigned to the 25-mg plozasiran group, the 50-mg plozasiran group, and the placebo group. I bars indicate the interquartile range.

Results from a subgroup analyses of triglyceride levels according to sex showed similar outcomes in women and men (Table S7).

SAFETY

Adverse events among the patients in the two plozasiran dose groups were generally similar to those in the placebo group (Table 3) with the exception of the incidence of coronavirus disease 2019 (Covid-19), which was diagnosed in 5 patients in the 25-mg group and in 7 patients in the 50-mg group, as compared with none in the placebo group. The most common adverse events were abdominal pain, Covid-19, nasopharyngitis, headache, nausea, upper respiratory tract infection, and diarrhea. An increased glycated hemoglobin level occurred in 3 patients in each plozasiran group and in no patients in the placebo group. At 12 months, the mean glycated hemoglobin level remained similar to the baseline level in both plozasiran groups and the placebo group (Table 3 and Table S8). Mean glycated hemoglobin values were mildly increased with plozasiran in patients with diabetes or prediabetes (Table S9); new diabetic medications were initiated during the trial in 2 of 26 patients in the 25-mg plozasiran group, in 5 of 24 patients in the 50-mg plozasiran group, and in 6 of 25 patients in the placebo group (Table S9).

Premature discontinuation of plozasiran or placebo occurred in 3 patients in the 25-mg plozasiran group, in 2 patients in the 50-mg plozasiran group, and in 6 patients in the placebo group. Of those 6 patients, 3 patients discontinued placebo because of acute pancreatitis and were entered the open-label extension phase. Severe and serious adverse events were more common in the placebo group (Table 3). There were no deaths or adverse events involving hypersensitivity or anaphylaxis. Injection-site reactions occurred in 1 patient each in the 50-mg plozasiran group and the placebo group, and 4 events occurred in the 25-mg plozasiran group; all these reactions were mild in intensity and resolved without treatment. Plozasiran treatment was associated with a nonprogressive mean increase in the alanine aminotransferase (ALT) level and, to a lesser extent, in the aspartate aminotransferase (AST) level, with at least one ALT value surpassing the upper limit of the normal range in 23% of patients in the 25-mg plozasiran group, in 46% of those in the 50-mg plozasiran group,

Table 2. Triglyceride and Apolipoprotein C-III Levels.*

Variable	Placebo (N=25)	Plozasiran, 25 mg (N=26)	Difference, 25-mg Dose vs. Placebo (95% CI)†	Plozasiran, 50 mg (N=24)	Difference, 50-mg Dose vs. Placebo (95% CI)†
	median (IQR)	median (IQR)	percentage points	median (IQR)	percentage points
Triglycerides					
Baseline value — mg/dl	2053 (1435 to 2755)	2008 (1204 to 3361)		1902 (1434 to 2948)	
Percent change from baseline					
Month 10	−17 (−49 to 47)	−80 (−90 to −61)	−59 (−90 to −28)	−78 (−88 to −49)	−53 (−83 to −22)
Mean at months 10 and 12	−3 (−45 to 33)	−78 (−89 to −59)	−60 (−92 to −28)	−71 (−87 to −53)	−51 (−84 to −18)
Apolipoprotein C-III					
Baseline value — mg/dl	39 (29 to 50)	39 (27 to 44)		30 (18 to 37)	
Percent change from baseline					
Month 10	−1 (−17 to 27)	−93 (−98 to −88)	−91 (−108 to −73)	−96 (−98 to −90)	−93 (−109 to −77)
Month 12	8 (−34 to 31)	−89 (−94 to −80)	−87 (−113 to −61)	−88 (−93 to −79)	−88 (−112 to −63)

* Shown are the baseline values and percent changes from baseline in the plozasiran and placebo groups, reported as the median and interquartile range (IQR). The Hodges–Lehmann method was used for calculating nonlinear properties of medians was used to estimate the between-group differences, so the differences do not compute mathematically.
† P<0.001 for all listed between-group differences. Statistical significance was determined by means of nonparametric tests used to analyze medians. P values were calculated from the Wilcoxon rank-sum test.

and in 4% of those in the placebo group. There were no increases in ALT or AST levels of more than three times the upper limit of the normal range (Table S10). Platelet levels remained unchanged from baseline in all three groups.

DISCUSSION

We found that plozasiran markedly reduced triglyceride and apolipoprotein C-III levels and decreased the incidence of acute pancreatitis in patients with persistent chylomicronemia, including those with genetically defined FCS. The results for the primary end point and all key secondary end points showed significant improvements in the patients who received quarterly doses of 25 mg or 50 mg of plozasiran as compared with those in the placebo group. These findings are consistent with reports of the effects of plozasiran in patients with severe hypertriglyceridemia and mixed hyperlipidemia.[16,23] The results are also consistent with a sustained reduction in triglyceride levels brought about through a reduction in apolipoprotein C-III levels and activation of both lipoprotein lipase–dependent and lipoprotein lipase–independent pathways.[12,24]

The risk of adverse events was similar across all three trial groups. Severe and serious adverse events and discontinuations of the assigned regimen during the blinded treatment period were less common with plozasiran than with placebo, findings that were consistent with the high incidence of acute pancreatitis in the placebo group. Thrombocytopenia was the key issue that precluded the approval of another triglyceride-reducing drug, antisense oligonucleotide volanesorsen; we observed no differences in platelet counts or the frequency of thrombocytopenia between the plozasiran and placebo groups. Plozasiran treatment was associated with minor transient increases in ALT and AST levels, which did not result in dose interruptions. Hyperglycemia occurred in some patients in the plozasiran groups who had diabetes or prediabetes, a finding that was also reported in previous trials of plozasiran.[23,24] The mechanism of this finding is unclear but may relate to enhanced hydrolysis of triglyceride-rich lipoproteins, with increased central delivery of lipid substrates that increases hepatic gluconeogenesis.[24] The hyperglycemia observed in patients receiving volanesorsen, which was presumably caused by a similar mechanism, could be offset with increased antiglycemic medication and was not sustained over time.[25]

Our principal findings are consistent with those of a recent study of olezarsen,[26] an antisense
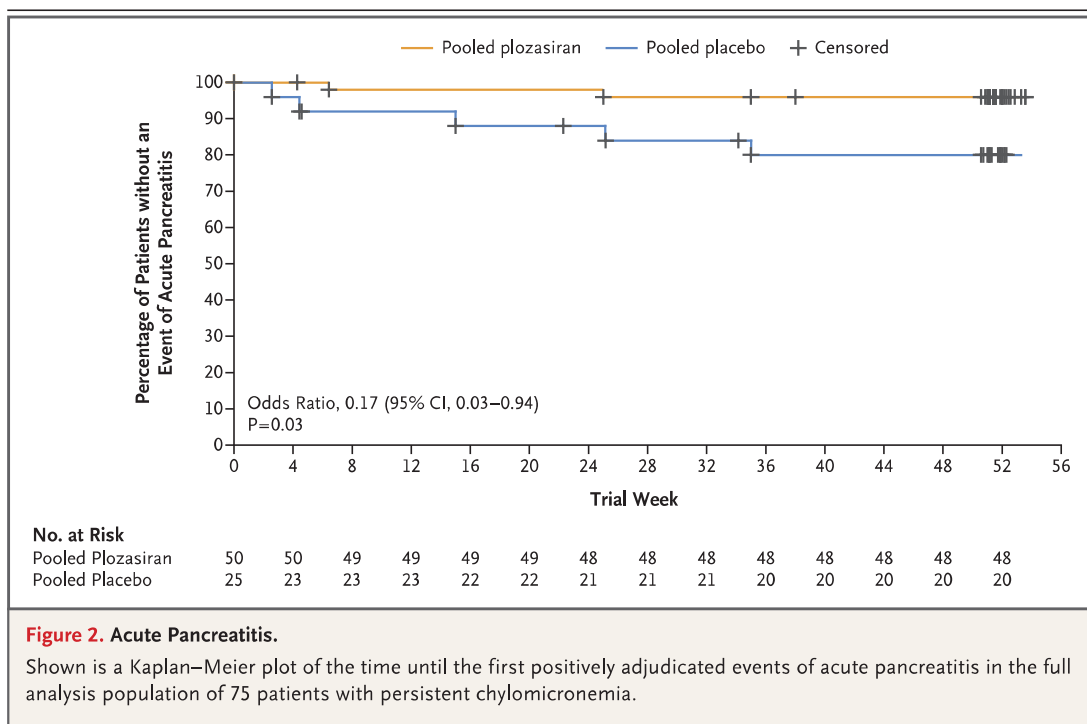

Figure 2. Acute Pancreatitis.

Shown is a Kaplan–Meier plot of the time until the first positively adjudicated events of acute pancreatitis in the full analysis population of 75 patients with persistent chylomicronemia.

Table 3. Adverse Events.*

Adverse Event	Plozasiran, 25 mg (N=26)	Plozasiran, 50 mg (N=24)	Placebo (N=25)
Any event — no.	23	20	20
Most common event — no. (%)			
Abdominal pain	7 (27)	6 (25)	5 (20)
Covid-19	5 (19)	7 (29)	0
Nasopharyngitis	5 (19)	2 (8)	3 (12)
Headache	3 (12)	5 (21)	2 (8)
Nausea	4 (15)	3 (12)	2 (8)
Back pain	3 (12)	2 (8)	2 (8)
Upper respiratory tract infection	3 (12)	2 (8)	2 (8)
Diarrhea	1 (4)	4 (17)	2 (8)
Severe event — no. (%)	3 (12)	3 (12)	5 (20)
Serious event — no. (%)	5 (19)	2 (8)	7 (28)
Premature discontinuation — no. (%)	3 (12)	2 (8)	6 (24)
Laboratory values			
Glycated hemoglobin — %			
Baseline	5.7±0.9	5.6±1.2	6.1±1.3
Month 12	6.0±1.0	5.8±1.6	6.2±1.2
Platelet count†			
Baseline	204.4±70.4	192.9±50.7	217.9±80.5
Change from baseline at month 10	28.7±61.2	−4.4±48.2	25.9±38.2
Change from baseline at month 12	−4.3±40.8	−8.7±50.8	8.6±47.5

* Plus–minus values are means ±SD. There were no deaths in the trial groups during the treatment period. Covid-19 denotes coronavirus disease 2019.
† Platelet counts are listed as 1/1000 of the actual value per microliter.

therapeutic targeting *APOC3* messenger RNA. In that trial, investigators reported reductions in chylomicron and triglyceride levels associated with a lower incidence of pancreatitis among patients with genetically defined FCS, although the difference was not significant. In contrast to that study, our trial did not require that patients have biallelic loss-of-function variants.[17-20] However, results from a prespecified subgroup analysis in our trial were consistent with the similarity in therapeutic response to plozasiran regardless of the presence of canonical genetic defects causative of FCS. These results were also consistent with the findings of a previous study of *APOC3*-silencing methods in which similar extents of triglyceride lowering were observed in mixed populations with persistent symptomatic chylomicronemia independent of the presence of the classic pathogenic variants affecting lipoprotein lipase.[27] Studies with a predominant representation of patients with multifactorial chylomicronemia have not been designed to assess the effect of therapies directed at *APOC3* on acute pancreatitis.[6,24]

The risk of acute pancreatitis is directly and causally related to triglyceride levels in chylomicrons, especially when such levels are persistently elevated above 880 mg per deciliter.[5,14,28] Effective and durable treatment is essential because triglyceride-induced pancreatitis has a worse prognosis than pancreatitis from other causes.[29,30] Beyond diet and lifestyle measures, current guidelines recommend targeting a triglyceride goal of less than 500 mg per deciliter with pharmacotherapies that include statins, n–3 fatty acids, fibrates, and niacin.[2,7,8,31] However, such drugs only weakly inhibit apolipoprotein C-III, and none have been shown to reduce the risk of acute pancreatitis in clinical

trials.[1,2,7] This factor may be most relevant in patients with extreme hypertriglyceridemia with FCS and other forms of persistent chylomicronemia who have recurrent abdominal pain, pancreatic endocrine and exocrine deficiencies, and a poor quality of life despite appropriate standard of care and intensive dietary counseling.[2,3,7]

Our trial has several limitations. The sample population was relatively small, and blinded follow-up was limited to 1 year. However, FCS and symptomatic persistent chylomicronemia are rare conditions, and the safety and efficacy of plozasiran are currently being evaluated in a linked open-label extension study.[32,33] We did not insist on genetic confirmation of FCS before randomization[17,34,35] on the basis of findings that patients who meet published criteria for symptomatic persistent chylomicronemia with recurrent pancreatitis[17,19,36] also have complications associated with substantial morbidity and mortality. With the advent of more effective therapies for extreme hypertriglyceridemia or chylomicronemia and further genetic characterization of affected patients, we think that a revised, universally accepted diagnostic definition and nomenclature will be required.[12,32,37,38] Such advances will better capture the spectrum of clinical risks and lead to more effective use of medicines. We studied mainly White patients, so further investigation involving patients of other races is warranted.[39]

We are further characterizing the genetic spectrum of our trial population and its effect[17,34,35] on the response to plozasiran. However, we note that the effect of plozasiran seemed to be independent of the presence of known biallelic pathogenic variants that cause FCS.[10,17,35] Finally, we evaluated fasting triglyceride levels to measure responses to treatment. We have not ascertained the effect of plozasiran on postprandial lipemia, a presumptive major driver of pancreatitis risk,[2,7] or whether therapy could have an effect on the quality of life of patients with FCS, who often struggle with onerous dietary and lifestyle restrictions.[29,40] We cannot exclude the possibility that nonadherence to diet and physical activity might have contributed to larger variations in triglyceride levels and widening in the confidence intervals of the effects of plozasiran.

Our findings underpin the rapid development of plozasiran for the treatment of extreme hypertriglyceridemia to prevent acute pancreatitis in patients with FCS or other causes of persistent chylomicronemia with a history of pancreatitis.[7,11,32,37] Beyond pancreatitis, triglyceride-rich lipoproteins may also be causally involved in atherosclerotic and cardiometabolic disease,[41-43] hypotheses that support further research with plozasiran.[23,24] Ultimately, the clinical value of plozasiran will depend on further demonstration of long-term efficacy, safety, cost-effectiveness, and equity of access for patients in need.

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