ORIGINAL ARTICLE

Plozasiran for Severe Hypertriglyceridemia and Risk of Pancreatitis

G.F. Watts,[1] C.M. Ballantyne,[2] A. Blanco Echevarria,[3] J. Smith,[4] R.S. Rosenson,[5] S. Subramanian,[6] J. Trippi,[7] N. Lepor,[8] A. Bajaj,[9] V. Blaha,[10] R. Scott,[11] A. Baass,[12] I.J. Goldberg,[13] A. Gallo,[14] J.L. Diaz,[15] M. Saxena,[16] J. Li,[17] R. Zhou,[18] L. Aiyer,[18] J. Hellawell,[18] J. Hamilton,[18] and D. Gaudet,[19] for the SHASTA-3 and SHASTA-4 Study Groups*

ABSTRACT

BACKGROUND

Severe hypertriglyceridemia is associated with an increased risk of acute pancreatitis. Plozasiran, a small interfering RNA targeting *APOC3* messenger RNA, lowers triglyceride levels and potentially mitigates the risk of acute pancreatitis.

METHODS

In two double-blind, placebo-controlled trials, 757 adults with severe hypertriglyceridemia were randomly assigned in a 2:1 ratio to receive plozasiran (25 mg) or placebo at baseline and at months 3, 6, and 9. These trials had identical designs, end points, and analytic plans. The primary end point was the percent change in the fasting plasma triglyceride level from baseline to month 12. Key secondary end points were the percent change in the fasting triglyceride level from baseline to month 10, a fasting triglyceride level of less than 500 mg per deciliter (5.6 mmol per liter) and less than 150 mg per deciliter (1.7 mmol per liter), the percent change in the fasting serum triglyceride level at month 12 for patients with a baseline triglyceride level of 880 mg per deciliter or greater, and changes in remnant cholesterol and non–HDL cholesterol. A pooled analysis addressed adjudicated acute pancreatitis, incidence, and first-event timing.

RESULTS

At month 12, patients in the plozasiran groups had a median triglyceride level that was lower than the baseline level by 79% and 81% in the two trials. These reductions corresponded to a median difference in the plozasiran groups as compared with the placebo groups (placebo-adjusted change) of −45 percentage points (95% confidence interval [CI], −51 to −38) and −47 percentage points (95% CI, −54 to −39). A triglyceride level of less than 500 mg per deciliter at 12 months was reported in 91% and 93% of the patients in the plozasiran groups and in 51% and 50% of those in the placebo groups ($P<0.001$). The rates of acute pancreatitis were 1 per 100 patient-years with plozasiran and 5 per 100 patient-years with placebo (rate ratio, 0.22; $P=0.008$). Adverse events during treatment occurred in 73% of the patients in both the pooled plozasiran and placebo groups.

CONCLUSIONS

Among patients with severe hypertriglyceridemia, the use of plozasiran resulted in lower triglyceride levels and a lower risk of acute pancreatitis than placebo at 12 months. (Funded by Arrowhead Pharmaceuticals; SHASTA-3 ClinicalTrials.gov number, NCT06347003; SHASTA-4, NCT06347016.)

The authors' full names, academic degrees, and affiliations are listed at the end of the article. Gerald Watts can be contacted at gerald.watts@uwa.edu.au or at the School of Medicine, University of Western Australia, Level 3, Medical Research Foundation Bldg., Royal Perth Hospital Campus, 50 Murray St., Perth WA 6001, Australia.

*A list of the investigators in the SHASTA-3 and SHASTA-4 Study Groups is provided in the Supplementary Appendix, available at NEJM.org.

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Severe hypertriglyceridemia, which is defined by a triglyceride level of at least 500 mg per deciliter [5.6 mmol per liter], has an estimated worldwide population prevalence of 1 to 2%. This condition is associated with an increased risk of acute pancreatitis, which may be recurrent, life-threatening, and accompanied by additional complications.[1,2] Severe hypertriglyceridemia is a heterogeneous disorder arising from polygenic susceptibility and secondary factors including overnutrition, alcohol abuse, medications, and metabolic conditions, principally obesity and type 2 diabetes mellitus.[3,4]

A smaller subgoup of patients with severe hypertriglyceridemia have triglyceride elevations associated with markedly impaired or absent lipoprotein lipase activity, the principal enzyme involved in the intravascular hydrolysis of triglyceride-rich lipoproteins. These patients are at particularly high risk for recurrent acute pancreatitis. In some patients with severe hypertriglyceridemia, the receipt of fibrates and prescription n–3 fatty acids, along with lifestyle or dietary modifications[5,6] with or without statins, can result in reductions in triglyceride levels. However, some of these patients have persistent severe hypertriglyceridemia despite optimized standard-care therapy, which places them at increased risk for pancreatitis.[7,8] Although a reduction of triglyceride levels to less than 500 mg per deciliter is commonly considered to be a therapeutic goal in the mitigation of pancreatitis risk, such levels are difficult to achieve in clinical practice with current standard care for many patients with severe hypertriglyceridemia.[9-17]

Apolipoprotein C-III (APOC3) is a key inhibitor of lipoprotein lipase that regulates triglyceride-rich lipoprotein metabolism. Lipoprotein lipase and hepatic receptors mediate clearance of lipoproteins from the circulation. Genetic deficiency of APOC3 is associated with lower triglyceride levels and reduced cardiometabolic risk.[3,13,18-20] Plozasiran is a hepatocyte-targeted, N-acetylgalactosamine–conjugated small interfering RNA that reduces APOC3 synthesis and lowers triglyceride levels through lipoprotein lipase–dependent and –independent mechanisms. Plozasiran has been shown to lower the risks of hypertriglyceridemia and pancreatitis that are caused by familial chylomicronemia syndrome, a condition that is defined both genetically and clinically.[21-25] However, data are needed on the ability of plozasiran to lower triglyceride levels and mitigate the risk of acute pancreatitis in adult patients with severe hypertriglyceridemia, a population that is larger and more clinically heterogeneous than the patients with the familial syndrome.

METHODS

TRIAL DESIGN AND OVERSIGHT

SHASTA-3 and SHASTA-4 were phase 3, multicenter, randomized, double-blind, placebo-controlled trials designed to evaluate the efficacy and safety of plozasiran in adults with severe hypertriglyceridemia. The trials were conducted in 24 countries at 214 sites in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol and all amendments (available with the full text of this article at NEJM.org) were approved by the institutional review board or ethics committee at each site. All the patients provided written informed consent before undergoing any trial procedures.

The trial was funded by Arrowhead Pharmaceuticals, the manufacturer of plozasiran. Representatives of the company were involved in the design and conduct of the trial and participated in the collection, management, and analysis of the data. An independent data monitoring committee periodically reviewed unblinded trial data according to a prespecified charter. Abdominal events, including suspected cases of acute pancreatitis, and major adverse cardiovascular events were adjudicated by independent committees whose members were unaware of trial-group assignments.

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 first and second 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 POPULATION

Adults (≥18 years of age) with established severe hypertriglyceridemia were eligible for participation. The key inclusion criteria were a documented history of a fasting triglyceride level of at least 500 mg per deciliter (≥5.6 mmol per liter), confirmed by a mean of two consecutive

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fasting measurements obtained during a screening period of up to 8 weeks, and a screening glycated hemoglobin level of less than 9.0%. Patients received standard background lipid-lowering therapy in accordance with local clinical guidelines unless unacceptable side effects were documented.

The key exclusion criteria were a known diagnosis of familial chylomicronemia syndrome caused by biallelic loss-of-function variants in lipoprotein lipase pathway genes, recent use (≤1 year) of hepatocyte-targeted RNA-based therapies (other than inclisiran), acute pancreatitis within 4 weeks before screening, or severe obesity (body-mass index [the weight in kilograms divided by the square of the height in meters], >45). Additional eligibility criteria are provided in the protocol and in the Supplementary Appendix.

RANDOMIZATION AND TREATMENT

The patients were randomly assigned in a 2:1 ratio to receive subcutaneous plozasiran (25 mg) or matching placebo. Randomization was performed with the use of a computer-generated schedule that was adopted before the start of the trial, and each patient received a unique randomization number. Randomization was stratified according to the screening triglyceride level (≥880 mg per deciliter [≥10 mmol per liter] or <880 mg per deciliter [<10 mmol per liter]) and a history of acute pancreatitis within the previous 5 years (history or no history).

The double-blind treatment period lasted 12 months, during which time four doses were administered at 3-month intervals. After month 12, patients were enrolled in an optional open-label extension study (a separate protocol) or underwent a follow-up assessment 3 months after the end of treatment. All the patients received standardized counseling regarding adherence to a low-fat diet and continuation of background lipid-lowering therapy throughout the trial. Management of concomitant conditions, including glycemic control, was permitted at the discretion of the investigator to maintain clinical stability.

END POINTS

The sequence of testing of the seven trial hypotheses was scheduled as follows: first, the percent change from baseline in the fasting serum triglyceride level at month 12,[26] as compared with placebo (primary efficacy end point); second, the percent change from baseline in the triglyceride level at month 10,[26] as compared with placebo (first secondary end point); third, a fasting triglyceride level of less than 500 mg per deciliter at month 12, as compared with placebo; fourth, a fasting triglyceride level of less than 150 mg per deciliter (1.7 mmol per liter) at month 12, as compared with placebo; fifth, the percent change in remnant cholesterol (including very-low-density lipoprotein cholesterol, measured by ultracentrifugation) at month 12, as compared with placebo; sixth, the percent change from baseline in the fasting serum triglyceride level at month 12 for the subgroup of patients with a baseline triglyceride level of at least 880 mg per deciliter (≥10 mmol per liter), as compared with placebo; and seventh, the percent change from baseline in non–high-density lipoprotein (non-HDL) cholesterol at month 12, as compared with placebo.

If all seven hypotheses were confirmed in each trial, we addressed the following three hypotheses in a pooled analysis of data from both SHASTA-3 and SHASTA-4: the event rate per 100 patient-years of positively adjudicated acute pancreatitis (documented, probable, or possible) from baseline to month 12; the incidence of positively adjudicated acute pancreatitis (documented, probable, or possible) from baseline to month 12 (prespecified pooled analysis); and the time until the first positively adjudicated case of acute pancreatitis (documented, probable, or possible) from baseline to month 12 (prespecified pooled analysis).

Exploratory end points included changes in apolipoprotein B, APOC3, total cholesterol, HDL cholesterol, low-density lipoprotein (LDL) cholesterol, and biomarkers related to cardiometabolic risk. Safety end points are described in the Supplementary Appendix.

BLINDING, DATA INTEGRITY, AND DATA SHARING

The present report describes the prespecified primary, secondary, pooled, and selected exploratory efficacy analyses conducted after all the patients had completed the month 12 assessment or discontinued earlier. All the patients, investigators, site personnel, end-point assessors, and members of the operational trial team remain unaware of trial-group assignments while longer-term safety follow-up through month 15 is completed. Unblinded data were accessible only

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to the independent statistical group and designated sponsor personnel who were not involved in the trial conduct. The safety data should be interpreted in the context of ongoing blinded follow-up.

STATISTICAL ANALYSIS

On the basis of previous clinical trial experience, we assumed that patients receiving placebo would have a relative 29% reduction from baseline in the fasting triglyceride level at month 12 and hypothesized that patients receiving plozasiran would have a relative 76% reduction. We assumed a standard deviation of 50% for the change from baseline in the fasting triglyceride level at month 12 in the two groups. In each trial, we determined the planned enrollment — 405 patients in SHASTA-3 and 300 patients in SHASTA-4 — to provide nearly 100% power to detect a between-group difference of 47 percentage points in the difference from baseline (placebo-adjusted change) in the fasting triglyceride level using a two-sided alpha level of 0.05. The inflation of the sample size was deemed necessary for regulatory requirements to adequately assess between-group differences in adverse events and also included adjustment for the withdrawal of 10 to 15% of the patients.

In all statistical analyses and descriptive summaries for efficacy and safety end points, we used appropriate methods and analysis populations, according to the statistical analysis plan for each trial. The efficacy analyses were performed in the intention-to-treat population, which included all the patients who had undergone randomization. Two stratification factors (history of acute pancreatitis and baseline triglyceride level) were used in the randomization to balance the two trial groups.

The statistical comparisons for the primary, secondary, and pooled efficacy end points were performed in the hierarchical order that is described above. Statistically significant results for each comparison, beginning with the primary end point, were required to initiate the testing of the next comparison. In both SHASTA-3 and SHASTA-4, the step-down procedure for the first seven testing positions for the lipid end points was followed. Only when all seven end points from both SHASTA-3 and SHASTA-4 had been successfully tested was testing performed on the three pooled end points involving acute pancreatitis events. Since a step-down procedure was used, an overall alpha level of 0.05 was preserved.

For the primary efficacy end points, a nonparametric approach was prespecified for the primary analysis. For secondary efficacy end points, Wilcoxon rank-sum testing with the Hodges–Lehmann method was used to test and evaluate the median difference and its corresponding 95% confidence interval between plozasiran and placebo. To account for missing data, multiple imputations with a pattern-mixture model were used. This imputation model included the stratification factors, patient demographic characteristics, baseline triglyceride level, and an indicator of adherence to therapy.

For exploratory end points, an analysis of covariance model was used, with treatment group, history of acute pancreatitis, and baseline triglyceride level as factors and the baseline value of the measure as a covariate. Because the statistical analysis plan did not include a provision for correcting for multiplicity when conducting tests for exploratory end points or in subgroups, results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used to infer definitive treatment effects. Additional details regarding the statistical analysis are provided in the Supplementary Appendix.

RESULTS

PATIENTS

From April 2024 through June 2026, a total of 446 patients were enrolled in SHASTA-3 and 311 patients in SHASTA-4 (Fig. S1 in the Supplementary Appendix). In SHASTA-3, trial discontinuation was reported in a total of 23 patients (5%), which included 6% of the patients in the plozasiran group and 5% of those in the placebo group. In SHASTA-4, trial discontinuation was reported in a total of 28 patients (9%), which included 9% in each group (Fig. S2). All four planned trial injections were administered to 95% of the patients in SHASTA-3 and to 91% of those in SHASTA-4.

The demographic and clinical characteristics of the patients at baseline were generally well balanced between the two groups in each trial (Table 1 and Table S1). The patients were gener-

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

Characteristic	SHASTA-3		SHASTA-4	
	Plozasiran (N=297)	Placebo (N=149)	Plozasiran (N=207)	Placebo (N=104)
Demographic				
Age — yr	52±12	51±12	53±11	53±12
Male sex at birth — no. (%)	247 (83)	122 (82)	160 (77)	69 (66)
Race — no. (%)†				
White	223 (75)	109 (73)	184 (89)	87 (84)
Asian	62 (21)	38 (26)	9 (4)	9 (9)
Black	3 (1)	0	13 (6)	3 (3)
Hispanic ethnic group — no. (%)	57 (19)	33 (22)	39 (19)	21 (20)
Medical history				
Body-mass index‡	31±5.3	30±4.8	32±4.9	31±5.4
Metabolic syndrome — no. (%)	4 (1)	3 (2)	4 (2)	1 (1)
Cardiovascular disease — no. (%)	104 (35)	37 (25)	68 (33)	35 (34)
Hypertension — no. (%)	187 (63)	92 (62)	147 (71)	71 (68)
Diabetes mellitus — no. (%)	174 (59)	81 (54)	130 (63)	57 (55)
Acute pancreatitis — no. (%)				
Any	57 (19)	37 (25)	45 (22)	21 (20)
Within 5 yr	33 (11)	21 (14)	27 (13)	14 (13)
Laboratory measures				
Triglycerides				
Median (IQR) — mg/dl	663 (537–956)	674 (545–979)	737 (566–1108)	704 (558–1076)
Mean — mg/dl	835±504	827±512	956±657	939±683
Plasma value ≥880 mg/dl — no. (%)	91 (31)	44 (30)	77 (37)	38 (37)
Apolipoprotein — mg/dl				
C-III	33±15	31±15	37±17	35±18
B	98±28	96±27	99±27	99±27
Cholesterol — mg/dl				
Total	206±69	205±80	221.5±81.4	223.5±94.9
Remnant	108±64	109±80	131±84	131±97
Non–high-density lipoprotein	177±69	176±81	194±82	195±96
High-density lipoprotein	29±10	29±12	28±10	29±12
Low-density lipoprotein: UC	68±33	67±33	62±32	64±34
Other				
Glycated hemoglobin — %§	6.4±1.1	6.4±1.1	6.6±1.2	6.4±1.1

* Plus–minus values are means ±SD. 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. IQR denotes interquartile range.
† Race was reported by the patients. A patient may be classified under one or more race categories.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ For glycated hemoglobin, baseline is defined as the worst value measured any time during screening before the first dose on day 1.

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ally representative of the population with severe hypertriglyceridemia (Table S2). The overall mean (±SD) age was 52±12 years in SHASTA-3 and 53±12 years in SHASTA-4; women represented 17% and 26%, respectively, of the trial population. Most patients were receiving concomitant lipid-lowering therapy, including fibrates. Diabetes mellitus was present in 57% and 60% of patients, respectively. The median triglyceride level at baseline was 671 mg per deciliter (interquartile range, 537 to 958) in SHASTA-3 and 731 mg per deciliter (interquartile range, 560 to 1095) in SHASTA-4. A triglyceride level of at least 880 mg per deciliter was present in 30% of the patients in SHASTA-3 and in 37% of those in SHASTA-4; 21% of the patients in each group had a history of acute pancreatitis.

PRIMARY END POINT

Plozasiran resulted in reductions in the median triglyceride level in both trials (Table 2 and Figs. S3 and S4). The percent change from baseline in the fasting serum triglyceride level at month 12 was a median of −79% (interquartile range, −85 to −65) in SHASTA-3 and −81% (interquartile range, −88 to −68) in SHASTA-4 (Table 2 and Fig. S4). The percent change from baseline in the median triglyceride level in the placebo groups was −28% (interquartile range, −50 to 5.3) in SHASTA-3 and −27% (interquartile range, −50 to 0.4) in SHASTA-4. At month 12, the median placebo-adjusted change was −45 percentage points (95% confidence interval [CI], −51 to −38; P<0.001) in SHASTA-3 and −47 percentage points (95% CI, −54 to −39; P<0.001) in SHASTA-4.

SECONDARY END POINTS

In the plozasiran groups, the median percent change from baseline in the triglyceride level at month 10 was −84% (interquartile range, −90 to −75) and −85% (interquartile range, −90 to −76) in SHASTA-3 and SHASTA-4, respectively. The median percent change in the triglyceride level in the placebo groups was −19% (interquartile range, −53 to 12) and −26% (interquartile range, −48 to 2), respectively (Table 2 and Figs. S4 and S5). At month 10, the median placebo-adjusted change in triglyceride levels in the plozasiran groups was −55 percentage points (95% CI, −63 to −46; P<0.001) and −53 percentage points (95% CI, −61 to −45; P<0.001) (Table 2). At month 12 in the two trials, a triglyceride level of less than 500 mg per deciliter was reported in 91% and 93% of the patients, respectively, in the plozasiran groups and in 51% and 50%, respectively, of those in the placebo groups; a triglyceride level of less than 150 mg per deciliter was reported in 52% and 55%, respectively, of those in the plozasiran groups and in 8% and 2%, respectively, of those in the placebo groups (P<0.001 for all comparisons) (Fig. S6). At month 12, the median percent change from baseline in the fasting serum triglyceride level in the subgroup of patients with a baseline triglyceride level of at least 880 mg per deciliter in SHASTA-3 and SHASTA-4, respectively, was −85% (interquartile range, −91 to −73) and −85% (interquartile range, −91 to −75). The median placebo-adjusted change in the plozasiran groups was −42 percentage points (95% CI, −58 to −26) and −47 percentage points (95% CI, −62 to −32), respectively (Table 2).

At month 12, the least-squares mean percent change from baseline in remnant cholesterol in SHASTA-3 and SHASTA-4 was −51% (95% CI, −61 to −40) and −49% (95% CI, −59 to −39), respectively, in the plozasiran groups, as compared with 2.7% (95% CI, −8.9 to 14) and 7.6% (95% CI, −4.4 to 20), respectively, in the placebo groups (Table 2 and Figs. S4 and S7). The least-squares mean placebo-adjusted change in the remnant cholesterol level in the plozasiran groups was −53 percentage points (95% CI, −65 to −42) and −56 percentage points (95% CI, −69 to −44) (P<0.001), respectively, which was equivalent to absolute reductions of 51 mg and 49 mg per deciliter, respectively (Table 2). The least-squares mean percent change from baseline in non-HDL cholesterol was −17% (95% CI, −23 to −11) and −24% (95% CI, −31 to −19) in the plozasiran groups, as compared with 3.4% (95% CI, −3.8 to 11) and 3.9% (95% CI, −4.7 to 12) in the placebo groups in SHASTA-3 and SHASTA-4, respectively (Table 2). The median placebo-adjusted change in the non-HDL cholesterol level in the plozasiran groups was −21 percentage points (95% CI, −28 to −13) and −28 percentage points (95% CI, −37 to −19), respectively (P<0.001).

Across the two trials, in the plozasiran and placebo groups combined, 18 adjudicated acute pancreatitis events occurred in 14 patients. In the pooled plozasiran groups, 5 events occurred in 5 patients during 504 patient-years of follow-up, corresponding to an event rate of 1 per 100 patient-years; in the pooled placebo groups, 13

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events occurred in 9 patients during 253 patient-years of follow-up, corresponding to an event rate of 5 per 100 patient-years (Table S3). The risk ratio of all adjudicated acute pancreatitis events in the pooled plozasiran groups, as compared with the pooled placebo groups, was 0.22 (95% CI, 0.07 to 0.67; P=0.008) (Fig. 1A). The odds ratio for the first occurrence of adjudicated acute pancreatitis was 0.26 (95% CI, 0.08 to 0.82; P=0.02) (Fig. 1B). The time until the first adjudicated acute pancreatitis event was 283 days in the plozasiran group and 182 days in the placebo group (hazard ratio, 0.26; 95% CI, 0.09 to 0.78; P=0.02) (Fig. S8).

EXPLORATORY END POINTS

The least-squares mean percent change from baseline to month 12 in the APOC3 level was −68% (95% CI, −73 to −62) in SHASTA-3 and −64% (95% CI, −72 to −57) in SHASTA-4; the corresponding changes were −1.3% (95% CI, −6.0 to 3.5) and −7.8% (95% CI, −13 to −2.8) in the apolipoprotein B level (Table S4 and Figs. S9 and S10). The median percent change from baseline to month 12 in the LDL cholesterol level, as compared with the change in placebo, was 27 percentage points (95% CI, 14 to 39) in SHASTA-3 and 25 percentage points (95% CI, 12 to 39) in SHASTA-4 (Table S4 and Fig. S9). LDL cholesterol levels in the two groups were low at baseline (<70 mg per deciliter), probably because most patients were receiving cholesterol-lowering therapy (Table 1 and Table S1).

SAFETY

The incidence of adverse events, serious adverse events, and adverse events leading to the discontinuation of plozasiran or placebo were low and generally similar in the two groups (Table 3 and Tables S5 through S8). The incidence of adverse events that were reported during the trial period was identical (73%) in the two groups. Treatment-related adverse events (as determined by the investigators) were reported in 118 patients (23%) in the pooled plozasiran groups and in 40 patients (16%) in the pooled placebo groups. Serious adverse events occurred in 42 patients (8%) in the pooled plozasiran groups and in 24 patients (10%) in the pooled placebo groups. Treatment-related serious adverse events occurred in 1 patient (<1%) in the plozasiran group and in no patients in the placebo group. In SHASTA-3, three deaths were reported in the plozasiran group: two deaths from cardiovascular events (from cardiogenic shock during the catheterization procedure and from cardiac arrest during an automobile accident) in patients who had extensive underlying cardiovascular disease and one death from chronic myelomonocytic leukemia. These deaths were assessed by the investigators and by the independent data and safety monitoring committee as not being related to plozasiran.

The most commonly reported adverse events (occurring in ≥5% of the patients in the two groups) were worsening of glycemic control, diarrhea, and abdominal pain in the two trials (Table 3). Worsening of glycemic control occurred in 72 patients (14%) in the pooled plozasiran groups and in 22 patients (9%) in the pooled placebo groups. Consistent with these findings, the mean glycated hemoglobin level in the pooled plozasiran groups showed a modest increase from baseline to month 3, which remained stable through month 12 (Fig. S11). Injection-site reactions were reported in 16 patients (3%) in the plozasiran groups and in 5 patients (2%) in the placebo groups (Table 3). No adverse events that were suggestive of hypersensitivity or anaphylaxis were reported in either group during the two trials.

Elevations in levels of alanine aminotransferase or aspartate aminotransferase that exceeded three times the upper limit of the normal range occurred in 1% of the patients in the plozasiran group and in 2% of those in the placebo group in each trial; none of these cases met Hy's law criteria.

A subgroup of 36 patients in SHASTA-3 underwent hepatic imaging by magnetic resonance imaging (MRI) at baseline and at month 12. The mean hepatic fat fraction was elevated at baseline in both groups (14% in the plozasiran group and 16% in the placebo group). The mean change from baseline to month 12 was 1 percentage point in the plozasiran group and −0.5 percentage points in the placebo group. The change in the proton density fat fraction on MRI was slightly higher in the plozasiran group than in the placebo group (least-squares mean difference, 1 percentage point). The correlation between the change in the proton density fat fraction and the change in the glycated hemoglobin level was r=0.615 (Table S9 and Fig. S11).

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Table 2. Efficacy According to Levels of Triglycerides and Remnant and Non-HDL Cholesterol.*

Measure	SHASTA-3		SHASTA-4	
	Plozasiran (N = 297)	Placebo (N = 149)	Plozasiran (N = 207)	Placebo (N = 104)
Triglycerides				
Median level at baseline (IQR) — mg/dl	663 (537 to 956)	674 (545 to 979)	737 (566 to 1108)	704 (558 to 1076)
Median level at 12 mo (IQR) — mg/dl	142 (101 to 233)	489 (316 to 767)	141 (101 to 241)	500 (335 to 892)
Median change from baseline (IQR) — mg/dl	−500 (−783 to −333)	−158 (−342 to 35)	−551 (−845 to −393)	−192 (−421 to 2.9)
Median percent change from baseline (IQR)	−79 (−85 to −65)	−28 (−50 to 5.3)	−81 (−88 to −68)	−27 (−50 to 0.4)
Estimated difference from placebo (95% CI) — percentage points†‡	−45 (−51 to −38)	—	−47 (−54 to −39)	—
Median level at month 10 (IQR) — mg/dl	104 (77 to 164)	525 (290 to 881)	107 (78 to 167)	505 (355 to 781)
Median change from baseline (IQR) — mg/dl	−546 (−822 to −393)	−144 (−348 to 106)	−605 (−893 to −426)	−194 (−422 to 11)
Median percent change from baseline (IQR)	−84 (−90 to −75)	−19 (−53 to 12)	−85 (−90 to −76)	−26 (−48 to 2)
Estimated difference from placebo (95% CI) — percentage points†‡	−55 (−63 to −46)	—	−53 (−61 to −45)	—
Patients with triglyceride level <500 mg/dl at month 12				
No. of patients/total no. (%)	255/279 (91)	71/140 (51)	175/189 (93)	49/98 (50)
Risk difference vs. placebo (95% CI)†‡	0.4 (0.3 to 0.5)	—	0.4 (0.3 to 0.5)	—
Patients with triglyceride level <150 mg/dl at month 12				
No. of patients/total no. (%)	146/279 (52)	11/140 (8)	104/189 (55)	2/98 (2)
Risk difference vs. placebo (95% CI)†‡	0.4 (0.3 to 0.5)	—	0.5 (0.4 to 0.6)	—
Triglyceride level ≥880 mg/dl at baseline				
No. of patients	91	44	77	38
Median triglyceride level at baseline (IQR) — mg/dl	1241 (1036 to 1559)	1258 (1062 to 1499)	1259 (1042 to 1821)	1154 (1023 to 1686)
Median triglyceride level at month 12 (IQR) — mg/dl	193 (115 to 420)	776 (456 to 1362)	215 (127 to 342)	878 (511 to 1988)
Median change from baseline (IQR) — mg/dl	−955 (−1243 to −794)	−372 (−978 to 101)	−1072 (−1612 to −816)	−421 (−791 to 47)
Median percent change from baseline (IQR) — percentage points	−85 (−91 to −73)	−38 (−70 to 8.0)	−85 (−91 to −75)	−25 (−60 to 4)
Least-squares mean difference from placebo (95% CI) — percentage points†‡	−42 (−58 to −26)	—	−47 (−62 to −32)	—
Remnant cholesterol				
Level at baseline — mg/dl	108±64	109±80	131±84	131±97
Level at month 12 — mg/dl	33±29	94±84	35±34	111±91
Change from baseline — mg/dl	−75±62	−16±87	−97±81	−19±93

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Least-squares mean percent change from baseline (95% CI)	−51 (−61 to −40)	2.7 (−8.9 to 14)	−49 (−59 to −39)	7.6 (−4.4 to 20)
Least-squares mean difference from placebo (95% CI) — percentage points†‡	−53 (−65 to −42)	—	−56 (−69 to −44)	—
Non-HDL cholesterol				
Level at baseline — mg/dl	177±69	176±81	194±82	194±95
Level at month 12 — mg/dl	126±53	167±85	119±51	177±92
Change from baseline — mg/dl	−51±73	−11±85	−75±79	−16±93
Least-squares mean percent change from baseline (95% CI)	−17 (−23 to −11)	3.4 (−3.8 to 11)	−24 (−31 to −19)	3.9 (−4.7 to 12)
Least-squares mean difference from placebo (95% CI) — percentage points†‡	−21 (−28 to −13)	—	−28 (−37 to −19)	—

* HDL denotes high-density lipoprotein.
† The Hodges–Lehmann method was used to estimate the difference in the median percent change and its corresponding 95% confidence interval for percent changes between plozasiran and placebo.
‡ P<0.001 as calculated with the Wilcoxon rank-sum test.

DISCUSSION

Our findings and the results of trials of the monthly antisense drug olezarsen[27] have shown that APOC3 inhibitors can produce greater triglyceride reductions than those obtained with conventional triglyceride-lowering agents, including in patients with a persistent total triglyceride level in the severe hypertriglyceridemia range. Given the monotonic and causal relationship between triglyceride levels and the risk of acute pancreatitis[28-30] and between reductions in the triglyceride level and in the risk of acute pancreatitis in patients with familial chylomicronemia syndrome,[31,32] we anticipated that attaining and maintaining a maximal triglyceride reduction with plozasiran would decrease the risk of acute pancreatitis in patients with severe hypertriglyceridemia, some of whom would have had multifactorial chylomicronemia.[16,17,31,32]

A fasting triglyceride threshold of 500 mg per deciliter is recognized as the threshold above which the risk of pancreatitis increases.[5,6,33-35] This threshold is particularly relevant in patients with a history of recurrent acute pancreatitis.[11,12,36] In SHASTA-3 and SHASTA-4, a triglyceride level of less than 500 mg per deciliter at 12 months was reported in just over 90% of the patients in the pooled plozasiran groups, and 50% of the patients had reductions to below the upper limit of the normal range for triglycerides (<150 mg per deciliter). These results are generally consistent with those reported for other APOC3-targeted therapies.[3,16,27]

Severe hypertriglyceridemia, especially when chylomicrons accumulate and are persistently present in the circulation (triglyceride level, ≥880 mg per deciliter [≥10 mmol per liter]), can be associated with moderate-to-severe symptoms, including abdominal pain and discomfort.[14,16,37] Unlike most patients with genetic familial chylomicronemia syndrome, patients with severe hypertriglyceridemia frequently have coexisiting illnesses such as obesity, diabetes, and metabolic syndrome, as shown in our trials.[5,37,38] Such patients have a clinical presentation that is manifested as multifactorial chylomicronemia, which can closely resemble the signs and symptoms of adults with familial chylomicronemia syndrome,[34] with a clear indication for effective triglyceride-lowering therapies.[16,37,38] Proven treatments are needed for this group of patients, be-

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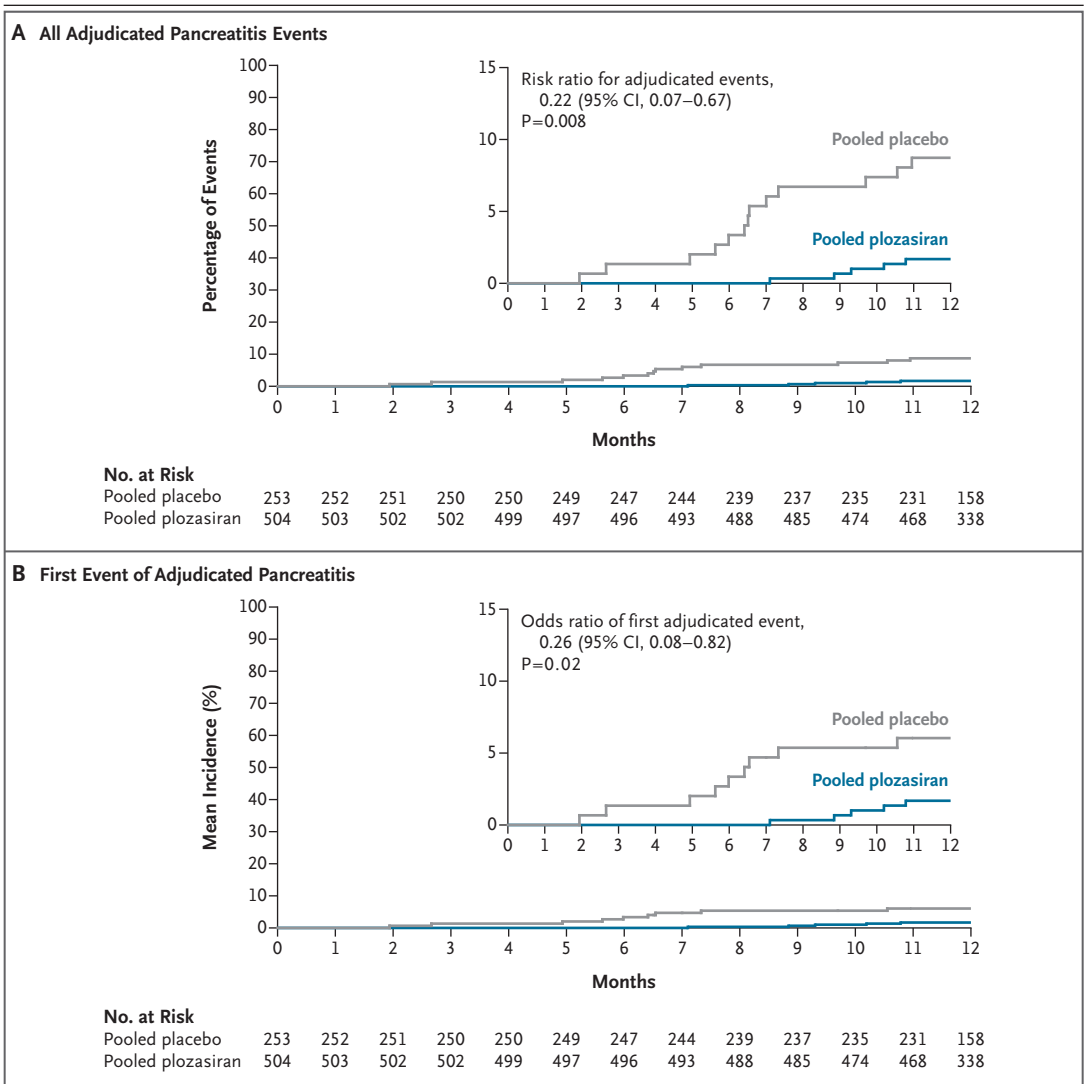


Figure 1. Incidence of Adjudicated Acute Pancreatitis Events.

Shown is the percentage of any adjudicated acute pancreatitis event (Panel A) and the mean incidence of a first adjudicated pancreatitis event (Panel B) in the pooled plozasiran groups, as compared with the pooled placebo groups, in the SHASTA-3 and SHASTA-4 trials. Positively adjudicated events of acute pancreatitis included documented, probable, and possible events. The insets show the same data on an expanded y axis. P values were calculated with the Wald chi-square test.

cause the risk of pancreatitis at any given triglyceride level is substantially greater in patients who have already had one or more episodes of pancreatitis[16,34,39] and have already shown the propensity for a potentially fatal event.

In the PALISADE trial involving patients with genetic or clinically defined familial chylomicronemia syndrome and a history of at least three fasting triglyceride measurements of more than 1000 mg per deciliter, plozasiran showed a significant 82% reduction in the risk of pancreatitis.[32] The SHASTA-3 and SHASTA-4 trials excluded patients with genetic familial chylomicronemia syndrome and did not require a history of chylomicronemia but included 21% of patients with a history of pancreatitis. The results of our pooled analysis — which supported a reduction of 78 percentage points in acute pancreatitis risk relative to placebo — were consistent with those of the PALISADE trial.[32]

Most of the patients in our trial were receiving statins, fibrates, or both at trial entry yet contin-

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Table 3. Adverse Events in the Pooled Trial Groups.*

Event	Pooled Plozasiran (N = 504)	Pooled Placebo (N = 252)	Total (N = 756)
	number of patients (percent)		
Any adverse event	368 (73)	184 (73)	552 (73)
Most common adverse events reported in ≥5% of patients in either group			
Worsening of glycemic control†	72 (14)	22 (9)	94 (12)
Diarrhea	28 (6)	8 (3)	36 (5)
Abdominal pain	13 (3)	17 (7)	30 (4)
Serious adverse event	42 (8)	24 (10)	66 (9)
Maximum severity			
Mild	91 (18)	50 (20)	141 (19)
Moderate	227 (45)	106 (42)	333 (44)
Severe	42 (8)	26 (10)	68 (9)
Death‡	3 (1)	0	3 (<1)
Leading to discontinuation of plozasiran or placebo	7 (1)	2 (1)	9 (1)
Injection-site reaction§	16 (3)	5 (2)	21 (3)
Decrease in platelet count	2 (<1)	4 (2)	6 (1)
Hypersensitivity	1 (<1)	1 (<1)	2 (<1)
Increase in ALT or AST level at any postbaseline visit			
≥3× ULN	5 (1)	4 (2)	9 (1)
≥5× ULN	2 (<1)	2 (1)	4 (<1)

* Listed are adverse events that were reported during the trial period. Patients with multiple events were counted only once within a category. One patient who was randomly assigned to the placebo group did not receive placebo for any duration and was not included in the safety analysis. ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and ULN upper limit of the normal range.

† Adverse events related to glycemic control included inadequate control of diabetes mellitus, hyperglycemia, increase in level of blood glucose or glycated hemoglobin, impaired glucose tolerance, glycosuria, and insulin resistance.

‡ Fatal events consisted of two cardiovascular deaths (cardiogenic shock after the catheterization procedure and cardiac arrest during an automobile accident, both in patients with extensive underlying cardiovascular disease) and one death from chronic myelomonocytic leukemia. All events were attributable to preexisting cardiovascular or hematologic disease and were assessed by the investigators and independent data and safety monitoring committee as being unrelated to plozasiran.

§ Injection-site reactions included pain, erythema, bruising, hypersensitivity, inflammation, and pruritus.

ued to have severe hypertriglyceridemia and remained at risk for acute pancreatitis.[1,30] This finding indicates that substantial residual triglyceride-related risk persists in many patients despite currently available therapies and supports the use of APOC3 inhibition as a treatment approach in such patients.[39]

Treatment with plozasiran led to greater reductions than placebo at 12 months in the levels of remnant cholesterol and non-HDL cholesterol (in addition to triglyceride levels), measures that represent established markers of total atherogenic lipoprotein burden.[40,41] Severe hypertriglyceridemia is associated with an increased risk of atherosclerotic cardiovascular disease,[42-44] and future studies may investigate the effect of targeting either APOC3 or angiopoietin-like proteins jointly with LDL cholesterol–lowering therapies on this risk.[28,44-47]

Serious adverse events and discontinuation of plozasiran or placebo occurred at similar frequencies across the trial groups. No apparent increase in the hepatic fat fraction during the trial was reported, although only a small subgroup of patients who received plozasiran were studied and the trial was not powered to detect a difference. We observed a modest mean increase in the glycated hemoglobin level among

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the patients who received plozasiran, along with a worsening of glycemic control (in 14% of the patients in the plozasiran group and in 9% of those in the placebo group). Perhaps this apparent difference results from increased delivery of glycerol and fatty acid substrate to the liver because of enhanced catabolism of triglycerides in the patients who received plozasiran. Plozasiran was not associated with elevations in alanine aminotransferase or aspartate aminotransferase levels as compared with placebo. None of the three deaths in the plozasiran groups was assessed as being related to plozasiran.

Our trials have several limitations. Most of the patients were White men, which limits the generalizability of the findings to women and patients of other races. Another limitation is a lack of data regarding abdominal pain reported by patients in the trials.[14-16] The duration of the trials was only 1 year but is continuing with an open-label extension.[38]

Among patients with severe hypertriglyceridemia, the use of plozasiran led to greater reductions in triglyceride levels and in the incidence of acute pancreatitis than the use of placebo at 12 months. Additional work is required to fully establish the role of plozasiran in the clinical treatment of these patients.

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AUTHOR INFORMATION

Gerald F. Watts, D.Sc., M.D., Ph.D.,[1] Christie M. Ballantyne, M.D.,[2] Agustin Blanco Echevarria, M.D., Ph.D.,[3] Jamie Smith, M.D.,[4] Robert S. Rosenson, M.D.,[5] Savitha Subramanian, M.D.,[6] James Trippi, M.D.,[7] Norman Lepor, M.D.,[8] Archna Bajaj, M.D.,[9] Vladimir Blaha, M.D., Ph.D.,[10] Russell Scott, M.D., Ph.D.,[11] Alexis Baass, M.D.,[12] Ira J. Goldberg, M.D.,[13] Antonio Gallo, M.D., Ph.D.,[14] Jose Luis Diaz, M.D., Ph.D,[15] Manish Saxena, M.B., B.S.,[16] Jianping Li, M.D.,[17] Rong Zhou, Ph.D.,[18] Lalitha Aiyer, M.D.,[18] Jennifer Hellawell, M.D.,[18] James Hamilton, M.D.,[18] and Daniel Gaudet, M.D., Ph.D.[19]

[1] University of Western Australia and Department of Cardiology, Royal Perth Hospital, Perth; [2] Baylor College of Medicine and the Texas Heart Institute, Houston; [3] Hospital Universitario 12 de Octubre, Madrid; [4] Torbay and South Devon NHS Foundation Trust–Torbay Hospital (Department of Diabetes and Endocrinology), Torquay, United Kingdom; [5] Metabolism and Lipids Program, Mount Sinai Fuster Heart Hospital, Icahn School of Medicine, Mount Sinai, New York; [6] University of Washington, Seattle; [7] Ascension St. Vincent Heart Center, Indianapolis; [8] National Heart Institute, Beverly Hills, CA; [9] University of Pennsylvania, Philadelphia; [10] Third Department of Internal Medicine–Metabolism and Gerontology, Faculty of Medicine in Hradec Králové, University Hospital Hradec Králové and Charles University, Hradec Kralove, Czech Republic; [11] New Zealand Clinical Research, Christchurch; [12] Institut de Recherches Cliniques de Montréal and McGill University, Montreal; [13] NYU Langone Health, New York; [14] Assistance Publique–Hôpitaux de Paris Hôpital Universitaire Pitié–Salpêtrière, Paris; [15] Complejo Hospitalario Universitario de A Coruña, Galicia, Spain; [16] Barts Health NHS Trust and Queen Mary University, London; [17] Peking University First Hospital, Beijing; [18] Arrowhead Pharmaceuticals, Pasadena, CA; [19] Université de Montréal and ECOGENE 21, Montreal.

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