ORIGINAL ARTICLE

Plozasiran, an RNA Interference Agent Targeting APOC3, for Mixed Hyperlipidemia

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ABSTRACT

BACKGROUND

Persons with mixed hyperlipidemia are at risk for atherosclerotic cardiovascular disease due to an elevated non–high-density lipoprotein (HDL) cholesterol level, which is driven by remnant cholesterol in triglyceride-rich lipoproteins. The metabolism and clearance of triglyceride-rich lipoproteins are down-regulated through apolipoprotein C3 (APOC3)–mediated inhibition of lipoprotein lipase.

METHODS

We carried out a 48-week, phase 2b, double-blind, randomized, placebo-controlled trial evaluating the safety and efficacy of plozasiran, a hepatocyte-targeted APOC3 small interfering RNA, in patients with mixed hyperlipidemia (i.e., a triglyceride level of 150 to 499 mg per deciliter and either a low-density lipoprotein [LDL] cholesterol level of ≥70 mg per deciliter or a non-HDL cholesterol level of ≥100 mg per deciliter). The participants were assigned in a 3:1 ratio to receive plozasiran or placebo within each of four cohorts. In the first three cohorts, the participants received a subcutaneous injection of plozasiran (10 mg, 25 mg, or 50 mg) or placebo on day 1 and at week 12 (quarterly doses). In the fourth cohort, participants received 50 mg of plozasiran or placebo on day 1 and at week 24 (half-yearly dose). The data from the participants who received placebo were pooled. The primary end point was the percent change in fasting triglyceride level at week 24.

RESULTS

A total of 353 participants underwent randomization. At week 24, significant reductions in the fasting triglyceride level were observed with plozasiran, with differences, as compared with placebo, in the least-squares mean percent change from baseline of −49.8 percentage points (95% confidence interval [CI], −59.0 to −40.6) with the 10-mg-quarterly dose, −56.0 percentage points (95% CI, −65.1 to −46.8) with the 25-mg-quarterly dose, −62.4 percentage points (95% CI, −71.5 to −53.2) with the 50-mg-quarterly dose, and −44.2 percentage points (95% CI, −53.4 to −35.0) with the 50-mg-half-yearly dose ($P<0.001$ for all comparisons). Worsening glycemic control was observed in 10% of the participants receiving placebo, 12% of those receiving the 10-mg-quarterly dose, 7% of those receiving the 25-mg-quarterly dose, 20% of those receiving the 50-mg-quarterly dose, and 21% of those receiving the 50-mg-half-yearly dose.

CONCLUSIONS

In this randomized, controlled trial involving participants with mixed hyperlipidemia, plozasiran, as compared with placebo, significantly reduced triglyceride levels at 24 weeks. A clinical outcomes trial is warranted. (Funded by Arrowhead Pharmaceuticals; MUIR ClinicalTrials.gov number NCT04998201.)

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A Quick Take is available at NEJM.org

Mixed hyperlipidemia is a highly prevalent disorder characterized by elevated low-density lipoprotein (LDL) cholesterol and triglyceride levels.[1,2] The incidence of mixed hyperlipidemia is increasing owing to the growing epidemics of obesity and diabetes. A fasting triglyceride level higher than 150 mg per deciliter (1.69 mmol per liter) indicates an increased risk of atherosclerotic cardiovascular disease.[1,2] Triglycerides are a surrogate marker for the more atherogenic triglyceride-rich lipoproteins, including chylomicrons, chylomicron remnants, very-low-density lipoproteins (VLDLs), and VLDL remnants, such as intermediate-density lipoproteins (IDLs). In each of these triglyceride-rich lipoproteins,[3] the concentration of cholesterol per particle is up to four times as high as that in LDL.[3-5] Remnant particles of triglyceride-rich lipoproteins can infiltrate into the subendothelial space of the arterial wall and bind proteoglycans, thereby delivering remnant cholesterol — the cholesterol content of triglyceride-rich lipoproteins (henceforth referred to as TRL–cholesterol remnants) — into the intima and initiating cholesterol deposition and foam-cell formation. As with the delivery of LDL cholesterol into the subendothelial space of the arterial wall, the delivery of remnant cholesterol also contributes to the development of atherosclerotic plaque (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[6] Thus, elevations in triglyceride levels identify persons with elevated levels of atherogenic triglyceride-rich lipoproteins and cholesterol remnants that promote atherogenesis and atherosclerotic cardiovascular disease.[7,8]

Despite the efficacy of LDL cholesterol–lowering therapies in reducing the risk of atherosclerotic cardiovascular disease among persons with mixed hyperlipidemia, substantial residual risk remains owing to elevated levels of triglyceride and cholesterol remnants.[4,9-11] Observational and epidemiologic studies have reported an association between elevated triglyceride-rich lipoprotein and remnant cholesterol levels and an increased risk of atherosclerotic cardiovascular disease and death. In a meta-analysis of eight randomized, controlled trials of statins, the strongest predictor of major cardiovascular events was non–high-density lipoprotein (HDL) cholesterol (combining cholesterol content of LDL cholesterol, lipoprotein[a], and triglyceride-rich lipoproteins), not LDL cholesterol or apolipoprotein B (apoB) alone.[12] The importance of triglyceride-rich lipoproteins, with the use of triglycerides as a surrogate, was also shown in the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE-IT TIMI 22) trial, in which triglyceride levels lower than 150 mg per deciliter during treatment were independently associated with reduced recurrence of coronary heart disease after acute coronary syndrome.[12,13] A causal role of TRL–cholesterol remnants in atherosclerotic cardiovascular disease is also supported by genetic and mendelian randomization studies.[4,10,14-16] However, studies of triglyceride-lowering therapies have not shown a reduction in the incidence of major adverse cardiovascular events or a clear linkage between such a reduction and a reduced triglyceride level, especially among patients receiving statins.[17,18]

Pathways specific to the metabolism and clearance of TRL–cholesterol remnants are targets for new therapies. A key regulator of triglyceride-rich lipoprotein metabolism is apolipoprotein C3 (APOC3), a glycoprotein that is synthesized principally in the liver.[19] APOC3 resides on the surface of all lipoproteins, chylomicrons, and VLDL, LDL, lipoprotein(a), and HDL particles[20,21] and affects plasma triglyceride levels by inhibiting lipoprotein lipase–mediated triglyceride-rich lipoprotein metabolism and its uptake by hepatocytes, leading to increased levels of circulating chylomicrons and triglyceride-rich lipoproteins.[22-24] *APOC3* loss-of-function variants are associated with reduced (cumulative and postprandial) plasma triglyceride levels,[25] protection against coronary heart disease (as assessed indirectly through coronary-artery calcium scoring and directly by means of reported clinical events), and increased longevity.[25-27] In the aggregate, loss-of-function mutations in *APOC3* were associated with reductions in triglyceride and remnant cholesterol levels and in the risk of atherosclerotic cardiovascular disease of approximately 40%.[28]

Pharmacologic approaches to reduce *APOC3* expression have been developed, including gene silencing of *APOC3* RNA with antisense oligonucleotides or with small interfering RNA.[29] Plozasiran is an *N*-acetylgalactosamine–conjugated small interfering RNA designed to reduce *APOC3* expression in the liver.[30] Small interfering RNAs have advantages such as high specificity,

potent activity, and reversibility and have a generally good side-effect profile, features that often allow for durable gene silencing with infrequent dose administration (Fig. S2).[31] Proof of concept was shown in a phase 1 study in which plozasiran led to substantial, sustained, dose-dependent reductions in APOC3 and triglyceride levels among healthy volunteers and among patients with hypertriglyceridemia (i.e., a triglyceride level of >300 mg per deciliter [3.39 mmol per liter]) and chylomicronemia.[30] Here, we describe the results of the MUIR trial, a phase 2b clinical trial that evaluated the safety and efficacy of plozasiran in adults with mixed hyperlipidemia.

METHODS

TRIAL OVERSIGHT

This trial was conducted at 36 centers across the United States, Europe, New Zealand, Australia, and Canada from September 28, 2021, to August 14, 2023, in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Council for Harmonisation. Arrowhead Pharmaceuticals funded the trial and was involved in the design and conduct of the trial and in the collection, management, analysis, and interpretation of the data. All the authors had unrestricted access to trial data. The first author, coauthors employed by the sponsor, and a representative of the sponsor wrote the first draft of the manuscript. The sponsor was involved in the preparation, review, and approval of the manuscript and in the decision to submit the manuscript for publication. All the athors were responsible for the writing and review of all drafts of the manuscript. The first and last authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The trial protocol and amendments, available at NEJM.org, were approved by the institutional review board or ethics committee at each trial site. All the participants provided written informed consent.

TRIAL DESIGN AND PARTICIPANTS

The MUIR trial was a phase 2b, double-blind, randomized, placebo-controlled trial (Fig. S3). The trial population included men or nonpregnant, nonlactating women (age, ≥18 years) with a fasting triglyceride level of 150 to 499 mg per deciliter (1.69 to 5.63 mmol per liter) and either an LDL cholesterol level of 70 mg per deciliter (1.81 mmol per liter) or higher or a non-HDL cholesterol level of 100 mg per deciliter (2.59 mmol per liter) or higher. Enrolled participants had maintained a stable diet for at least 2 weeks, had received a stable maximal tolerated dose of a statin (unless they were unable or unwilling to receive statins) for at least 4 weeks, and had been receiving background medications at stable doses (Table S1). The participants were assigned in a 3:1 ratio to receive plozasiran or placebo within each of four cohorts. In the first three cohorts, the participants received a subcutaneous injection of plozasiran (10 mg, 25 mg, or 50 mg) or volume-matched placebo on day 1 and at week 12 (quarterly doses). In the fourth cohort, participants received 50 mg of plozasiran or volume-matched placebo on day 1 and at week 24 (half-yearly dose). The four cohorts were enrolled in parallel, and the data from the participants who were assigned to receive placebo were pooled. Trial participants received unique identifiers and were assigned to a cohort according to a block randomization algorithm. Each participant received an injection of either plozasiran at the assigned dose or volume-matched placebo. The participants and the investigators were unaware of the active-drug or placebo assignments within each cohort. The dose-group assignment was not concealed because of differences in injection volume as dictated by the dose level.

END POINTS

The primary end point was the least-squares mean percent change in the fasting plasma triglyceride level from baseline to week 24. Secondary end points included changes from baseline in the APOC3 level at week 24, in the fasting triglyceride level through week 48, and in the fasting levels of APOC3, non-HDL cholesterol, apoB, LDL cholesterol, and HDL cholesterol at week 24 through week 48. Exploratory efficacy end points included the change from baseline in fasting laboratory measures, including remnant cholesterol (calculated as total cholesterol level minus the HDL cholesterol and LDL cholesterol levels, as measured by ultracentrifugation), lipoprotein(a), and high-sensitivity C-reactive protein; plozasiran pharmacokinetics; and the incidence of antibodies against plozasiran (results not reported here).

STATISTICAL ANALYSIS

Repeated-measures analysis of covariance was used for statistical modeling and included trial-group assignment, trial visit, baseline triglyceride level, and interaction by trial-group assignment and visit as model terms. Assuming a 30 to 70% reduction in the fasting triglyceride level with plozasiran and no reduction with placebo, we estimated that 320 randomly assigned participants would provide the trial with more than 99% power to detect a significant difference between at least one active-dose group and the placebo group and more than 91% power to detect a significant difference between all active-dose groups and the placebo group with the use of a two-sided test at a 5% level of significance and adjustment for multiplicity of testing. When available, the triglyceride value at week 24 represents the mean of two measures.

Holm's step-down multiplicity-adjustment procedure was used for the primary end-point analysis (all trial groups), and the corresponding P value from the comparison between each active-dose group and the placebo group was evaluated at the 5% significance level. Secondary and exploratory end-point estimates are reported with 95% confidence intervals, and the results should not be interpreted as hypothesis tests.

Efficacy and safety analyses were performed with data from all randomly assigned participants who received at least one dose of plozasiran or placebo. Missing values were not imputed except for missing or partial dates of adverse events, concomitant status for medications and procedures, and instances in which a complete date was required for calculations. Other than control for type I error in the analysis of the primary end point (with missing observations assumed to be missing at random), no control for the effect of multiple comparisons was planned. Since there was no adjustment for multiplicity in the analyses of the secondary and exploratory end points, the data are reported as point estimates with 95% confidence intervals. The widths of the confidence intervals should not be used to infer treatment effect.

RESULTS

PARTICIPANTS

A total of 353 participants underwent randomization, and 324 (91.8%) completed the trial (Fig. S4). The baseline characteristics of the participants were generally balanced across trial groups, with the exception of the percentage of women and participants taking statins assigned to the 50 mg half-yearly group. The mean age of the participants was 61 years, and the mean body-mass index (the weight in kilograms divided by the square of the height in meters) was 32 (Table 1). Among all the participants at baseline, the mean plasma triglyceride level was 244 mg per deciliter (2.75 mmol per liter), the mean fasting LDL cholesterol level was 103 mg per deciliter (2.66 mmol per liter), the non-HDL cholesterol level was 151 mg per deciliter (3.90 mmol per liter), and the mean remnant cholesterol level was 47 mg per deciliter (1.22 mmol per liter). A total of 18% of the participants had an LDL cholesterol level lower than 70 mg per deciliter (1.81 mmol per liter), and 92% were receiving statins, with 54% receiving high-intensity statins. Other cholesterol-lowering agents included proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitor therapy (2% of the participants), fibrates (14%), icosapent ethyl (3%), and other n–3 fatty acids (3%). A total of 61% of the participants had diabetes, and 12% were determined to be at high risk for cardiovascular disease (10-year risk, >20% [based on the third Adult Treatment Panel guidelines of the National Cholesterol Education Program]). The representativeness of the trial participants relative to the broader population with mixed hyperlipidemia is described in Table S2. The percentage of men was higher than that of women (56% vs. 44%), but no meaningful between-group differences in triglyceride values were observed on the basis of sex, thereby confirming the generalizability of the findings (Table S3).

EFFICACY ANALYSIS AT WEEK 24

At week 24, a time point that represents the trough effect after two quarterly doses, significant reductions in fasting triglyceride level (primary end point) were observed with plozasiran, with differences, as compared with placebo, in the least-squares mean percent change from baseline of −49.8 percentage points (95% confidence interval [CI], −59.0 to −40.6) with the 10-mg-quarterly dose, −56.0 percentage points (95% CI, −65.1 to −46.8) with the 25-mg-quarterly dose, −62.4 percentage points (95% CI, −71.5 to −53.2) with the 50-mg-quarterly dose, and −44.2 percentage points

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

Characteristic	Pooled Placebo (N=87)	Plozasiran, 10 mg Quarterly (N=67)	Plozasiran, 25 mg Quarterly (N=67)	Plozasiran, 50 mg Quarterly (N=66)	Plozasiran, 50 mg Half-Yearly (N=66)
Age — yr	58.9±9.7	60.2±11.7	61.3±11.3	62.6±10.5	61.3±11.8
Sex — no. (%)					
Female	41 (47)	31 (46)	30 (45)	29 (44)	23 (35)
Male	46 (53)	36 (54)	37 (55)	37 (56)	43 (65)
White race — no. (%)†	79 (91)	62 (93)	60 (90)	63 (95)	62 (94)
Body-mass index	31.2±5.4	30.5±5.7	32.4±6.7	32.6±6.5	32.0±5.6
APOC3 — mg/liter‡	14.6±4.7	15.5±5.5	15.6±5.5	15.0±5.7	15.0±5.5
Triglyceride level — mg/dl	237.2±76.2	253.2±81.4	234.1±72.7	250.3±81.3	248.0±80.6
Remnant cholesterol level — mg/dl§	45.0±18.9	48.3±20.5	46.1±20.3	48.8±27.2	47.4±23.1
Non-HDL cholesterol level — mg/dl	148.3±43.4	153.5±42.0	147.7±48.4	151.8±49.3	153.0±42.7
ApoB level — mg/dl	102.3±29.6	102.6±23.0	100.9±27.2	100.6±27.6	104.5±24.2
HDL cholesterol level — mg/dl	42.1±11.1	42.2±11.1	44.7±13.6	42.7±11.7	40.8±12.6
LDL cholesterol — mg/dl	101.6±38.7	105.1±37.0	101.6±43.4	103.0±39.7	105.6±31.8
Current medication use — no. (%)					
Statins	84 (97)	61 (91)	61 (91)	60 (91)	57 (86)
High-intensity statins	49 (56)	38 (57)	33 (49)	35 (53)	34 (52)
Fibrates	15 (17)	10 (15)	6 (9)	6 (9)	9 (14)
n–3 Fatty acids	5 (6)	2 (3)	1 (1)	1 (2)	3 (5)
Icosapent ethyl	3 (3)	1 (1)	3 (4)	2 (3)	0 (0)
PCSK9 inhibitor	1 (1)	3 (4)	3 (4)	0	1 (2)
GLP-1 receptor agonist	11 (13)	2(3)	5 (7)	9 (14)	8 (12)
Diabetes¶	51 (59)	39 (58)	41 (61)	45 (68)	39 (59)
10-year risk of coronary heart disease of >20% — no. (%)	8 (9)	7 (10)	5 (7)	13 (20)	10 (15)
Tobacco use — no. (%)	18 (21)	9 (13)	13 (19)	12 (18)	13 (20)
Chronic kidney disease — no. (%)	13 (15)	5 (7)	9 (13)	5 (8)	9 (14)

* Plus–minus values denote means ±SDs. The quarterly dose of plozasiran was given on day 1 and at week 12, and the half-yearly dose on day 1 and at week 24. To convert the values for triglycerides to micromoles per liter, multiply by 0.01129. To convert the values for cholesterol to micromoles per liter, multiply by 0.02586. ApoB denotes apolipoprotein B, APOC3 apolipoprotein C3, GLP-1 glucagon-like peptide 1, HDL high-density lipoprotein, LDL low-density lipoprotein, and PCSK9 proprotein convertase subtilisin–kexin type 9 serine protease.
† Race was reported by the participants.
‡ Data from three participants with baseline values below the limit of quantification were removed from the analysis (ad hoc).
§ The remnant cholesterol level was calculated as the total cholesterol level minus the HDL cholesterol level minus the LDL cholesterol level.
¶ Participants were considered to have diabetes if they had a glycated hemoglobin level of 6.5% or higher or a fasting glucose level of 126 mg per deciliter or higher or if they had a medical history of diabetes or were receiving diabetic medications at baseline.

(95% CI, −53.4 to −35.0) with the 50-mg-half-yearly dose (P<0.001 for all comparisons). The effect on the fasting triglyceride level was evident at 4 weeks after the initiation of treatment (Table 2 and Fig. 1). Table S4 shows the adjusted P values that were calculated with the use of the Holm's method for multiplicity adjustment. Absolute triglyceride levels (in milligrams per deciliter) at each visit are provided in Table S5 and Figure S5.

The percent changes from baseline in APOC3, non-HDL cholesterol, apoB, LDL cholesterol, and HDL cholesterol (secondary end points) and remnant cholesterol and lipoprotein(a) (exploratory end points) are provided in Table S6. Commensurate reductions in the APOC3 level were observed

Table 2. Percent Change From Baseline in the Plasma Fasting Triglyceride Level at Weeks 24 and 48.*

Variable	Pooled Placebo (N=87)	Plozasiran, 10 mg Quarterly (N=67)	Plozasiran, 25 mg Quarterly (N=67)	Plozasiran, 50 mg Quarterly (N=66)	Plozasiran, 50 mg Half-Yearly (N=66)
Triglyceride level at baseline — mg/dl	237.2±76.2	253.2±81.4	234.1±72.7	250.3±81.3	248.0±80.6
Percent change at wk 24					
LS mean percent change ±SE — %	−1.7±3.1	−51.5±3.5	−57.7±3.5	−64.1±3.5	−45.9±3.5
95% CI — %	−7.8 to 4.3	−58.5 to −44.6	−64.6 to −50.8	−71.0 to −57.2	−52.8 to −39.0
Difference in percent change vs. placebo at wk 24					
LS mean difference — percentage points	NA	−49.8†	−56.0†	−62.4†	−44.2†
95% CI — percentage points		−59.0 to −40.6	−65.1 to −46.8	−71.5 to −53.2	−53.4 to −35.0
Percent change at wk 48					
LS mean percent change ±SE — %	1.7±4.4	−33.2±5.0	−42.8±4.9	−50.2±4.9	−55.0±4.9
95% CI	−6.8 to 10.3	−43.0 to −23.5	−52.4 to −33.3	−59.9 to −40.5	−64.7 to −45.3
Difference in percent change vs. placebo at wk 48					
LS mean difference — percentage points	NA	−34.9	−44.5	−51.9	−56.7
95% CI — percentage points		−47.9 to −22.0	−57.3 to −31.7	−64.8 to −38.9	−69.6 to −43.7

* Plus–minus values denote means ±SDs unless otherwise noted. The quarterly dose of plozasiran was given on day 1 and at week 12, and the half-yearly dose on day 1 and at week 24. The analysis was performed in the full analysis population. The 48-week trial period was completed by 78 participants in the placebo group; by 60, 64, and 61 participants in the quarterly-dose plozasiran groups (10 mg, 25 mg, and 50 mg, respectively); and by 61 participants in the 50-mg-half-yearly plozasiran group. To convert the values for triglycerides to micromoles per liter, multiply by 0.01129. LS denotes least squares, and NA not applicable.

† P<0.001 by the Wilcoxon rank-sum test.

with plozasiran, with differences, as compared with placebo, in the least-squares mean percent change from baseline of −57.3 percentage points (95% CI, −66.6 to −48.1) with the 10-mg-quarterly dose, −72.5 percentage points (95% CI, −81.7 to −63.3) with the 25-mg-quarterly dose, and −78.5 percentage points (95% CI, −87.8 to −69.3) with the 50-mg-quarterly dose, with strong, positive correlations with the changes in the triglyceride level (Pearson correlation coefficient, 0.85 [nonprespecified exploratory outcome]) (Fig. S6). We observed reductions in the non-HDL cholesterol level with plozasiran, with differences, as compared with placebo, in the least-squares mean percent change from baseline of −16.7 percentage points (95% CI, −24.3 to −9.0) with the 10-mg-quarterly dose, −17.5 percentage points (95% CI, −25.1 to −9.8) with the 25-mg-quarterly dose, and −24.2 percentage points (95% CI, −31.9 to −16.6) with the 50-mg-quarterly dose.

The reductions in the non-HDL cholesterol level were driven primarily by changes in the remnant cholesterol level (exploratory end point), with a difference in the least-squares mean percent change from baseline of −42.9 percentage points (95% CI, −56.8 to −29.0) with the 10-mg-quarterly dose, −48.9 percentage points (95% CI, −62.7 to −35.2) with the 25-mg-quarterly dose, and −47.5 percentage points (95% CI, −61.4 to −33.7) with the 50-mg-quarterly dose. The changes in the remnant cholesterol level showed strong correlations with the changes in the triglyceride level (Pearson correlation coefficient, 0.68 [nonprespecified exploratory end point]) (Fig. S7) and were accompanied by favorable changes in the LDL cholesterol level.

Reductions in apoB level were also observed with plozasiran. The difference (plozasiran vs. placebo) in the least-squares mean percent change from baseline in the apoB level was −10.3 percentage points (95% CI, −17.9 to −2.6) with the 10-mg-quarterly dose, −13.0 percentage points (95% CI, −20.6 to −5.4) with the 25-mg-quarterly dose, and −19.1 percentage points (95% CI, −26.7 to −11.5) with the 50-mg-quarterly dose. The difference (plozasiran vs. placebo) in the least-squares mean percent change from baseline in the LDL cholesterol level was −4.1 percentage points (95% CI, −13.9 to 5.7) with the 10-mg-quarterly dose, −2.7 percentage points (95% CI, −12.4 to 7.0) with the 25-mg-quarterly dose, and −13.6 percentage points (95% CI, −23.3 to −3.8) with the 50-mg-quarterly dose. We also observed increases in the HDL cholesterol level with plozasiran (Fig. 1).

In a prespecified subgroup analysis, we found that participants in the highest tertile of triglyceride level at baseline had a modest increase in the LDL cholesterol level at the 10-mg and 25-mg doses, but they also had the highest baseline levels of non-HDL cholesterol and remnant cholesterol, along with greater absolute reductions in both of these measures as compared with those in the other tertiles of triglyceride level. The reduction in the apoB level was similar among the participants in the highest tertile of triglyceride level and those in the other tertiles (Table S7).

At week 24, reductions in the lipoprotein(a) level, an exploratory end point, were observed with plozasiran, with differences, as compared with placebo, in least-squares mean percent change from baseline of −23.8 percentage points (95% CI, −134.4 to 86.8) with the 10-mg-quarterly dose, −23.8 percentage points (95% CI, −134.1 to 86.4) with the 25-mg-quarterly dose, and −9.0 percentage points (95% CI, −119.4 to 101.4) with the 50-mg-quarterly dose. No apparent meaningful differences in the change in the high-sensitivity C-reactive protein level were noted between each active-dose group and the placebo group (Fig. S8).

The fasting triglyceride level had normalized (i.e., <150 milligrams per deciliter) at week 24 in most participants in the active-dose groups (in 48 [79%] in the 10-mg-quarterly group, in 58 [92%] in the 25-mg-quarterly group, in 57 [92%] in the 50-mg-quarterly group, and in 47 [77%] in the 50-mg-half-yearly group) (Fig. 2). The use of concomitant medications seemed to be consistent across the trial groups and with the previous medications that had been used; the medications used had generally not changed during the conduct of the trial (Table S8).

EFFICACY ANALYSIS AT WEEK 48

Overall, 78 participants in the placebo group, 60 in the 10-mg-quarterly group, 64 in the 25-mg-quarterly group, 61 in the 50-mg-quarterly group, and 61 in the 50-mg-half-yearly group completed 48 weeks of trial. The effects of plozasiran remained evident at week 48 (Table 2 and Fig. 1), 36 weeks after the last dose had been received.

SAFETY AND ADVERSE EVENTS

The overall incidence of adverse events and discontinuations that occurred during the 48-week

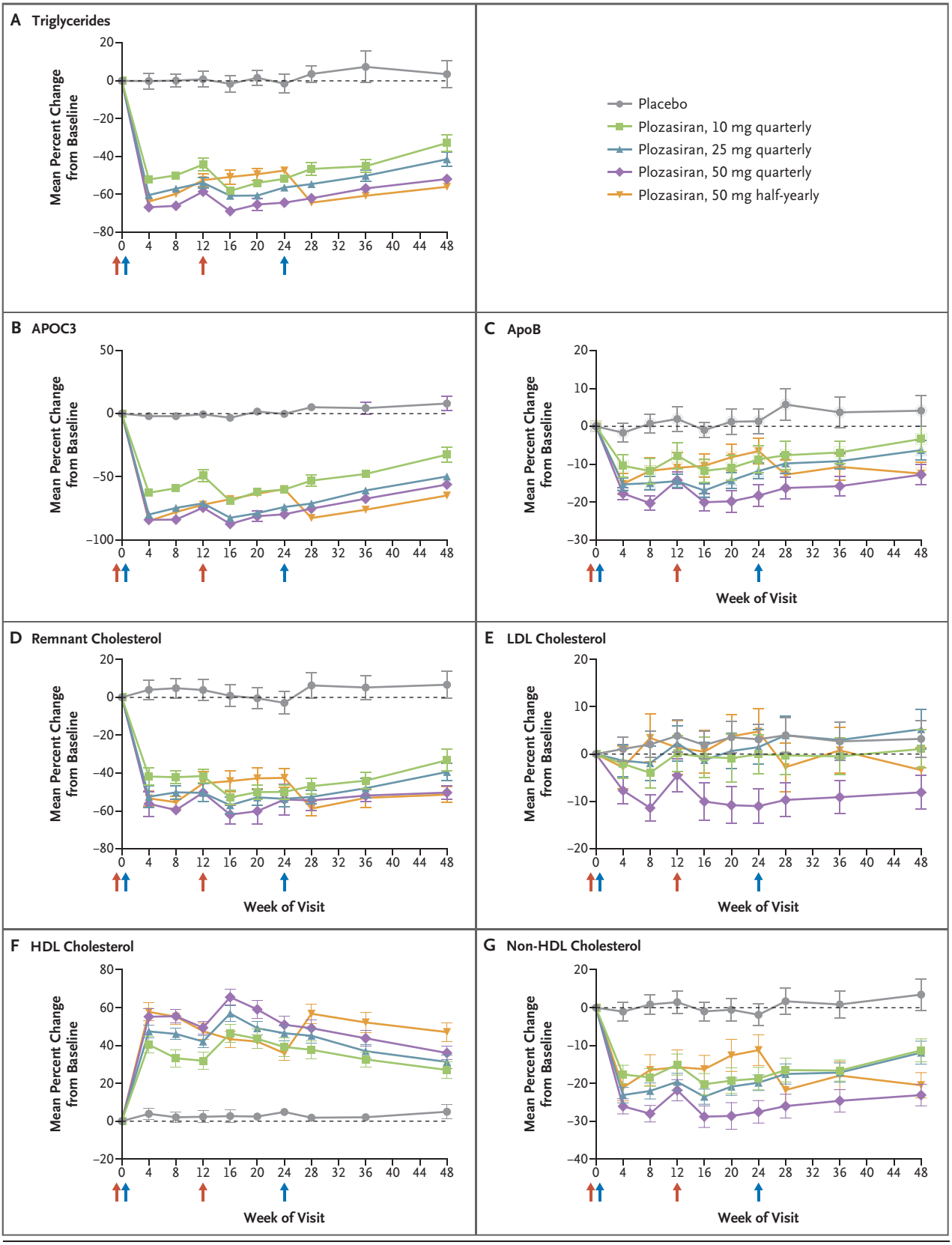

Figure 1 (facing page). Temporal Relationships of Changes in Laboratory Measures.

The remnant cholesterol level was calculated as the total cholesterol level minus the high-density lipoprotein (HDL) cholesterol level minus the low-density lipoprotein (LDL) cholesterol level (LDL cholesterol as measured by the ultracentrifuge method). In an ad hoc analysis of the apolipoprotein C3 (APOC3) level, data from three participants with baseline values below the limit of quantification were removed. In the analyses of lipids and other clinical laboratory measures, if a value that was below the limit of quantification (BLOQ) was reported, half the lower-limit-of-quantification (LLOQ) value was used (e.g., if the laboratory returns a BLOQ value of "<0.94 mg per deciliter," where 0.94 is the lower-limit-of-quantification value, then 0.47 is used in the analysis). The arrows represent the timing of the dose: the quarterly dose (red arrows) was given on day 1 and at week 12, and the half-yearly dose (blue arrows) on day 1 and at week 24. I bars indicate the standard error. ApoB denotes apolipoprotein B.

trial period appeared to be similar in the active-dose groups and the placebo group (Table 3). The adverse events that occurred in five or more participants in any trial group were coronavirus disease 2019, worsening glycemic control, upper respiratory tract infection, urinary tract infection, headache, and bronchitis. No meaningful changes in the mean platelet count or aminotransferase levels were observed (Table 3). Worsening glycemic control occurred in 10% of the participants in the placebo group, 12% of those in the 10-mg-quarterly group, 7% of those in the 25-mg-quarterly group, 20% of those in the 50-mg-quarterly group, and 21% of those in the 50-mg-half-yearly group (Table 3). No change in the homeostasis model assessment of insulin resistance was observed for any dose of plozasiran or placebo, a finding indicating that insulin sensitivity had not changed (Fig. S9).

In a post hoc analysis, we assessed the effects of plozasiran and placebo in participants meeting American Diabetes Association criteria for normoglycemia (glycated hemoglobin level, <5.7%), prediabetes (glycated hemoglobin level, 5.7 to <6.5%), and glycated hemoglobin level in the diabetic range (≥6.5% [in this analysis, the data from participants with prediabetes and from those with normoglycemia were combined, unless they were receiving medications for diabetes]) at trial entry. The mean glycated hemoglobin levels over time are provided in Table 3. The numbers of participants with glycated hemoglobin values in the diabetic range and who had a new antidiabetic medication added during the 48-week trial period are provided in Table S9, and the degree of heterogeneity in the measurements of the glycated hemoglobin level in these trial groups is shown in Figure S10. At baseline, 10 of 90 participants (11%) with normoglycemia, 40 of 117 (34%) with prediabetes, and 131 of 144 (91%) with a glycated hemoglobin level in the diabetic range were receiving antidiabetic therapy. Glycated hemoglobin levels showed variability across plozasiran-dose cohorts during the trial. With respect to the reported incidence of worsened diabetic control, excursions of the glycated hemoglobin level into the diabetic range, or the addition of new antidiabetic therapies, participants in the placebo group and those in the 10-mg- and 25-mg-quarterly groups had similar findings regardless of baseline glycemic status, whereas those in the 50-mg groups (quarterly and half-yearly doses) had more adverse events related to glycemic control, excursions into the diabetic range for glycated hemoglobin, and receipt of additional therapies (Table 3). Participants who had diabetes at baseline generally showed more variability in glycated hemoglobin levels at baseline and during the 48-week trial period than those without diabetes.

Serious adverse events are shown in Table 3. Four deaths occurred during the trial, all of which were determined by the trial investigator to be unrelated to plozasiran or placebo. No participants receiving a quarterly dose of plozasiran had increased levels of alanine aminotransferase or aspartate aminotransferase.

DISCUSSION

In this trial involving participants with mixed hyperlipidemia, we found that plozasiran significantly lowered triglyceride levels as compared with placebo at 24 weeks. Commensurate reductions in the levels of APOC3, non-HDL cholesterol, and remnant cholesterol were observed in the plozasiran groups as compared with the placebo group. At week 24, the fasting triglyceride levels were below 150 mg per deciliter in most participants in the plozasiran groups. The reductions in apoB and non-HDL cholesterol levels should be interpreted in light of the results of recent studies supporting non-HDL cholesterol and apoB levels as predictors of the risk of coronary artery

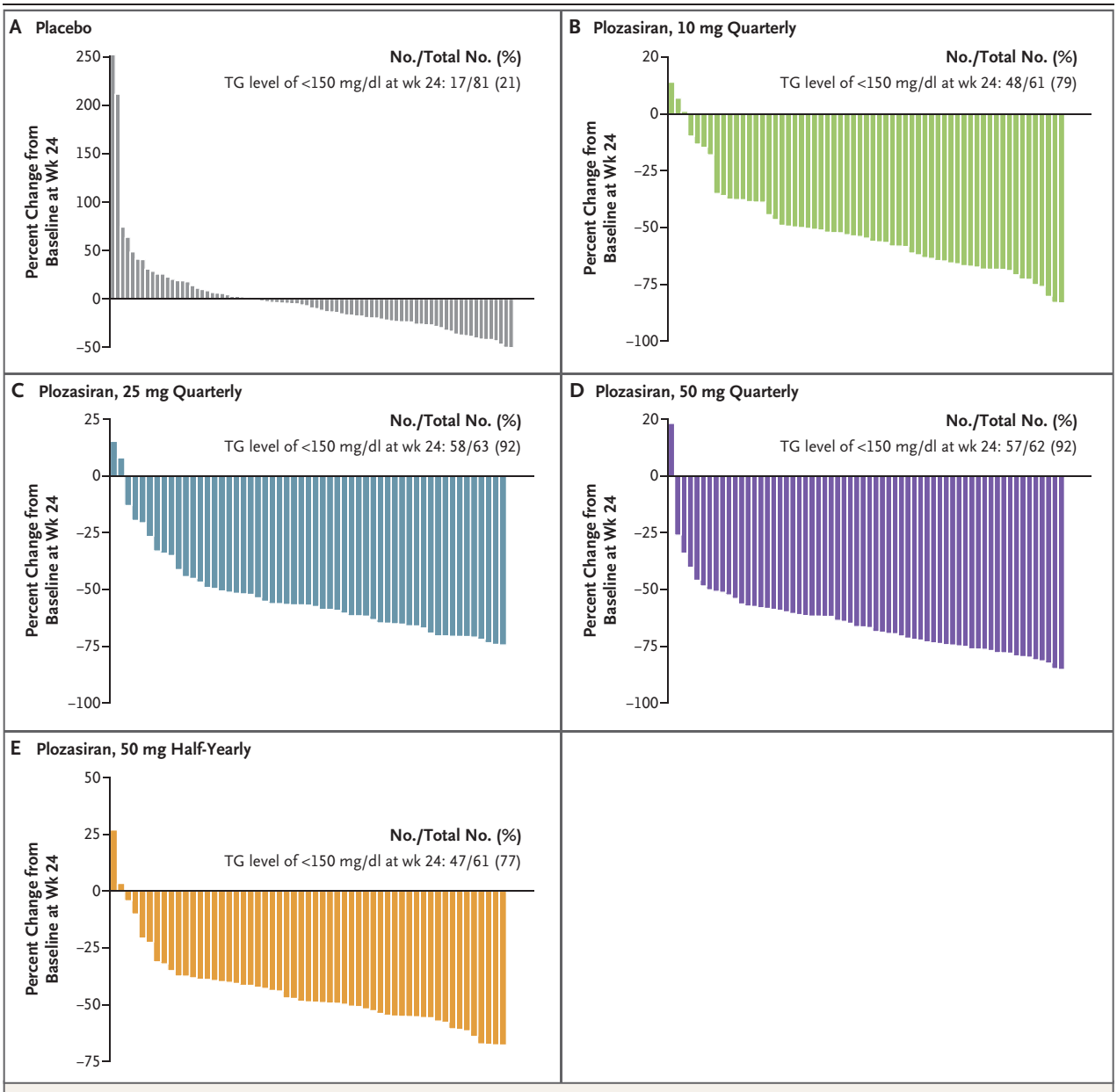

Figure 2. Change from Baseline in the Fasting Triglyceride (TG) Level.

Shown is the percent change from baseline in the fasting TG level at week 24 and the proportion of participants in whom the TG level had normalized (i.e., <150 milligrams per deciliter) at week 24. The quarterly dose of plozasiran was given on day 1 and at week 12, and the half-yearly dose on day 1 and at week 24. Each bar represents an individual patient. To convert the values for triglycerides to micromoles per liter, multiply by 0.01129.

disease.[32,33] Historically, reductions in both non-HDL cholesterol and apoB, effected through decreases in the LDL cholesterol level, have translated into clinical benefit. In contrast, our findings indicate that the reductions in the non-HDL cholesterol level that were observed in the MUIR trial (involving participants who had been treated with statins and other lipid-lowering therapies) were brought about by reductions in the level of cholesterol remnants rather than reductions in the LDL cholesterol level. The effects of plozasiran were durable at 24 weeks, with reductions in APOC3 and triglyceride levels persisting 36 weeks after receipt of the last dose.

Table 3. Safety Results.*

Variable	Pooled Placebo (N=87)	Plozasiran, 10-mg Quarterly (N=67)	Plozasiran, 25-mg Quarterly (N=67)	Plozasiran, 50-mg Quarterly (N=66)	Plozasiran, 50-mg Half-Yearly (N=66)
Any adverse event	55 (63)	46 (69)	45 (67)	47 (71)	49 (74)
Adverse events affecting ≥5 participants in any group					
Covid-19	11 (13)	7 (10)	10 (15)	8 (12)	5 (8)
Upper respiratory tract infection	7 (8)	3 (4)	7 (10)	1 (2)	9 (14)
Headache	3 (3)	1 (1)	2 (3)	4 (6)	5 (8)
Urinary tract infection	6 (7)	3 (4)	4 (6)	4 (6)	0
Worsening glycemic control†	9 (10)	8 (12)	5 (7)	13 (20)	14 (21)
Bronchitis	1 (1)	4 (6)	2 (3)	2 (3)	5 (8)
Any serious adverse event — no. (%)	5 (6)	2 (3)	5 (7)	7 (11)	5 (8)
Adverse event leading to interruption or discontinuation of plozasiran or placebo or to withdrawal from the trial — no. (%)	2 (2)	0	0	1 (2)	2 (3)
Adverse event associated with death‡	0	0	1 (1)	2 (3)	1 (2)
Glycated hemoglobin — %§					
All participants					
Mean at baseline	6.36±1.1	6.30±0.9	6.43±1.1	6.58±1.1	6.45±1.1
Mean at wk 24	6.31±1.1	6.47±1.1	6.68±1.3	6.92±1.6	6.57±1.2
Mean at wk 48	6.24±1.0	6.49±1.1	6.53±1.1	6.77±1.2	6.44±1.1
Participants without diabetes					
Mean at baseline	5.60±0.4	5.66±0.4	5.63±0.3	5.50±0.4	5.60±0.3
Mean at wk 24	5.59±0.4	5.68±0.4	5.77±0.5	5.54±0.5	5.59±0.3
Mean at wk 48	5.58±0.3	5.74±0.5	5.78±0.5	5.63±0.6	5.59±0.3
Participants with diabetes					
Mean at baseline	6.89±1.0	6.75±0.9	6.95±1.1	7.08±1.0	7.05±1.0
Mean at wk 24	6.86±1.2	6.95±1.1	7.28±1.4	7.55±1.5	7.20±1.2
Mean at wk 48	6.72±1.1	6.98±1.1	6.97±1.1	7.30±1.1	6.99±1.1
Alanine aminotransferase — U/liter					
Mean at baseline	24.1±13.2	22.8±10.4	25.5±13.4	25.5±13.5	26.4±15.3
Mean change from baseline at wk 24	−1.0±7.3	2.6±11.7	4.4±8.5	3.1±11.1	0.7±14.3
Mean change from baseline at wk 48	−0.5±9.0	−0.1±12.2	0.6±9.9	−3.3±9.3	1.7±15.1
Aspartate aminotransferase — U/liter					
Mean at baseline	18.3±6.5	19.7±11.7	19.6±8.4	20.7±9.6	19.7±8.1
Mean change from baseline at wk 24	0.2±4.6	0.0±12.4	1.7±4.6	−0.2±8.4	0.4±7.7
Mean change from baseline at wk 48	1.6±6.5	0.2±13.7	1.5±6.8	−1.8±6.4	2.5±11.2
Platelet count — $\times 10^{-9}$/liter					
Mean at baseline	254.4±63.6	250.7±68.4	244.0±65.7	245.8±58.5	241.3±68.5
Mean change from baseline at wk 24	9.8±43.7	4.1±51.3	6.4±41.1	10.2±38.0	12.0±53.0
Mean change from baseline at wk 48	2.9±33.2	−2.6±38.0	13.8±52.2	9.6±35.6	9.7±37.8

* Plus–minus values denote means ±SDs. The quarterly dose of plozasiran was given on day 1 and at week 12, and the half-yearly dose on day 1 and at week 24. To convert the values for triglycerides to micromoles per liter, multiply by 0.01129. To convert the values for cholesterol to micromoles per liter, multiply by 0.02586. Covid-19 denotes coronavirus disease 2019.

† Worsening glycemic control was defined according to multiple measures of glycemic control, including, but not limited to, glycated hemoglobin, new-onset diabetes mellitus, type 2 diabetes mellitus, type 1 diabetes mellitus, hyperglycemia, and insulin resistance.

‡ There were four serious adverse events with the outcome of death reported: one death was due to pneumonia in a participant in the 25-mg-quarterly group, one death was due to septic shock in a participant in the 50-mg-quarterly group, one death by suicide was due to a psychiatric disorder in a participant in the 50-mg-quarterly group, and one death from aortic aneurysm rupture was due to a vascular disorder in a participant in the 50-mg-half-yearly group. All deaths were determined by the investigator and confirmed by the data safety committee to be not related to plozasiran or placebo.

§ Participants were considered to have diabetes if they had a glycated hemoglobin level of 6.5% or higher or a fasting glucose level of 126 mg per deciliter or higher or if they had a medical history of diabetes or were receiving diabetic medications at baseline.

No changes in mean platelet counts were observed, a finding consistent with those in previous reports showing no association with thrombocytopenia, an adverse effect that has been reported for antisense oligonucleotide drugs.[34] In terms of safety, plozasiran generally performed similarly to placebo except in relation to glycemia in the quarterly and half-yearly 50-mg dose group, largely because of the effects in the subgroup of participants with diabetes.[35]

The increases in the glycated hemoglobin level at the quarterly and half-yearly 50-mg dose may be related to postprandial glycemia, which results from increased substrate delivery to the liver. Enhanced lipoprotein lipase activity on chylomicrons and remnant cholesterol would be predicted to drive gluconeogenesis in the liver. Volanesorsen, an APOC3-targeting antisense oligonucleotide that had previously shown worsening glycemic control in participants with familial chylomicronemia syndrome, showed no long-term deleterious effects on glucose homeostasis over the course of 5 years.[36] Similar findings of worsening glycemic control have been described with other lipid-lowering treatments, including statins, and the condition has proved to be manageable and offset by clinical benefit.[37-40] Given the glycemic findings and the relatively small incremental responses shown for the primary and secondary efficacy end points in both the MUIR trial and SHASTA-2 (Study to Evaluate ARO-APOC3 in Adults with Severe Hypertriglyceridemia) with the 50-mg dose, the 25-mg-quarterly dose of plozasiran was selected for phase 3 trials in the populations with mixed hyperlipidemia and with severe hypertriglyceridemia.

Although recent mendelian randomization studies suggest a causal relationship between triglyceride-rich lipoprotein and remnant cholesterol levels and atherosclerotic cardiovascular disease, large-scale clinical trials of fibrates have yet to show convincingly that a reduction in the triglyceride-rich lipoprotein level, in combination with the effects of statin therapy, can lead to improvements in clinical outcomes.[14,16] Genetic modeling studies published in the past several years have estimated that reductions in the remnant cholesterol level of 13 to 32 mg per deciliter could lead to 20% reductions in the incidence of recurrent major adverse cardiovascular events[10] and that each 1-SD reduction in the APOC3 level would be associated with a nearly 15% reduction in the lifetime risk of coronary artery disease (odds ratio, 0.86; 95% CI, 0.80 to 0.93).[14,41] No currently approved pharmacologic treatments can consistently achieve this magnitude of reduction. A phase 3 trial of the effect of plozasiran on the risk of atherosclerotic cardiovascular disease is therefore warranted.[10,14]

Rosenson et al.[42] now report in the *Journal* the results of a clinical trial (ARCHES-2) of the effect of zodasiran on an identical patient population. Similar to plozasiran, zodasiran is a hepatocyte-targeted small interfering RNA therapy that inhibits production of angiopoietin-like 3 (ANGPTL3), another genetically validated protein that affects the metabolism of triglyceride-containing particles.[43] Although both APOC3 and ANGPTL3 are genetically validated targets, they have different biologic effects: therapies targeting APOC3 have lowered triglyceride levels in patients with familial chylomicronemia syndrome, who lack lipoprotein lipase activity, whereas targeting ANGPTL3 in such patients was not effective.[22,44] Therapies targeting ANGPTL3 have been shown to reduce the LDL cholesterol level in patients with homozygous familial hypercholesterolemia, who lack any LDL receptors.[45] Both plozasiran and zodasiran reduce triglyceride levels to a similar degree in patients with mixed hyperlipidemia, but their effects on other lipoprotein particles, such as HDL cholesterol, appear to differ. The results of a placebo-controlled trial that was planned to investigate cardiovascular outcomes with these two drugs and designed to compare each drug individually against placebo will therefore be of interest. Such a trial, however, would not be designed to directly compare the two agents.

In this randomized, controlled trial involving participants with mixed hyperlipidemia, plozasiran, as compared with placebo, significantly reduced triglyceride levels at 24 weeks. This trial has helped in laying the groundwork for a more extensive outcomes trial, which would more rigorously test whether plozasiran reduces levels of non-HDL cholesterol and cholesterol remnants and the risk of atherosclerotic cardiovascular disease.

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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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