ORIGINAL ARTICLE

ANGPTL4 Inhibition in Adults with Elevated Triglyceride Levels

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ABSTRACT

BACKGROUND

Angiopoietin-like protein 4 (ANGPTL4) inhibits lipoprotein lipase and regulates triglyceride-rich lipoprotein metabolism. MAR001 is a monoclonal antibody against ANGPTL4 that is being evaluated for lowering triglyceride levels.

METHODS

We conducted a two-part, phase 2b, double-blind, randomized, placebo-controlled trial. In part A, the focus of this report, we enrolled adults who had a nonfasting triglyceride level of at least 175 mg per deciliter and a remnant cholesterol level of at least 35 mg per deciliter at initial screening, followed by a fasting triglyceride level of at least 150 mg per deciliter and a remnant cholesterol level of at least 30 mg per deciliter on confirmatory screening. Participants were randomly assigned in a 1:1:1:1 ratio to receive MAR001 at a dose of 300, 450, or 900 mg or matching placebo subcutaneously every 4 weeks for 24 weeks. The primary end point was the percent change from baseline in the fasting triglyceride level at week 12, reported as the difference between each MAR001 dose group and the placebo group (placebo-adjusted change).

RESULTS

A total of 236 participants were enrolled in the trial, with 177 assigned to receive MAR001 and 59 to receive placebo; a total of 235 participants received at least one dose of MAR001 or placebo and were included in the primary efficacy analyses. The mean age of the participants was 60.4 years, and 39% were women. The median triglyceride level at baseline was 249.5 mg per deciliter (interquartile range, 210.0 to 313.0). At week 12, in an intention-to-treat analysis, the placebo-adjusted least-squares mean percent changes in the fasting triglyceride level were −39.1 percentage points, −40.5 percentage points, and −45.3 percentage points for the 300-mg, 450-mg, and 900-mg doses, respectively ($P<0.001$ for all comparisons). Adverse events occurred in 123 of 177 participants (69%) in the pooled MAR001 group and in 45 of 58 participants (78%) in the placebo group.

CONCLUSIONS

Inhibition of ANGPTL4 with MAR001 significantly reduced fasting triglyceride levels at 12 weeks. (Funded by Marea Therapeutics; TYDAL-TIMI 78 ClinicalTrials.gov number, NCT07028749.)

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*A list of the TYDAL-TIMI 78 investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Elevated triglyceride levels are common in persons with obesity, type 2 diabetes, and metabolic syndrome.[1,2] Severe forms of hypertriglyceridemia are associated with an increased risk of acute pancreatitis.[3] Although therapeutic options for hypertriglyceridemia have expanded, the optimal pathway by which to achieve substantial and sustained triglyceride lowering and to reduce the risk of potential hypertriglyceridemia-associated complications remains undefined.[3]

Lipoprotein lipase is the principal enzyme responsible for hydrolyzing triglycerides in circulating triglyceride-rich lipoproteins, and its activity is regulated by angiopoietin-like proteins, including angiopoietin-like protein 4 (ANGPTL4), ANGPTL3, ANGPTL8, and apolipoprotein C-III.[4] Drugs that target ANGPTL3 and apolipoprotein C-III have been shown to reduce levels of triglycerides.[5-8] ANGPTL4 is an endogenous inhibitor of lipoprotein lipase whose expression is increased during fasting and in response to fatty acids.[9] Inhibition of ANGPTL4 therefore represents a potential strategy to enhance lipoprotein lipase activity and promote the clearance and tissue uptake of circulating triglyceride-rich lipoproteins.

Carriers of *ANGPTL4* loss-of-function variants have lower triglyceride levels than noncarriers, as well as reduced risks of diabetes mellitus and coronary disease.[10-12] Preclinical studies have shown that ANGPTL4 inhibition lowers triglyceride levels in mice and nonhuman primates.[13] MAR001 is a humanized monoclonal antibody directed against ANGPTL4. Early clinical studies of MAR001 showed reductions in triglyceride levels, which provided initial proof of mechanism in humans.[14] We therefore conducted a dose-ranging trial of MAR001 in adults with elevated triglyceride levels.

METHODS

TRIAL DESIGN AND OVERSIGHT

TYDAL-TIMI 78 is a phase 2b, double-blind, dose-ranging, randomized, placebo-controlled trial of MAR001. The trial has two parts. Part A enrolled participants with serum triglyceride levels of 150 to 879 mg per deciliter (1.69 to 9.92 mmol per liter) and elevated remnant cholesterol levels. Part B will enroll participants with severe hypertriglyceridemia (nonfasting triglyceride level of ≥500 mg per deciliter [5.64 mmol per liter] and fasting triglyceride level of ≥450 mg per deciliter [5.08 mmol per liter]).

The trial was designed by the Thrombolysis in Myocardial Infarction (TIMI) Study Group at Brigham and Women's Hospital and Harvard Medical School in collaboration with the sponsor, Marea Therapeutics (see the Supplementary Appendix, available with the full text of this article at NEJM.org). Data were analyzed by the TIMI Study Group with the use of a complete, independently held database. The trial protocol and amendments were approved by the relevant ethics committees and are available at NEJM.org. All the participants provided written informed consent. An independent data monitoring committee reviewed unblinded safety data. The first author wrote the first draft of the manuscript. All the coauthors participated in subsequent revisions. The academic authors made the decision to submit the manuscript for publication, and the authors who had access to the data (see the Supplementary Appendix) vouch for the accuracy and completeness of the data. All the authors vouch for the fidelity of the trial to the protocol.

TRIAL POPULATION

Eligible participants in part A were 18 to 75 years of age with a nonfasting triglyceride level of at least 175 mg per deciliter (1.98 mmol per liter) and a remnant cholesterol level of at least 35 mg per deciliter (0.91 mmol per liter) at the first screening visit and a fasting triglyceride level of at least 150 mg per deciliter (1.69 mmol per liter) and a remnant cholesterol level of at least 30 mg per deciliter (0.78 mmol per liter) at a second screening visit conducted at a central laboratory. Key exclusion criteria were a triglyceride level of at least 880 mg per deciliter (9.94 mmol per liter), poorly controlled type 2 diabetes (glycated hemoglobin level, ≥9.0%), severe hepatic or renal impairment, recent acute coronary syndrome or coronary revascularization, or the use of another investigational therapy. Full eligibility criteria are provided in the Supplementary Appendix.

RANDOMIZATION AND BLINDING

Eligible participants in part A were randomly assigned in a 1:1:1 ratio to the 300-mg, 450-mg, or 900-mg dose group and then in a 3:1 ratio to

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receive MAR001 or matching placebo. Participants assigned to the placebo group received matching-volume placebo corresponding to each MAR001 dose. Investigators were unaware of the assigned agent (active drug vs. placebo) but were aware of the dose level. Randomization was performed by means of a central computerized system, with stratification according to fasting triglyceride level at screening (<200 mg per deciliter [2.26 mmol per liter], 200 to <500 mg per deciliter, and ≥500 mg per deciliter).

TRIAL PROCEDURES

After a screening period of up to 8 weeks, eligible participants underwent randomization on day 1 and received subcutaneous injections of MAR001 or placebo every 4 weeks for 24 weeks. Lipid assessments were obtained at prespecified visits through week 24 and measured at a central laboratory, including the measurement of nonfasting lipid levels at week 16. Remnant cholesterol was calculated as total cholesterol minus high-density lipoprotein (HDL) cholesterol minus directly measured low-density lipoprotein (LDL) cholesterol (additional information is provided in the Supplementary Appendix). Safety assessments were performed at each trial visit.

EFFICACY AND SAFETY ASSESSMENTS

The primary efficacy end point was the percent change from baseline in the fasting triglyceride level at week 12, reported as the difference between each MAR001 dose group and the placebo group (placebo-adjusted change). Key secondary end points included a fasting triglyceride level of less than 150 mg per deciliter at week 12 among participants with a baseline value of at least 150 mg per deciliter, the percent change from baseline to week 12 in the fasting remnant cholesterol level, the percent change from baseline to week 16 in the nonfasting triglyceride level, and, among participants with a baseline triglyceride level of at least 300 mg per deciliter (3.39 mmol per liter), the percent change from baseline to week 12 in the fasting triglyceride level. For efficacy analyses, values at baseline, week 12, and week 24 were defined as the averages of two fasting lipid measurements obtained at screening visit 2 and day 1, or week 10 and 12, or week 22 and 24, respectively. A list of prespecified exploratory end points is provided in the Supplementary Appendix. Safety was assessed through the reporting of adverse events that occurred during the treatment period and through the collection of safety laboratory data assessed by the central laboratory.

STATISTICAL ANALYSIS

The planned sample size was based on a treatment difference of 30 percentage points in the mean percent change from baseline in the fasting triglyceride level between each active-dose group and the placebo group. Assuming a 35% reduction with active treatment as compared with a 5% reduction with placebo and a standard deviation of 40%, we calculated that a sample size of 216 participants would provide the trial with more than 90% power to detect a difference at each active dose as compared with placebo at a two-sided alpha level of 0.05.

The efficacy population included all the participants who had undergone randomization and received at least one dose of MAR001 or placebo. The primary efficacy analysis used a prespecified on-treatment approach, with assessments performed while participants continued to receive MAR001 or placebo. Results of a sensitivity analysis of the primary end point in the intention-to-treat population are also reported. The safety population included all the participants who had received at least one dose of MAR001 or placebo and was analyzed according to the agent received.

The primary and secondary end points were analyzed with the use of a mixed model for repeated measures including trial group, baseline lipid value, visit, and trial-group-by-visit interaction without imputation for missing data. Placebo was pooled across the three matching-volume placebo groups, and each MAR001 dose was compared with pooled placebo. Least-squares mean percent changes from baseline and between-group treatment differences were estimated with corresponding 95% confidence intervals and two-sided P values. Sensitivity analyses were conducted for missing data with multiple imputation.

Multiplicity across the primary and secondary end points was controlled with the use of a prespecified hierarchical fixed-sequence testing procedure (additional information is provided in the Supplementary Appendix). All analyses were conducted with the use of SAS software, version 9.4 (SAS Institute).

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RESULTS

PARTICIPANTS

From July 2025 through January 2026, a total of 236 participants were enrolled in part A, with 177 participants assigned to receive MAR001 and 59 assigned to receive placebo across 48 participating centers in the United States, Canada, Australia, and New Zealand (Fig. S1 and Table S1 in the Supplementary Appendix). Of these 236 participants, all but 1 (in the placebo group) received at least one dose of the assigned agent and were included in the primary efficacy analyses. The baseline characteristics of the participants are shown in Table 1. The mean age of the participants was 60.4 years, and 39% were women. The median fasting triglyceride level at baseline was 249.5 mg per deciliter (interquartile range, 210.0 to 313.0 [2.82 mmol per liter; interquartile range, 2.37 to 3.53]).

EFFICACY OF ANGPTL4 INHIBITION WITH MAR001

At week 12, the least-squares mean percent changes from baseline in the fasting triglyceride level were −33.9%, −35.7%, and −40.3% for MAR001 doses of 300 mg, 450 mg, and 900 mg, respectively, as compared with 5.2% for placebo when the trial regimen was not discontinued early (Fig. 1). In the primary efficacy analysis, the corresponding placebo-adjusted least-squares mean percent changes were −39.1 percentage points (95% confidence interval [CI], −46.8 to −31.5), −40.9 percentage points (95% CI, −48.7 to −33.1), and −45.5 percentage points (95% CI, −53.2 to −37.8) (P<0.001 for all comparisons) (Table 2). In the intention-to-treat analysis, the placebo-adjusted percent changes in the fasting triglyceride level were −39.1 percentage points, −40.5 percentage points, and −45.3 percentage points for the 300-mg, 450-mg, and 900-mg doses, respectively (P<0.001 for all comparisons). The effect of MAR001 as compared with placebo on serum triglyceride levels through week 24 was −32.0 percentage points (95% CI, −40.9 to −23.0), −42.1 percentage points (95% CI, −51.2 to −33.1), and −42.8 percentage points (95% CI, −51.7 to −33.9) for the 300-mg, 450-mg, and 900-mg doses, respectively. The results of sensitivity analyses with multiple imputation are provided in Table S2.

Among participants with a triglyceride level of at least 150 mg per deciliter at baseline, a triglyceride level of less than 150 mg per deciliter was observed in 31%, 35%, and 52% of the participants receiving MAR001 at a dose of 300 mg, 450 mg, and 900 mg, respectively. In comparison, a triglyceride level of less than 150 mg per deciliter was observed in only 3% of the participants receiving placebo (P<0.001 for all comparisons) (Fig. S2).

The placebo-adjusted percent changes from baseline in the fasting remnant cholesterol level at week 12 were −37.3 percentage points (95% CI, −45.0 to −29.5), −39.1 percentage points (95% CI, −47.0 to −31.2), and −40.8 percentage points (95% CI, −48.6 to −33.0) for the doses of 300 mg, 450 mg, and 900 mg, respectively (P<0.001 for all comparisons) (Table 2). At week 16, the placebo-adjusted percent changes from baseline in the nonfasting triglyceride level were −33.4 percentage points (95% CI, −46.6 to −20.2), −44.5 percentage points (95% CI, −57.8 to −31.1), and −48.6 percentage points (95% CI, −61.7 to −35.5) for MAR001 at a dose of 300 mg, 450 mg, and 900 mg, respectively (P<0.001 for all comparisons) (Table 2).

Among 73 participants with a baseline triglyceride level of at least 300 mg per deciliter (median, 351.5 mg per deciliter; interquartile range, 318.5 to 461.5 [3.97 mmol per liter; interquartile range, 3.60 to 5.21]), the placebo-adjusted percent changes in the fasting triglyceride level at week 12 were −52.8 percentage points (95% CI, −68.9 to −36.7) with 300-mg MAR001, −53.7 percentage points (95% CI, −70.2 to −37.1) with 450-mg MAR001, and −57.2 percentage points (95% CI, −71.9 to −42.5) with 900-mg MAR001 (P<0.001 for all comparisons). Changes from baseline to week 12 in levels of non-HDL cholesterol, HDL cholesterol, LDL cholesterol, and apolipoprotein B are summarized in Table 3.

PRESPECIFIED SUBGROUPS AND EXPLORATORY ASSESSMENTS

The effects of MAR001 on lowering fasting triglyceride levels appeared to be greater for participants with higher baseline levels than for those with lower baseline levels (Fig. S3 and Table S3). The efficacy of MAR001 otherwise appeared to be broadly consistent across prespecified subgroups (Figs. S4 and S5).

The effects of MAR001 on markers of glucose homeostasis (including fasting glucose level, fasting insulin level, glycated hemoglobin level, and homeostasis model assessment for insulin resistance [HOMA-IR] index) and on the level of

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high-sensitivity C-reactive protein are shown in Tables S4 and S5, respectively. Total ANGPTL4 levels (unbound and bound) suggestive of target engagement and ANGPTL4 clearance due to MAR001–ANGPTL4 complex formation are shown in Figure S6.

SAFETY

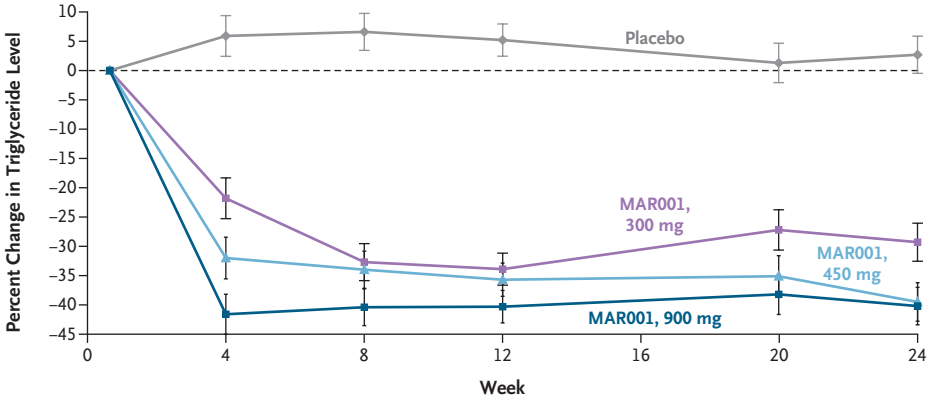
Adverse events through week 24 occurred in 123 of 177 participants (69%) receiving MAR001 and in 45 of 58 participants (78%) receiving placebo (Table 4). Serious adverse events occurred in 5 of 177 participants (3%) receiving MAR001 and in

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	MAR001, 300 mg (N=59)	MAR001, 450 mg (N=58)	MAR001, 900 mg (N=60)	Placebo (N=58)
Age — yr	59.6±11.9	59.4±11.0	61.2±10.0	61.3±8.2
Female sex — no. (%)	19 (32)	26 (45)	21 (35)	26 (45)
Race or ethnic group — no./total no. (%)†				
White	50/58 (86)	45/58 (78)	54/60 (90)	47/57 (82)
Asian	3/58 (5)	8/58 (14)	2/60 (3)	3/57 (5)
Black or African American	3/58 (5)	0/58	1/60 (2)	1/57 (2)
Native Hawaiian or other Pacific Islander	1/58 (2)	2/58 (3)	3/60 (5)	3/57 (5)
Multiple	0/58	1/58 (2)	0/60	2/57 (4)
Other	1/58 (2)	2/58 (3)	0/60	1/57 (2)
Geographic location of enrollment — no. (%)				
United States	31 (53)	31 (53)	34 (57)	23 (40)
Australia, Canada, or New Zealand	28 (47)	27 (47)	26 (43)	35 (60)
Median body-mass index (IQR)‡	33.1 (28.4–37.0)	32.1 (28.6–35.4)	32.1 (28.6–36.6)	30.8 (28.8–35.4)
Medical history				
Type 2 diabetes mellitus — no. (%)	29 (49)	21 (36)	24 (40)	29 (50)
Hypertension — no. (%)	33 (56)	43 (74)	39 (65)	43 (74)
Coronary artery disease — no. (%)	7 (12)	18 (31)	15 (25)	20 (34)
Previous myocardial infarction — no. (%)	3 (5)	8 (14)	3 (5)	8 (14)
Current smoker — no./total no. (%)	5/59 (8)	4/58 (7)	6/59 (10)	6/58 (10)
Former smoker — no./total no. (%)	15/59 (25)	19/58 (33)	22/59 (37)	19/58 (33)
Lipid-lowering therapy — no. (%)				
Statin	43 (73)	46 (79)	38 (63)	43 (74)
High-intensity statin	22 (37)	23 (40)	20 (33)	23 (40)
Fibrate	7 (12)	5 (9)	11 (18)	11 (19)
Median lipid levels (IQR) — mg/dl				
Triglycerides	268.0 (213.0–301.5)	228.0 (198.5–313.0)	264.3 (224.0–324.5)	241.8 (211.5–319.0)
Remnant cholesterol	45.5 (37.0–55.0)	41.0 (31.5–57.5)	44.0 (36.8–58.3)	45.0 (35.0–56.0)
HDL cholesterol	41.0 (35.0–47.0)	39.0 (34.5–46.0)	37.3 (32.3–43.0)	36.0 (33.5–41.5)
Non-HDL cholesterol	132.0 (115.5–157.0)	131.0 (111.5–154.5)	139.5 (123.0–165.8)	131.8 (113.5–158.5)
LDL cholesterol	87.0 (69.5–105.5)	80.8 (67.5–107.0)	93.3 (75.8–113.8)	85.8 (71.5–104.0)
Apolipoprotein B	88.0 (77.0–113.0)	85.0 (77.0–100.0)	95.0 (80.0–116.5)	92.5 (81.0–105.0)

* 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. HDL denotes high-density lipoprotein, IQR interquartile range, and LDL low-density lipoprotein.
† Race and ethnic group were reported by the participant.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

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No. of Participants						
Placebo	58	56	54	57	56	56
MAR001, 300 mg	59	56	54	58	53	53
MAR001, 450 mg	58	53	54	53	51	52
MAR001, 900 mg	60	58	55	56	53	55

Figure 1. Percent Change in the Fasting Triglyceride Level According to Trial Group through 24 Weeks.

Plotted are the least-squares mean percent changes ±SE. The value at week 0 was an average of the values at day 1 and at the final screening visit; the value at week 12 was an average of the values at weeks 10 and 12; and the value at week 24 was an average of the values at weeks 22 and 24. To convert triglyceride values to millimoles per liter, multiply by 0.01129.

4 of 58 participants (7%) receiving placebo. Injection-site reactions occurred in 25 of 177 participants (14.1%) receiving MAR001 and in 11 of 58 participants (19%) receiving placebo (Table S6). No deaths occurred during follow-up. The effect of MAR001 on serum aminotransferase levels and weight is shown in Table 4 and Table S7, respectively.

DISCUSSION

In this phase 2b trial, inhibition of ANGPTL4 with MAR001 resulted in significant reductions in fasting triglyceride levels at 12 weeks, with a placebo-adjusted percent change of −45.3 percentage points at the highest dose. The magnitude of triglyceride lowering appeared to be more pronounced among participants with higher baseline levels than among those with lower baseline levels. Treatment did not lead to adverse changes in glucose homeostasis markers or aminotransferase levels or to excess injection-site reactions.

Although ANGPTL3, ANGPTL4, and apolipoprotein C-III all influence lipoprotein lipase–mediated triglyceride clearance, their roles in triglyceride metabolism are distinct. ANGPTL3 is produced primarily in the liver and, in conjunction with ANGPTL8, is thought to regulate lipoprotein lipase activity predominantly in a feeding-dependent manner. In contrast, ANGPTL4 is expressed in multiple tissues, including adipose tissue, and is induced by fasting and fatty acids. In adipose tissue, ANGPTL4 is thought to inhibit lipoprotein lipase activity predominantly during fasting, thereby limiting the uptake of fatty acids derived from circulating triglyceride-rich lipoproteins and favoring their availability for energy production in other tissues.[4,15]

Apolipoprotein C-III inhibits lipoprotein lipase–mediated lipolysis in multiple tissues through reversible modulation of lipoprotein lipase activity in a concentration-dependent manner and is less tightly linked to feeding and fasting states than ANGPTL4 and ANGPTL3. In addition to inhibiting lipoprotein lipase–mediated lipolysis, apolipoprotein C-III impairs hepatic clearance of triglyceride-rich lipoprotein remnants through LDL receptor family pathways.[15,16] The adipose-tissue–specific, inducible, and catalytic role of

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Table 2. Primary and Secondary Efficacy Outcomes According to Trial Group.*

Outcome	MAR001, 300 mg (N=59)	MAR001, 450 mg (N=58)	MAR001, 900 mg (N=60)	Pooled Placebo (N=58)
Week 12				
Percent change in fasting triglyceride level				
Least-squares mean	−33.9±2.7	−35.7±2.8	−40.3±2.8	5.2±2.7
95% CI	−39.3 to −28.6	−41.3 to −30.1	−45.8 to −34.8	−0.2 to 10.6
Placebo-adjusted change				
Least-squares mean — percentage points	−39.1±3.9	−40.9±3.9	−45.5±3.9	—
95% CI — percentage points	−46.8 to −31.5	−48.7 to −33.1	−53.2 to −37.8	—
P value	<0.001	<0.001	<0.001	—
Triglyceride level <150 mg/dl				
No./total no. (%)	18/58 (31)	20/57 (35)	31/60 (52)	2/58 (3)
P value vs. placebo	<0.001	<0.001	<0.001	—
Percent change in fasting remnant cholesterol level				
Least-squares mean	−33.6±2.8	−35.4±2.9	−37.1±2.8	3.7±2.8
95% CI	−39.1 to −28.1	−41.1 to −29.7	−42.7 to −31.6	−1.8 to 9.2
Placebo-adjusted change				
Least-squares mean — percentage points	−37.3±3.9	−39.1±4.0	−40.8±4.0	—
95% CI — percentage points	−45.0 to −29.5	−47.0 to −31.2	−48.6 to −33.0	—
P value	<0.001	<0.001	<0.001	—
Percent change in fasting triglyceride level if ≥300 mg/dl at baseline				
Least-squares mean	−44.1±6.0	−45.0±6.3	−48.5±5.0	8.7±5.4
95% CI	−56.0 to −32.3	−57.6 to −32.4	−58.5 to −38.6	−2.1 to 19.4
Placebo-adjusted change				
Least-squares mean — percentage points	−52.8±8.1	−53.7±8.3	−57.2±7.4	—
95% CI — percentage points	−68.9 to −36.7	−70.2 to −37.1	−71.9 to −42.5	—
P value	<0.001	<0.001	<0.001	—
Week 16				
Percent change in nonfasting triglyceride level				
Least-squares mean	−29.7±4.0	−40.7±4.1	−44.9±4.0	3.7±3.8
95% CI	−37.6 to −21.8	−48.8 to −32.7	−52.7 to −37.1	−3.8 to 11.3
Placebo-adjusted change				
Least-squares mean — percentage points	−33.4±5.6	−44.5±5.6	−48.6±5.5	—
95% CI — percentage points	−46.6 to −20.2	−57.8 to −31.1	−61.7 to −35.5	—
P value	<0.001	<0.001	<0.001	—

* Plus–minus values are least-squares means ±SE. The difference between each MAR001 dose group and the placebo group is reported as the placebo-adjusted change. The mixed model for repeated measures includes trial group (with the placebo groups pooled), baseline lipid values, visit time point, and the interaction of trial group with visit time point in participants who did not discontinue the trial regimen early.

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Table 3. Percent Change in Fasting Lipoprotein Levels from Baseline According to Trial Group at Week 12.*

End Point	No. of Participants	MAR001, 300 mg	MAR001, 450 mg	MAR001, 900 mg	Placebo
Fasting non-HDL cholesterol					
Mean at baseline — mg/dl	235	138.2±30.3	134.2±31.4	145.2±31.9	139.0±31.6
Mean at week 12 — mg/dl	224	124.6±31.9	118.3±32.6	126.9±34.6	138.4±35.0
Percent change	224	−8.9±2.4	−9.8±2.5	−11.4±2.5	−0.6±2.5
Placebo-adjusted change — percentage points					
Least-squares mean		−8.2±3.5	−9.2±3.5	−10.8±3.5	—
95% CI		−15.1 to −1.4	−16.2 to −2.2	−17.7 to −3.9	—
Fasting HDL cholesterol					
Mean at baseline — mg/dl	235	42.2±9.8	40.3±8.8	38.6±9.5	37.7±6.2
Mean at week 12 — mg/dl	224	47.8±11.3	47.2±12.1	46.1±10.4	36.9±6.7
Percent change	224	15.3±1.7	17.4±1.8	20.4±1.7	−2.9±1.7
Placebo-adjusted change — percentage points					
Least-squares mean		18.1±2.5	20.3±2.5	23.2±2.4	—
95% CI		13.3 to 23.0	15.4 to 25.2	18.4 to 28.0	—
Fasting LDL cholesterol (direct)					
Mean at baseline — mg/dl	235	89.8±24.1	86.5±23.9	93.0±24.0	89.1±21.7
Mean at week 12 — mg/dl	225	93.6±29.5	89.5±28.0	97.5±29.6	88.3±23.6
Percent change	225	6.2±3.7	8.0±3.8	9.3±3.7	−1.2±3.7
Placebo-adjusted change — percentage points					
Least-squares mean		7.4±5.2	9.2±5.3	10.5±5.3	—
95% CI		−2.9 to 17.7	−1.3 to 19.7	0.2 to 20.9	—
Fasting apolipoprotein B					
Mean at baseline — mg/dl	234	94.6±24.2	89.5±22.0	97.7±25.1	94.1±18.3
Mean at week 12 — mg/dl	222	86.2±25.7	84.1±26.2	89.2±23.8	93.0±21.3
Percent change	222	−7.3±3.1	−4.4±3.2	−4.7±3.1	−0.5±3.1
Placebo-adjusted change — percentage points					
Least-squares mean		−6.8±4.3	−3.9±4.5	−4.2±4.3	—
95% CI		−15.3 to 1.7	−12.7 to 4.9	−12.7 to 4.3	—

* Plus–minus values are means ±SD or least-squares means ±SE. The mixed model for repeated measures includes trial group (with the placebo groups pooled), baseline lipid values, visit time point, and the interaction of trial group with visit time point in participants who did not discontinue the trial regimen early. Baseline and week 12 values were defined as averages of two fasting lipid measurements obtained at screening visit 2 and day 1, or week 10 and 12; apolipoprotein B was not assessed at week 10.

ANGPTL4 in regulating lipoprotein lipase activity may contribute to a greater dependence of effect on baseline triglyceride levels, and the adipose enrichment may lead to a more favorable metabolic profile with regard to markers of dysglycemia.[17]

Patients with more severe hypertriglyceridemia are at increased risk for acute pancreatitis.[1] There was evidence of greater triglyceride reduction with MAR001 in participants with higher baseline triglyceride levels up to 879 mg per deciliter. However, the number of participants with severe hypertriglyceridemia in the present trial was limited, and dedicated studies in this population will be needed to further characterize the efficacy of ANGPTL4 inhibition, includ-

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Table 4. Safety Outcomes through Week 24 According to Trial Group.*

Outcome	MAR001, 300 mg (N=59)	MAR001, 450 mg (N=58)	MAR001, 900 mg (N=60)	Pooled MAR001 (N=177)	Pooled Placebo (N=58)
	number of participants (percent)				
Any adverse event	37 (63)	43 (74)	43 (72)	123 (69)	45 (78)
Serious adverse event	2 (3)	2 (3)	1 (2)	5 (3)	4 (7)
Adverse event leading to discontinuation of MAR001 or placebo	3 (5)	3 (5)	2 (3)	8 (5)	2 (3)
Injection-site reaction	8 (14)	7 (12)	10 (17)	25 (14)	11 (19)
Nausea or vomiting	1 (2)	3 (5)	2 (3)	6 (3)	1 (2)
Diarrhea	1 (2)	2 (3)	7 (12)	10 (6)	4 (7)
Pancreatitis	0	0	0	0	0
Laboratory abnormalities					
AST or ALT >3× ULN	0	0	0	0	1 (2)
Total bilirubin >2× ULN	0	0	0	0	1 (2)
ALT or AST >3× ULN with bilirubin >2× ULN	0	0	0	0	1 (2)

* ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and ULN upper limit of the normal range.

ing its effects on reducing the risk of acute pancreatitis. Supporting this hypothesis, preclinical evidence in animal models suggests that the severity of pancreatitis is attenuated in the context of ANGPTL4 deficiency.[18]

Although the overall effect of MAR001 on reducing triglyceride levels was significant, some studies of other compounds have shown a larger percent reduction in triglyceride levels in populations with moderate hypertriglyceridemia.[19] Two apolipoprotein C-III inhibitors are available in the United States: olezarsen and plozasiran; they lower triglyceride levels by approximately 60%.[6,20] The ANGPTL3 inhibitor evinacumab, approved for use in homozygous familial hypercholesterolemia, has been shown to markedly reduce triglyceride levels in persons with moderate hypertriglyceridemia when given intravenously.[21] Investigational drugs that target ANGPTL3 have shown reductions in triglyceride levels of up to 63%, and a single-dose phase 1 study suggested an up to 70% reduction from targeting ANGPTL3 and ANGPTL8.[5,19,22,23] Given the results from part A of our trial, MAR001 will now be studied at a dose of 600 mg every 4 weeks in a dedicated population of patients with severe hypertriglyceridemia in part B of the protocol.

A small increase in LDL cholesterol levels with MAR001 at the highest dose was accompanied by a reduction in non-HDL cholesterol levels and numerically lower levels of apolipoprotein B. Similar changes in LDL cholesterol levels without a corresponding change in non-HDL cholesterol levels have been observed with other triglyceride-lowering therapies, may reflect redistribution of cholesterol among lipoprotein classes during triglyceride-rich lipoprotein remodeling, and have not been associated with increased cardiovascular risk.[20,24,25] It remains unknown how the observed effects on lipoproteins with MAR001 may influence the risk of atherosclerotic cardiovascular disease.[24,26] Of note, the lower risk of coronary artery disease seen among persons with *ANGPTL4* loss-of-function variants appears to be out of proportion to the effects on apolipoprotein B.[27]

We observed no apparent effects of MAR001 on serum aminotransferase levels, and the frequency of injection-site reactions was similar for participants who received placebo. The absence of adverse effects on markers of glucose homeostasis is of particular interest given observed effects of other therapies that influence lipoprotein lipase activity toward worsening some glycemic variables.[5,17,28,29] Genetic studies have also suggested favorable associations between reduced ANGPTL4 activity and the incidence of type 2 diabetes mellitus, including improvement in glucose

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and insulin homeostasis.[12] Studies of longer duration would be informative to better understand whether there may be beneficial metabolic effects of sustained ANGPTL4 inhibition. Concerns regarding ANGPTL4 inhibition arose from preclinical studies in ANGPTL4-deficient mice, in which mesenteric lipid accumulation and inflammation were observed with a high-fat diet.[30] These findings were evaluated during MAR001 development, and extended toxicology studies in nonhuman primates have not shown progressive mesenteric inflammation or systemic inflammatory effects.[13] In addition, in a phase 1b–2a study, MAR001 showed no changes in mesenteric lymph node size or inflammation or in systemic inflammation, and multiple large-scale genetic studies in humans show no adverse effects in persons with *ANGPTL4* loss-of-function variants.[14]

Our trial has limitations that should be considered. The trial population was not designed to provide broad representation across geographic, racial, and ethnic groups; therefore, additional studies in more diverse populations will be relevant. In addition, the trial was not powered to assess clinical outcomes, including acute pancreatitis or cardiovascular events. Finally, longer-term studies are needed to determine whether the observed reductions in triglyceride levels are sustained and whether prolonged ANGPTL4 inhibition has effects that are not apparent during the relatively short treatment period of this trial.

In this phase 2b trial, inhibition of ANGPTL4 with MAR001 significantly reduced fasting triglyceride levels at 12 weeks.

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

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

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