

A novel ANGPTL4 inhibitory antibody (MAR001) safely lowers plasma triglycerides and remnant cholesterol in humans



MAR001
Lancet paper

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Background /Aims

- ASCVD remains the leading global cause of morbidity and mortality despite advancements in effective therapies¹
 - Patients with elevated TG and RC, the cholesterol carried by TRL, are at increased risk of CV events even when traditional risk factors are well-controlled²
- LPL is a key enzyme in the hydrolysis of TG from TRL in muscle and adipose tissue³
- ANGPTL4 inhibits LPL and is enriched in adipose tissue⁴
- Genetic studies establish ANGPTL4 as a promising therapeutic target to manage ASCVD in patients remaining at high CV risk despite well-controlled LDL-C^{5,6}
 - ANGPTL4 LOF is strongly associated with lower levels of TG, RC, and ApoB, less insulin resistance, more favorable body composition, and protection from T2DM and CAD, without evident safety findings^{7,8}
- Angptl4-knockout mice fed a HSD, however, developed findings including lipid accumulation in MLN, local and systemic inflammation, and reduced survival⁹
 - These findings slowed development of therapies targeting ANGPTL4

Methods

- MAR001 is a humanized monoclonal antibody that binds with high affinity to the N-terminal domain of ANGPTL4
- Safety was assessed in NHPs, including those treated while on a HSD for 9 months. In NHPs, MAR001 improved plasma lipid profiles (e.g., reduced TG, RC, and ectopic fat, and improved insulin sensitivity) without clinical adversity¹⁰
- Safety, tolerability, and efficacy of MAR001 were subsequently assessed in Ph 1a single ascending dose* and Ph 1b/2a multiple-dose (NCT05896254) clinical studies that included participants with elevated TG¹¹
 - The primary objective of both studies was safety and tolerability; secondary efficacy endpoints included changes in TG and RC

* Developed and conducted by Novartis Institutes for BioMedical Research, Inc. (Cambridge, MA, USA).

Results

Figure 1. Ph 2a Study Design and Objectives

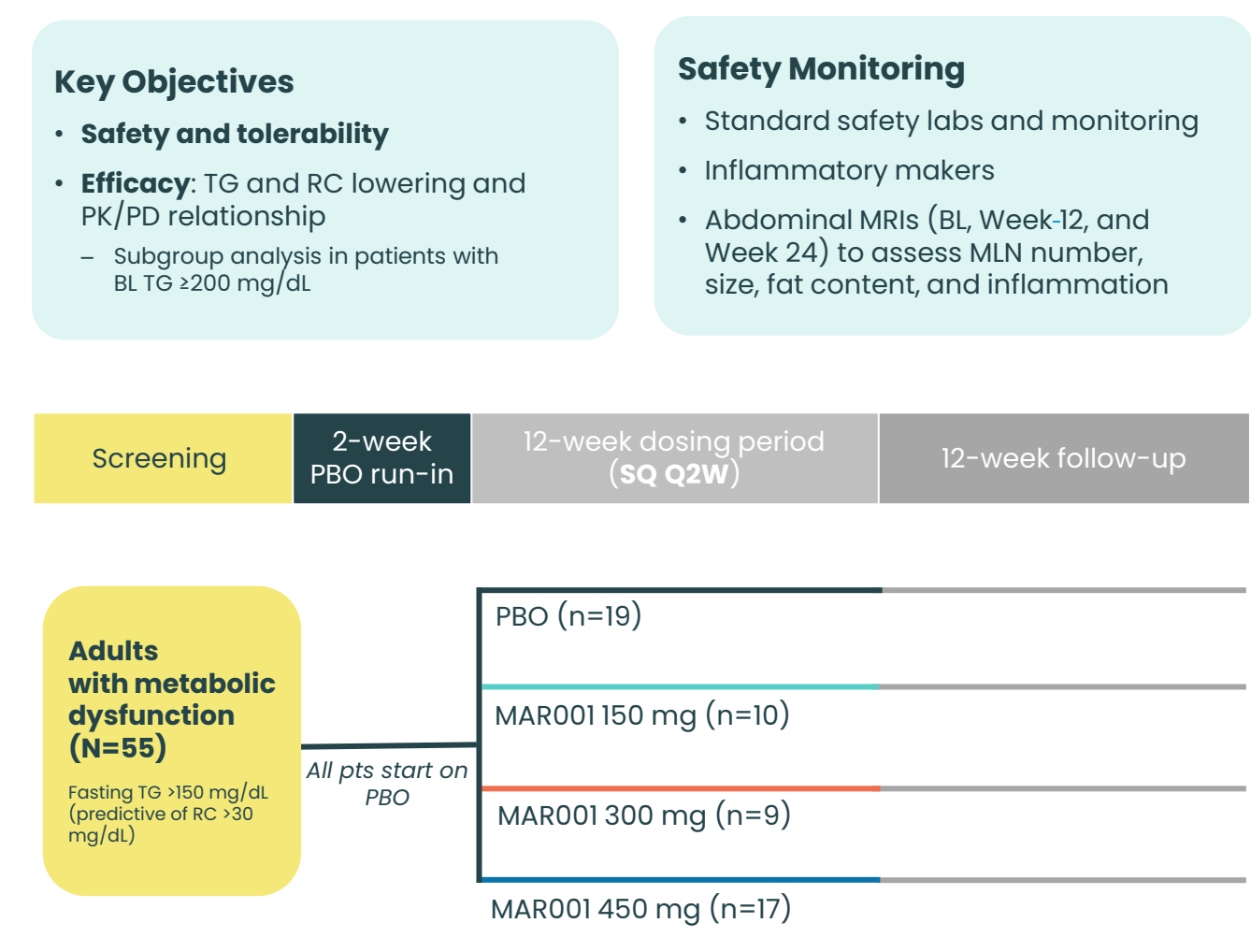


Table 1. Patient and BL Characteristics

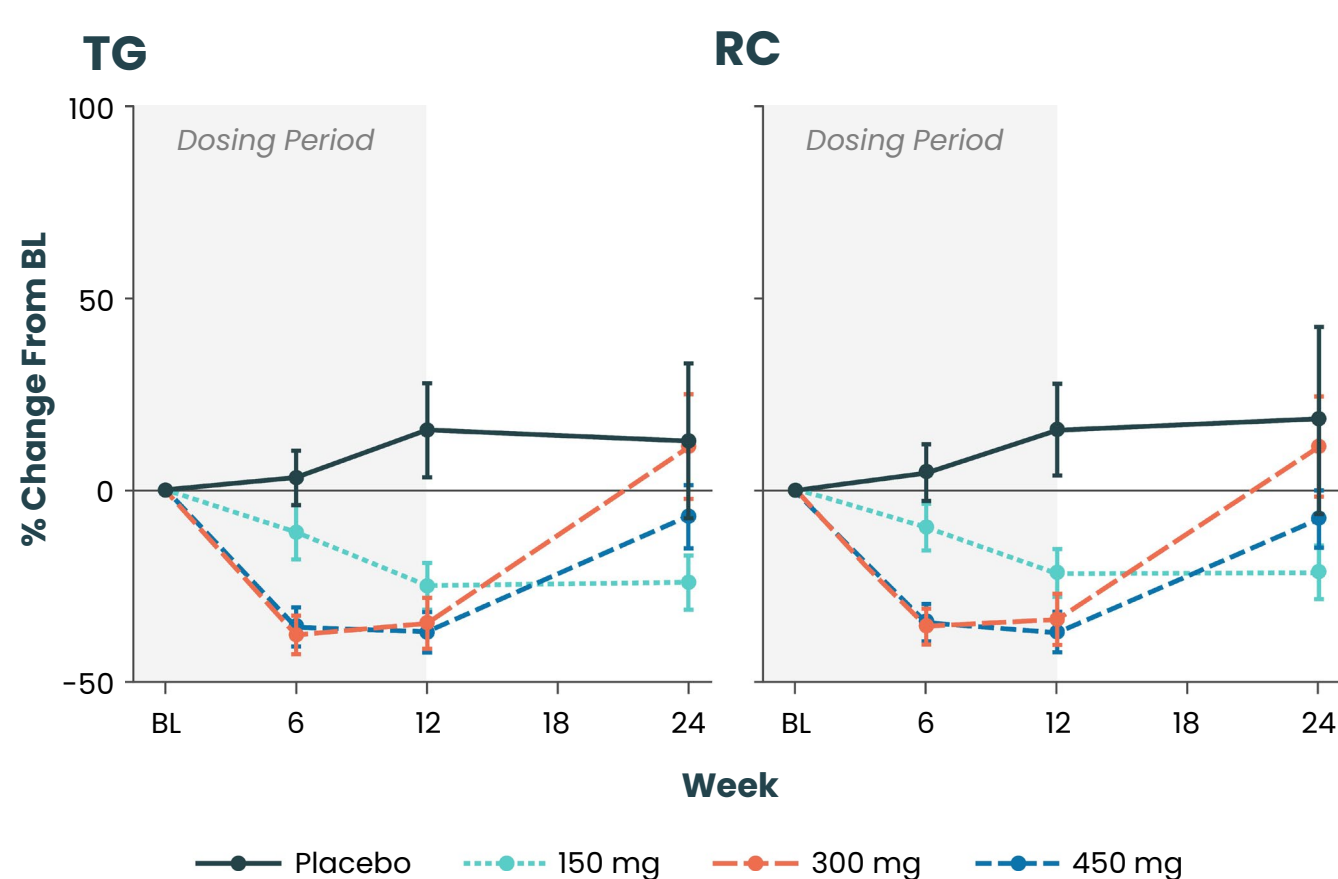
Characteristic	PBO n=19	MAR001 150 mg n=10	MAR001 300 mg n=9	MAR001 450 mg n=17	Total N=55
Age, mean±SD (years)	45.5 (11.6)	48.2 (13.9)	40.1 (11.5)	48.5 (12.2)	46.0 (12.2)
Sex—Female, n (%)	11 (57.9)	8 (80.0)	3 (33.3)	7 (41.2)	29 (52.7)
Race, n (%)					
White	15 (78.9)	5 (50.0)	6 (66.7)	12 (70.6)	38 (69.1)
Asian	3 (15.8)	4 (40.0)	1 (11.1)	1 (5.9)	9 (16.4)
Other	1 (5.3)	1 (10.0)	2 (22.2)	4 (23.6)	8 (14.5)
Ethnicity—Hispanic/Latino, n (%)	0	0	1 (11.1)	1 (5.9)	2 (3.6)
BMI (kg/m ²)	34.6±3.6	34.8±3.2	35.0±2.3	34.1±3.0	34.5±3.1
Waist circumference (cm)	109.8±9.7	106.3±9.0	112.9±13.5	110.6±7.4	109.9±9.6
Lipid Parameters, mean±SD (mg/dL)					
TG	181.6±49.9	169.9±46.2	191.4±58.0	219.2±100.7	192.7±71.0
≥150 mg/dL, n (%)	13 (68.4)	7 (70.0)	8 (88.9)	14 (82.4)	42 (76.4)
≥200 mg/dL, n (%)	9 (47.4)	3 (30.0)	4 (44.4)	9 (52.9)	25 (45.5)
RC	32.2±8.8	29.4±7.0	33.6±9.1	40.1±18.8	34.4±12.9
≥30 mg/dL, n (%)	11 (57.9)	3 (30.0)	6 (66.7)	11 (64.7)	31 (56.4)
≥40 mg/dL, n (%)	2 (10.5)	1 (10.0)	2 (22.2)	5 (29.4)	10 (18.2)
VLDL-C	36.0±9.9	33.6±9.0	37.9±11.4	43.5±19.8	38.2±14.0
non-HDL-C	159.5±31.2	139.1±35.7	163.9±38.9	175.1±44.7	161.3±38.8
HDL-C	46.1±9.7	47.7±10.5	41.1±8.3	42.8±6.9	44.5±8.9
LDL-C	122.5±31.4	104.8±38.8	125.6±45.3	131.1±33.9	122.5±36.2
HOMA-IR, mean±SD	3.32±1.7	3.71±3.2	4.6±3.8	2.9±1.4	3.5±2.4
HbA1c, mean±SD (%)	5.9±0.6	6.0±0.6	5.6±0.4	5.6±0.3	5.8±0.5
T2DM, n (%)	3 (15.8)	0	0	1 (5.9)	4 (7.3)
LFF by MRI-PDFF, mean±SD (%)	12.7±9.1	12.7±9.5	11.3±9.6	9.7±7.2	11.5±8.6
Fat fraction >5%, n (%)	15 (78.9)	7 (70.0)	6 (66.7)	9 (52.9)	37 (67.3)
Concomitant medication use, n (%)					
Metformin	3 (15.8)	1 (10.0)	1 (11.1)	2 (11.8)	7 (12.7)
Statin	1 (5.3)	1 (10.0)	1 (11.1)	2 (11.8)	5 (9.1)
SGLT2 inhibitors	2 (10.5)	0	0	0	2 (3.6)

Race and ethnic group were reported by participants. RC was calculated as TC minus HDL-C minus LDL-C. VLDL-C was calculated as TG (in mg/dL) divided by five. LDL-C was calculated using the Sampson equation.¹²

Results

- Overall, 56 and 55 participants were randomized in the single- and multiple-dose (Figure 1) studies, respectively
 - The Ph 1a single-dose study in 3 participant cohorts (healthy, obese, and high TG) established safety and PD¹¹
 - In the high TG cohort, reduction of TG-rich lipoproteins was demonstrated with MAR001 450 mg vs PBO
- In the Ph 2a multiple-dose study, the overall median age was 46.0 years (Table 1); 53% (n=23) were female and 69% (n=38) were White
 - BL values were similar across treatment groups, with some variability in fasting TG and related lipids
- Dosing of MAR001 450 mg (SQ every 2 weeks) for 12 weeks led to PBO-adjusted mean reductions of 52.7% (90% CI, -77.0 to -28.3%) in TG and 52.5% (90% CI, -76.1 to -28.9%) in RC (Figure 2), with greater reductions in those with elevated BL levels (Table 2)
 - Reductions in TG and RC were evident as early as Week 1 and reached maximal reductions ~by Week 6 in the higher-dose MAR001 groups¹¹
- Treatment-related reductions in VLDL-C and non-HDL-C (Figure 3) and an increase in HDL-C at Week 12 were observed; no treatment-related changes in LDL-C were observed
- MAR001 was generally safe and well-tolerated, including no findings of elevated systemic inflammatory biomarkers, or changes in MLN size or local inflammation as assessed by abdominal MRI

Figure 2. Overall Population*: MAR001 300 & 450 mg Doses Showed Substantial TG and RC Lowering



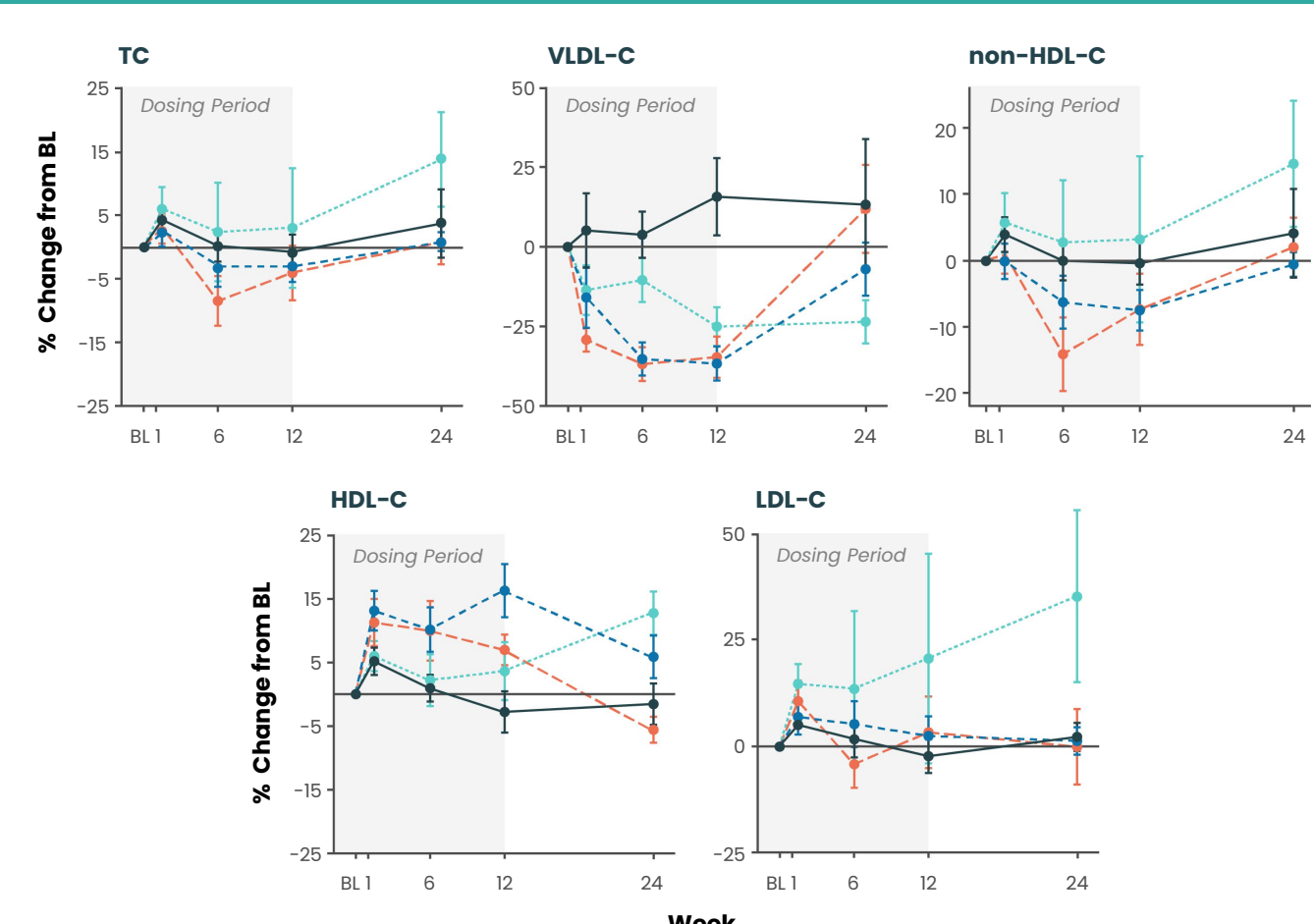
*Includes participants with TG <150 mg/dL at BL. Hodges-Lehmann estimator applied for PBO-adjusted changes. RC calculated by Sampson equation.¹²

Table 2. Subgroup Analysis of Participants with BL TGs ≥200 mg/dL: Numerically Greater TG Reduction and Especially Pronounced with the Highest MAR001 Dose

	PBO n=19	MAR001 150 mg n=10	MAR001 300 mg n=9	MAR001 450 mg n=17
Overall Population				
TG levels at BL, mean±SD (mg/dL)	181.6±49.9	169.9±46.2	191.4±58.0	219.2±100.7
Mean change from BL at Week 12 (mg/dL) (90% CI)	26.6 (-12.8, 65.9)	-42.5 (-64.0, -21.0)	-76.2 (-105.0, -47.4)	-85.0 (-115.6, -54.4)
PBO-adjusted % mean change from BL at Week 12 (90% CI)	--	-40.6 (-70.1, -11.2)	-50.3 (-88.0, -12.7)	-52.7 (-77.0, -28.3)
Population with BL TG ≥200 mg/dL				
TG levels at BL, mean±SD (mg/dL)	224.1±25.0	230.3±23.2	243.0±35.8	283.3±97.5
Mean change from BL at Week 12 (mg/dL) (90% CI)	38.4 (-40.6, 117.5)	-71.0 (-145.2, 3.2)	-90.3 (-106.1, -74.4)	-135.6 (-182.6, -88.6)
PBO-adjusted % mean change from BL at Week 12 (90% CI)	--	-45.9 (-104.4, 12.6)	-52.3 (-101.5, -3.0)	-64.0 (-101.5, -26.6)

Hodges-Lehmann estimator applied for PBO-adjusted changes.

Figure 3. Lipid Changes Through 24 Weeks



Error bars represent SEM. VLDL-C was calculated as TG (in mg/dL) divided by five. non-HDL-C was calculated as TC minus HDL-C. LDL-C was calculated using the Sampson equation.¹²

Results

No Safety or Tolerability Concerns

Clinical safety parameters

- No SAEs and no AEs leading to study drug discontinuation in any active treatment arm
- One participant who received PBO had two G3 or higher AEs (G3 and G4, 1 each)
- GI AEs occurred at a higher rate in the 450 mg arm, but across all groups, no GI AEs were G3 or higher
- There were no treatment-related trends in the standard safety labs (chemistry and hematology)

Inflammatory biomarkers

- No persistent increases in inflammatory biomarkers (e.g., hsCRP, fibrinogen) across any of the dosing groups
 - Notably, there was a trend toward a decrease in SAA in the 450 mg dose group across the 12-week dosing period

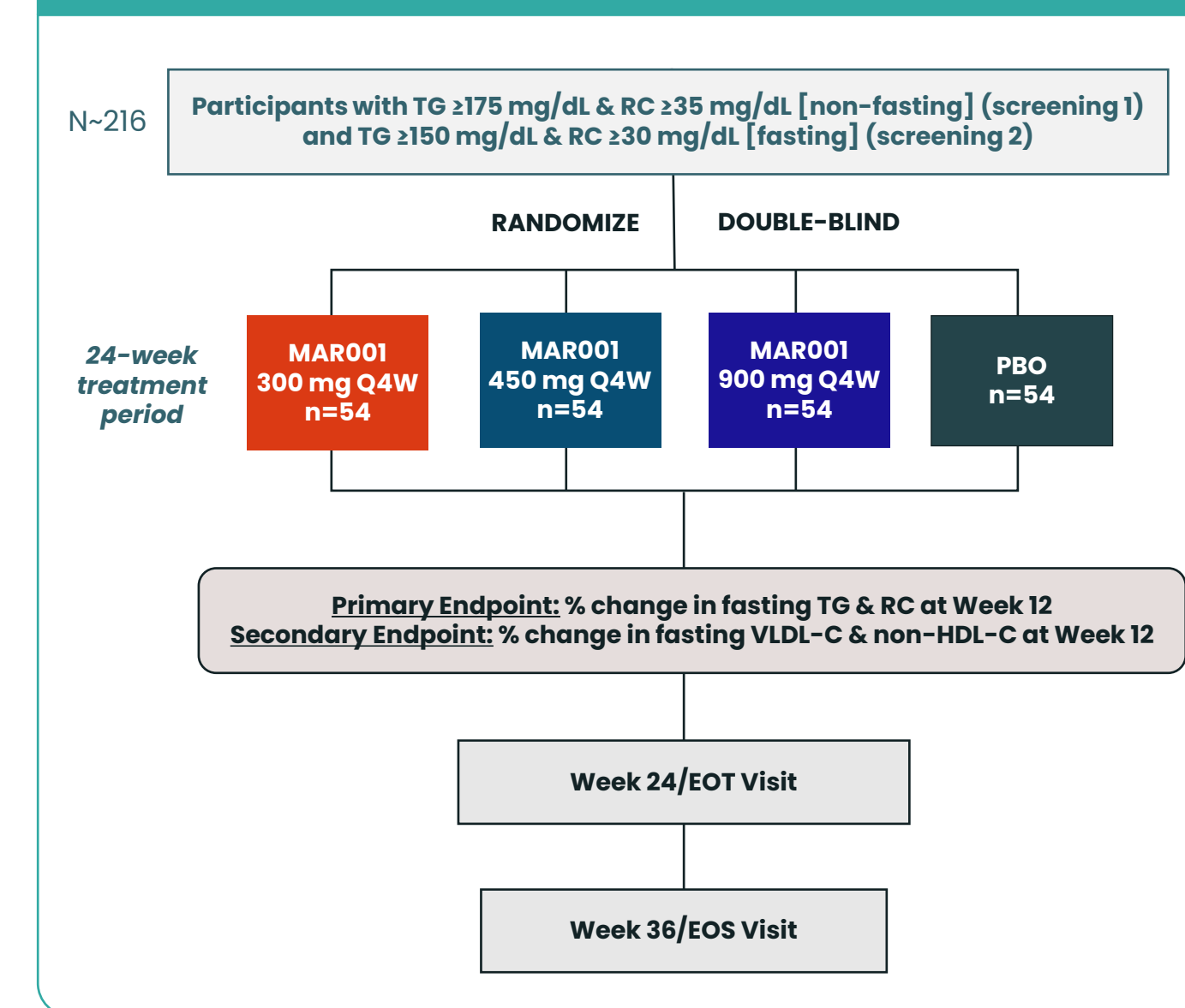
Abdominal MRI

- No treatment-dependent changes in MLN size or number across treatment groups
- No MAR001-dependent and no potentially clinically meaningful shifts of MLN <10 mm in size to ≥10 mm
- No ascites observed in all available MRIs
- No increase in inflammation in any participant that correlated with the presence of lymph nodes ≥10 mm or change in lymph node size

Conclusions

- Preclinical and clinical data with MAR001 is consistent with human genetic data suggesting that ANGPTL4 inhibition is safe and leads to reductions in TG and RC, as well as improvements in metabolic parameters, that may correlate to the reductions in the risk of T2DM and CAD observed with ANGPTL4 LOF
- This data supports the further development of MAR001 as a promising therapy for the treatment of ASCVD
- The ongoing Ph 2b TYDAL-TIMI 78 study (NCT07028749) (Figure 4) should provide additional insights into the efficacy and safety of MAR001 in patients with elevated TG and RC

Figure 4. TYDAL-TIMI 78 Study Design



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Disclosures

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Abbreviations

AE, adverse event; ANGPTL4, angiotensin-like 4; ApoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; BL, baseline; BMI, Body Mass Index; CAD, coronary artery disease; CI, confidence interval; CV, cardiovascular; DL, deciliter; EOS, end of study; EOT, end of treatment; FINBB, Finnish Biobank Cooperative; G, grade; GI, gastrointestinal; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; hsCRP, high-sensitivity C-reactive protein; HSD, high saturated fat diet; LFF, liver fat fraction; LDL-C, low-density lipoprotein cholesterol; LFF, loss-of-function; LPL, lipoprotein lipase; mg, milligram; MLN, mesenteric lymph nodes; mm, millimeter; MRI, magnetic resonance imaging; MRI-PDFF, Magnetic Resonance Imaging-Proton Density Fat Fraction; NHP, non-human primates; PBO, placebo; PD, pharmacodynamic; Ph, phase; PK, pharmacokinetic; pts, patients; Q4W, every 4 weeks; RC, remnant cholesterol; SAA, serum amyloid A; SAE, serious adverse event; SD, standard deviation; SEM, standard error of the mean; SGLT2, sodium-glucose cotransporter 2; SQ, subcutaneous; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglycerides; TRL, triglyceride-rich lipoproteins; VLDL-C, very low-density lipoprotein cholesterol.

For more information on the TYDAL-TIMI-78 study, please visit <https://clinicaltrials.gov/study/NCT07028749> or contact TYDAL_info@mareatx.com

