Exhibit U

Efficacy and Safety of Eicosapentaenoic Acid Ethyl Ester (AMR101) Therapy in Statin-Treated Patients With Persistent High Triglycerides (from the ANCHOR Study)

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AMR101 is an ω-3 fatty acid agent containing ≥96% pure icosapent-ethyl, the ethyl ester of eicosapentaenoic acid. The efficacy and safety of AMR101 were evaluated in this phase 3, multicenter, placebo-controlled, randomized, double-blinded, 12-week clinical trial (ANCHOR) in high-risk statin-treated patients with residually high triglyceride (TG) levels (≥200 and <500 mg/dl) despite low-density lipoprotein (LDL) cholesterol control (≥40 and <100 mg/dl). Patients (n = 702) on a stable diet were randomized to AMR101 4 or 2 g/day or placebo. The primary end point was median percent change in TG levels from baseline versus placebo at 12 weeks. AMR101 4 and 2 g/day significantly decreased TG levels by 21.5% (p <0.0001) and 10.1% (p = 0.0005), respectively, and non-high-density lipoprotein (non-HDL) cholesterol by 13.6% (p <0.0001) and 5.5% (p = 0.0054), respectively. AMR101 4 g/day produced greater TG and non-HDL cholesterol decreases in patients with higher-efficacy statin regimens and greater TG decreases in patients with higher baseline TG levels. AMR101 4 g/day decreased LDL cholesterol by 6.2% (p = 0.0067) and decreased apolipoprotein B (9.3%), total cholesterol (12.0%), very-low-density lipoprotein cholesterol (24.4%), lipoprotein-associated phospholipase A_2 (19.0%), and high-sensitivity C-reactive protein (22.0%) versus placebo (p <0.001 for all comparisons). AMR101 was generally well tolerated, with safety profiles similar to placebo. In conclusion, AMR101 4 g/day significantly decreased median placebo-adjusted TG, non-HDL cholesterol, LDL cholesterol, apolipoprotein B, total cholesterol, very-low-density lipoprotein cholesterol, lipoprotein-associated phospholipase A_2, and high-sensitivity C-reactive protein in statin-treated patients with residual TG elevations. **(Am J Cardiol 2012;xx:xxx)**

In association with an increasing prevalence of obesity and diabetes in recent decades, the number of patients with elevated serum triglycerides (TGs) has markedly increased.[1] In patients with fasting TG levels ≥200 and <500 mg/dl, low-density lipoprotein (LDL) cholesterol is the primary lipid target, with statins being first-line therapy for preventing atherosclerotic coronary heart disease.[2] If TG levels remain ≥200 and <500 mg/dl after optimization of LDL

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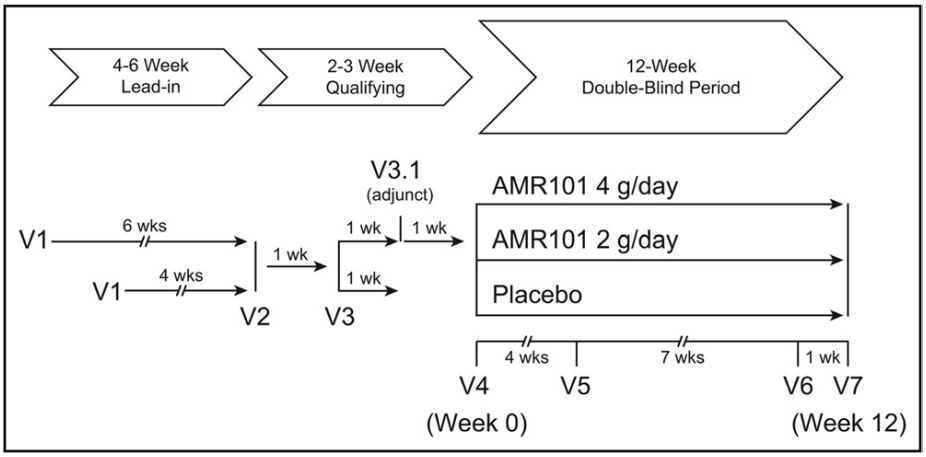

Figure 1. Study design. The screening period consisted of a 4- to 6-week lead-in period during which patients underwent diet and lifestyle stabilization and nonstatin lipid-altering treatment washout if necessary. At the first screening visit, patients not taking a statin were initiated on statin therapy and likely to achieve a low-density lipoprotein cholesterol goal of <100 mg/dl and all patients received counseling on the National Cholesterol Education Program Therapeutic Lifestyle Changes diet.[2] Patients then entered a 2- to 3-week qualifying period. Lipid qualifications included an average fasting triglyceride level ≥200 and <500 mg/dl and an average fasting low-density lipoprotein cholesterol level ≥40 and <100 mg/dl based on the average (arithmetic mean) of 2 visits. If the average triglyceride and/or low-density lipoprotein cholesterol level was outside the required range, an additional measurement could be obtained at a third visit 1 week later, with eligibility determined based on the last 2 visits. Eligible patients were randomized 1 week later to AMR101 4 g/day (2 AMR101 1-g capsules 2 times/day), AMR101 2 g/day (1 AMR101 1-g capsule plus 1 matching placebo capsule 2 times/day), or placebo (2 matching placebo capsules 2 times/day). Investigators and patients were blinded to treatment assignment throughout the double-blinded, placebo-controlled, 12-week treatment period. Visit 1 (V1) was 6 weeks for patients requiring washout and 4 weeks for patients not requiring washout. V2 to V7 = visits 2 to 7.

cholesterol levels with statin therapy, adjunctive treatment options include lifestyle interventions, fibrates, niacin, ezetimibe, and ω-3 fatty acids.[3] AMR101 is an ω-3 fatty acid investigational new drug containing ≥96% pure icosapent-ethyl (the ethyl ester of eicosapentaenoic acid [EPA]; United States Adopted Name [generic] and International Nonproprietary Name). This study (ANCHOR) assessed the efficacy and safety of AMR101 in statin-treated patients at high cardiovascular risk with well-controlled LDL cholesterol and residually high TG levels (≥200 and <500 mg/dl).

Methods

The ANCHOR study was a phase 3, multicenter, placebo-controlled, randomized, double-blinded, 12-week clinical trial conducted at 97 sites in the United States from December 2009 through February 2011. The protocol was approved by the appropriate institutional review boards, and all patients underwent the informed consent process before enrollment, as evidenced by their written informed consent. The clinical trial registration number was NCT01047501 (available at: *http://clinicaltrials.gov/ct2/show/NCT01047501*).

The study design is explained in Figure 1. Inclusion criteria included patients >18 years of age and at high risk for cardiovascular disease as defined by the National Cholesterol Education Program Adult Treatment Panel III guidelines[2] who were willing to maintain stable diet and exercise throughout the study; at the first TG-qualifying visit, patients were required to have been on ≥4 weeks of stable statin therapy (atorvastatin, rosuvastatin, or simvastatin <100 mg/dl) and continue such treatment throughout the study. To facilitate enrollment, a protocol amendment was implemented after approximately 1/2 of patients were randomized: the hemoglobin A1c exclusion criterion was increased from 9.0% to >9.5%; based on known within-patient variability for TG and LDL cholesterol, entry criteria were expanded so the mean of the 2 TG-qualifying values was ≥185 mg/dl with ≥1 of the 2 values ≥200 mg/dl; and the upper limit of the LDL cholesterol entry criteria was increased by 15% to ≤115 mg/dl.

Exclusion criteria included body mass index >45 kg/m^2, a weight change >3 kg from the first visit to the end of the qualifying period, non-high-density lipoprotein (non-HDL) cholesterol levels <100 mg/dl, known nephrotic range (>3 g/day) proteinuria, malignancy, bariatric surgery, long-term treatment with antihypertensive and antidiabetic medications, treatment with weight-loss drugs, thyroid-stimulating hormone >1.5 times upper limit of normal, alanine aminotransferase or aspartate aminotransferase >3 times upper limit of normal, and unexplained creatine kinase concentration >3 times upper limit of normal or creatine kinase increase from known muscle disease.

The primary end point was median placebo-adjusted percent change in TG levels from baseline to week 12 (study end). Baseline TG level was calculated as the average of levels at randomization and 1 week previously. TG value at study end was calculated as the average of weeks 11 and 12. Prespecified secondary efficacy end points included median placebo-adjusted percent change in non-HDL cholesterol, LDL cholesterol, apolipoprotein B, very-low-density lipoprotein (VLDL), and lipoprotein-associated phos-

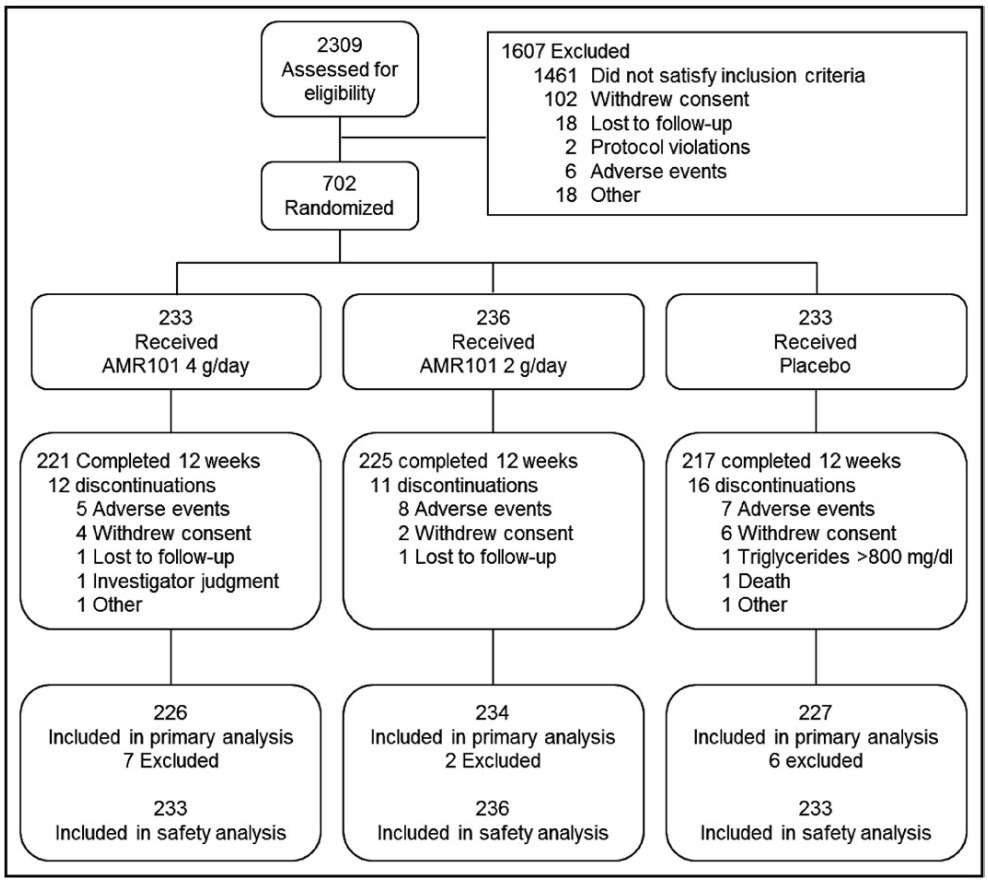

Figure 2. Patient disposition.

cholesterol, VLDL-TG, and high-sensitivity C-reactive protein. Safety assessments, blood and urine tests, and efficacy end-point assessments were analyzed as previously described; high-sensitivity C-reactive protein was measured with the same assay as previously described for lipoprotein-associated phospholipase A_2.[4]

A sample size of 194 completed patients per treatment arm was required to provide 90.6% power to detect a difference of 15% between AMR101 4 g/day and placebo in percent change from baseline in fasting TG levels, assuming an SD of 45% in TG measurements and a significance level (p value) <0.05, and 80% power to demonstrate noninferiority ($p < 0.025$, 1-sided) of the LDL cholesterol response between AMR101 4 g/day and placebo with a +6% margin. To accommodate a 10% drop-out rate, recruitment was planned for 648 randomized patients.

All efficacy analyses were performed on the intent-to-treat population (randomized patients who received ≥1 dose of study drug and had baseline and ≥1 postrandomization efficacy measurements) using an analysis of covariance model with treatment, type of statin, gender, and presence of diabetes as factors and baseline TG as a covariate. If no significant departure from normality was observed, parametric testing was planned for each comparison between AMR101 and placebo. For each efficacy end point, if range would be calculated for each treatment group and median differences and Hodges–Lehmann 2-tailed 95% confidence interval would be calculated for each comparison between AMR101 and placebo.

Nonparametric analysis p values were planned using Wilcoxon rank-sum test for each comparison between AMR101 and placebo. Missing data were imputed using the last-observation-carried-forward method. To control the family-wise error rate when performing multiple pairwise tests between the 2 dose levels of AMR101 and placebo, a prespecified step-down testing procedure was followed for the primary end point: differences in TG-lowering between AMR101 4 g/day and placebo were tested; if this first comparison showed a statistically significantly greater decrease in TG at the prespecified significance level of 0.05, the TG-lowering effects of AMR101 2 g/day versus placebo were also analyzed. For all end points, comparisons between AMR101 and placebo were made using a significance level of 0.05. The Hommel procedure was used to test the adequate control of type 1 error for multiple secondary end points. For non-HDL cholesterol, VLDL cholesterol, lipoprotein-associated phospholipase A_2, and apolipoprotein B, treatment groups were compared using the Dunnett test to control the type I error rate within each parameter. Changes in TG and non-HDL cholesterol were analyzed by select

Table 1
Baseline characteristics

Characteristic	AMR101 Dose		Placebo (n = 233)
	4 g/day (n = 233)	2 g/day (n = 236)	
Age (years), mean ± SD	61.1 ± 10.03	61.8 ± 9.42	61.2 ± 10.05
Age ≥65 years	91 (39%)	95 (40%)	87 (37%)
Men	142 (61%)	144 (61%)	145 (62%)
White	226 (97%)	226 (96%)	224 (96%)
Weight (kg), mean ± SD	94.5 ± 18.30	95.5 ± 18.29	97.0 ± 19.14
Body mass index (kg/m^2), mean ± SD	32.7 ± 4.99	32.9 ± 4.98	33.0 ± 5.04
Diabetes mellitus	171 (73%)	172 (73%)	171 (73%)
Fasting plasma glucose (mg/dl), mean ± SD (n = 225, 234, 227)	133.0 ± 37.1	135.4 ± 43.2	130.1 ± 35.8
Hemoglobin A1c (%), mean ± SD (n = 226, 234, 227)	6.6 ± 0.9	6.7 ± 1.1	6.5 ± 0.9
Statin use			
Atorvastatin	44 (19%)	43 (18%)	45 (19%)
Simvastatin	134 (58%)	136 (58%)	133 (57%)
Rosuvastatin	55 (24%)	57 (24%)	55 (24%)
Statin efficacy regimens*			
Lower	16 (7%)	17 (7%)	15 (6%)
Medium	148 (64%)	148 (63%)	144 (62%)
Higher	69 (30%)	71 (30%)	74 (32%)

Data are reported for the randomized population, with the exception of fasting plasma glucose and hemoglobin A1c, which are reported for the intent-to-treat population.

* Lower-efficacy statin regimens = simvastatin 5 to 10 mg; medium-efficacy statin regimens = rosuvastatin 5 to 10 mg, atorvastatin 10 to 20 mg, simvastatin 20 to 40 mg, simvastatin 10 to 20 mg plus ezetimibe 5 to 10 mg; higher-efficacy statin regimens = rosuvastatin 20 to 40 mg, atorvastatin 40 to 80 mg, simvastatin 80 mg, simvastatin 40 to 80 mg plus ezetimibe 5 to 10 mg.

performed in the safety population (randomized patients who received ≥1 dose of study medication). For hemoglobin A1c and fasting plasma glucose, differences in change from baseline between AMR101 and placebo were analyzed using an analysis of covariance model with treatment as a factor and baseline value as a covariate using a significance level of 0.05.

Results

Figure 2 shows the patient disposition; 663 patients (>90% in each treatment group) completed the 12-week double-blinded treatment phase. Baseline characteristics of randomized patients are listed in Table 1 and were comparable across treatment groups ($p > 0.14$ for all comparisons; not presented in Table 1). Patients with diabetes had well-controlled diabetes with mean baseline hemoglobin A1c <7% and fasting plasma glucose <136 mg/dl for all groups. Median LDL cholesterol level was 83.0 mg/dl and 21% of patients had baseline LDL cholesterol levels <70 mg/dl. Most patients (93.2%) were taking medium- or high-efficacy statin regimens (as defined a priori) and 90.2% were on

AMR101 produced significant decreases in TG and various efficacy end points in placebo-adjusted changes from baseline to study end (Figure 3 and Table 2). Because a significant departure from normality was observed for all efficacy end points ($p < 0.01$, Shapiro–Wilk test), nonparametric statistics were used. For the 2 AMR101 treatment groups, the maximum TG-lowering effect was reached by approximately week 4 (data not shown). AMR101 did not significantly increase LDL cholesterol at either dose. The noninferiority criterion for LDL cholesterol was met for the 2 AMR101 doses because the prespecified upper boundary of the 97.5% confidence interval (−1.7 to +0.5 for AMR101 4 and 2 g/day, respectively) did not cross the +6% noninferiority threshold (data not shown).

Analysis of subgroups by prespecified statin efficacy regimen indicated that patients treated with more effective statin regimens exhibited greater TG and non-HDL cholesterol decreases with AMR101 compared to lower-efficacy regimens (Table 3). Statistically significant decreases in TG levels with AMR101 4 g/day were observed for patients treated with atorvastatin, simvastatin, and rosuvastatin and with AMR101 2 g/day for patients treated with simvastatin. Analysis of subgroups by median baseline TG tertiles indicated that higher baseline TG levels resulted in greater TG decreases. Median decreases in TG levels were statistically significant versus placebo and similar in patients with and without diabetes mellitus.

During the double-blinded treatment period, 46.2% of patients had ≥1 treatment-emergent adverse event regardless of cause: 106 patients (45.5%) in the AMR101 4 g/day group, 106 patients (44.9%) in the AMR101 2 g/day group, and 112 patients (48.1%) in the placebo group. Most treatment-emergent adverse events were mild or moderate in severity and considered unrelated to study drug. Diarrhea, nausea, nasopharyngitis, and arthralgia occurred in >3% of patients, and only arthralgia occurred in a larger percentage of patients treated with AMR101 versus placebo (Table 4). The most common treatment-emergent adverse events were gastrointestinal disorders, which occurred in a larger percentage of patients in the placebo group. Eructations were reported by 2, 1, and 4 patients receiving AMR101 4 g/day, AMR101 2 g/day, and placebo, respectively. Twenty-five patients (3.6%) discontinued treatment during the double-blinded treatment phase because of a treatment-emergent adverse event (5 patients in AMR101 4 g/day group, 8 patients in AMR101 2 g/day group, and 12 patients in placebo group). In total, 18 serious adverse events were reported during the study (7 patients in AMR101 4 g/day group, 6 patients in AMR101 2 g/day group, and 5 patients in placebo group including 1 death related to myocardial infarction). No serious adverse events were considered related to study drug. No clinically significant increases in alanine aminotransferase, aspartate aminotransferase, and creatine kinase were observed in the AMR101 treatment groups. One patient in the AMR101 4 g/day group had an increase in alanine aminotransferase >3 times the upper limit of normal detected at week 12, which decreased during follow-up after the study. No statistically significant increases in fasting plasma glucose or hemoglobin A1c were

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