During the double-blind treatment period, patients will return to the site at Visit 5 (Week 4), Visit 6 (Week 11), and Visit 7 (Week 12) for efficacy and safety evaluations.

Patients who complete the 12-week double-blind treatment period will be eligible to enter a 40-week, open-label, extension period at Visit 7 (Week 12). All patients will receive open-label AMR101 4 g daily. From Visit 8 (Week 16) until the end of the study, changes to the lipid-altering regimen are permitted (e.g., initiating or raising the dose of statin or adding non-statin, lipid-altering medications to the regimen), as guided by standard practice and prescribing information. After Visit 8 (Week 16), patients will return to the site every 12 weeks until the last visit at Visit 11 (Week 52).

Eligible patients will be randomly assigned at Visit 4 (Week 0) to receive orally AMR101 2 g daily, AMR101 4 g daily, or placebo for the 12-week double-blind treatment period. AMR101 is provided in 1 g liquid-filled, oblong, gelatin capsules. The matching placebo capsule is filled with light liquid paraffin and contains 0 g of AMR101. During the double-blind treatment period, patients will take 2 capsules (AMR101 or matching placebo) in the morning and 2 in the evening for a total of 4 capsules per day. Patients in the AMR101 2 g/day treatment group will receive 1 AMR101 1 g capsule and 1 matching placebo capsule in the morning and in the evening. Patients in the AMR101 4 g/day treatment group will receive 2 AMR101 1 g capsules in the morning and evening.

Patients in the placebo group will receive 2 matching placebo capsules in the morning and evening. During the extension period, patients will receive open-label AMR101 4 g daily. Patients will take 2 AMR101 1 g capsules in the morning and 2 in the evening.

The primary efficacy variable for the double-blind treatment period is percent change in TG from baseline to Week 12 endpoint. The secondary efficacy variables for the double-blind treatment period include the following:

- Percent changes in total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), calculated low-density lipoprotein cholesterol (LDL-C), calculated non-high-density lipoprotein cholesterol (non-HDL-C), and very low-density lipoprotein cholesterol (VLDL-C) from baseline to Week 12 endpoint;
- Percent change in very low-density lipoprotein TG from baseline to Week 12;
- Percent changes in apolipoprotein A-I (apo A-I), apolipoprotein B (apo B), and apo A-I/apo B ratio from baseline to Week 12;
- Percent changes in lipoprotein(a) from baseline to Week 12 (selected sites only);
- Percent changes in LDL particle number and size, measured by nuclear magnetic resonance, from baseline to Week 12 (selected sites only);
- Percent change in remnant-like particle cholesterol from baseline to Week 12 (selected sites only);
- Percent change in oxidized LDL from baseline to Week 12 (selected sites only);
- Changes in FPG and HbA_{1c} from baseline to Week 12;
- Change in insulin resistance, as assessed by the homeostasis model index insulin resistance, from baseline to Week 12;
- Percent change in lipoprotein associated phospholipase A2 from baseline to Week 12 (selected sites only);
- Change in intracellular adhesion molecule-1 from baseline to Week 12 (selected sites only);
- Change in interleukin-6 from baseline to Week 12 (selected sites only);
- Change in plasminogen activator inhibitor-1 from baseline to Week 12 (selected sites only);
- Change in hsCRP from baseline to Week 12 (selected sites only);
- Change in serum phospholipid EPA content from baseline to Week 12;
- Change in red blood cell membrane EPA content from baseline to Week 12; and
- Change in serum phospholipid and red blood cell membrane content in the following fatty acids from baseline to Week 12: docosapentaenoic acid, docosahexaenoic acid, arachidonic acid, palmitic acid, stearic acid, and oleic acid.

The efficacy variable for the open-label extension period is percent change in fasting TG from extension baseline to end of treatment. Safety assessments will include adverse events, clinical laboratory measurements (chemistry, hematology, and urinalysis), 12-lead electrocardiograms (ECGs), vital signs, and physical examinations

For TG, TC, HDL-C, calculated LDL-C, calculated non-HDL-C, and VLDL-C, baseline will be defined as the average of Visit 4 (Week 0) and the preceding lipid qualifying visit (either Visit 3 [Week −1] or if it occurs, Visit 3.1) measurements. Baseline for all other efficacy parameters will be the Visit 4 (Week 0) measurement.

For TC, HDL-C, calculated LDL-C, calculated non-HDL-C, and VLDL-C, Week 12 endpoint will be defined as the average of Visit 6 (Week 11) and Visit 7 (Week 12) measurements. Week 12 endpoint for all other efficacy parameters will be the Visit 7 (Week 12) measurement.

The primary efficacy analysis will be performed using a 2-way analysis of covariance (ANCOVA) model with treatment as a factor and baseline TG value as a covariate. The least-squares mean, standard error, and 2-tailed 95% confidence interval for each treatment group and for each comparison will be estimated. The same 2-way ANCOVA model will be used for the analysis of secondary efficacy variables.

The primary analysis will be repeated for the per-protocol population to confirm the robustness of the results for the intent-to-treat population.

The primary efficacy variable will be the percent change in fasting TG levels from baseline to Week 12. A sample size of 69 completed patients per treatment group will provide ≧90% power to detect a difference of 30% between AMR101 and placebo in percent change from baseline in fasting TG levels, assuming a standard deviation of 45% in TG measurements and a significance level of $p<0.01$. To accommodate a 15% drop-out rate from randomization to completion of the double-blind treatment period, a total of 240 randomized patients is planned (80 patients per treatment group).

What is claimed is:

1. A method of reducing triglycerides and apolipoprotein B in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl, who does not receive a concurrent lipid altering therapy, comprising administering orally to the subject about 4 g per day of a pharmaceutical composition comprising at least about 96% by weight, ethyl eicosapentaenoate (ethyl-EPA) and substantially no docosahexaenoic acid (DHA) or its esters for a period of at least 12 weeks to effect a reduction in triglycerides and apolipoprotein B in the subject compared to a triglyceride level and apolipoprotein B level in a second subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl, who does not receive a concurrent lipid altering therapy, and who has not received the pharmaceutical composition.

2. The method of claim **1** wherein the composition is administered to the subject 1 to 4 times per day.