2 SYNOPSIS

Name of Sponsor: Amarin Pharma Inc.

Name of Finished Product: AMR101 1 g capsules

Name of Active Ingredient: Icosapent ethyl (ethyl-EPA)

Title of Study: A Phase 3, *M*ulti-Center, Pl*a*cebo-Controlled, *R*andomized, Double-Bl*in*d, 12-Week Study With an Open-Label *E*xtension to Evaluate the Efficacy and Safety of AMR101 in Patients With Fasting Triglyceride Levels ≥500 mg/dL and ≤2000 mg/dL: The AMR101 MARINE Study

Investigators: For the list of investigators, see Appendix 16.1.4.

Study Sites: 54 sites in North America, Europe, India, and South Africa

Publication (reference): None

Study Period: Double-Blind Treatment Period: 12 weeks

Double-Blind Treatment Period + Open-Label Extension: 52 weeks

Initiation Date (First Patient Screened): 14 Dec 2009

Last Patient Screened: 03 Jun 2010

First Patient Randomized: 28 Jan 2010

Last Patient Randomized: 27 Jul 2010

Completion Date of Double-Blind Treatment Period: 19 Oct 2010

Database Lock for Double-Blind Treatment Period: 12 Nov 2010

Database Unblinding for Double-Blind Treatment Period: 16 Nov 2010

Phase of Development: 3

Study Objectives:

Primary: The primary objective of the study was to determine the efficacy of AMR101 2 g daily and 4 g daily, compared to placebo, in lowering fasting triglyceride (TG) levels in patients with fasting TG levels ≥500 mg/dL and ≤2000 mg/dL (≥5.6 mmol/L and ≤22.6 mmol/L).

Secondary and exploratory: The secondary and exploratory objectives of the study were as follows:

1. To determine the safety and tolerability of AMR101 2 g daily and 4 g daily;
2. To determine the effect of AMR101 on lipid profiles, including total cholesterol (TC), non-high-density lipoprotein cholesterol (non-HDL-C),

low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and very low-density lipoprotein cholesterol (VLDL-C);

3. To determine the effect of AMR101 on very low-density lipoprotein triglycerides (VLDL-TG);
4. To determine the effect of AMR101 on apolipoprotein A-I (apo A-I), apolipoprotein B (apo B), apo A-I/apo B ratio, lipoprotein(a) (Lp[a]), and lipoprotein-associated phospholipase A_2 (Lp-PLA_2);
5. To determine the effect of AMR101 on low-density lipoprotein (LDL) particle number and size;
6. To determine the effect of AMR101 on oxidized LDL and remnant-like particle cholesterol (RLP-C);
7. To determine the effect of AMR101 on fasting plasma glucose (FPG) and hemoglobin A_{1c} (HbA_{1c});
8. To determine the effect of AMR101 on insulin resistance;
9. To determine the effect of AMR101 on high-sensitivity C-reactive protein (hsCRP);
10. To determine the effect of AMR101 on intracellular adhesion molecule-1 (ICAM-1), interleukin-6 (IL-6), and plasminogen activator inhibitor-1 (PAI-1);
11. To determine the effects of AMR101 on fatty acid concentrations (including eicosapentaenoic acid [EPA]) in plasma and red blood cell membranes;
12. To explore the relationship between baseline fasting TG levels and the reduction in fasting TG levels; and
13. To explore the relationship between changes in fatty acid concentrations (including EPA) in plasma and red blood cell membranes and the reduction in fasting TG levels.

Methodology: This Phase 3, multi-center study consisted of a 6- to 8-week screening/washout period (which included a diet and lifestyle stabilization period and a TG qualifying period), a 12-week double-blind treatment period, and a 40-week open-label extension period.

Note: Although the objectives and design of each period are included in this report, only the statistical methodology and results for the double-blind treatment period are presented. A separate report will be generated for the open-label extension period.

Screening Period

The screening period included a 4- to 6-week diet and lifestyle stabilization period and washout period followed by a 2-week TG qualifying period. Patients on statin therapy (with or without ezetimibe) at screening were evaluated by the investigator as to whether this therapy could have been safely discontinued at screening, or if it was to have been continued. If statin therapy (with or without ezetimibe) was to be continued, dose(s) must have been stable for ≥4 weeks prior to the TG baseline

qualifying measurements for randomization (i.e., Visit 2 [Week -2]). Patients taking non-statin, lipid-altering medications (niacin >200 mg daily, fibrates, fish oil, other products containing omega-3 fatty acids, or other herbal products or dietary supplements with potential lipid-altering effects), either alone or in combination with statin therapy (with or without ezetimibe), at the time of screening must have been able to safely discontinue them at screening.

The screening visit (Visit 1) was to occur at either 6 weeks before randomization for patients not on lipid-altering therapy at screening or for patients who did not need to discontinue their current lipid-altering therapy or at 8 weeks before randomization for patients who required washout of their current lipid-altering therapy at screening. All patients were to receive counseling regarding the importance of the National Cholesterol Education Program Therapeutic Lifestyle Changes diet and received instructions on how to follow this diet at the screening visit. In addition, patients who required washout of lipid-lowering therapy began the 6-week washout period at screening (Week -8).

At Week -2, all eligible patients were to enter the TG qualifying period. Patients were to have their fasting TG level measured at Visit 2 (Week -2) and Visit 3 (Week -1). In order to enter the 12-week double-blind treatment period, patients must have had an average fasting TG level ≥500 mg/dL and ≤2000 mg/dL (≥5.6 mmol/L and ≤22.6 mmol/L) based on the average (arithmetic mean) of the Visit 2 (Week -2) and Visit 3 (Week -1) values. If a patient's average TG level from Visit 2 to Visit 3 fell outside the required range for entry into the study, an additional TG measurement could have been made 1 week later at Visit 3.1. If a third sample was collected at Visit 3.1, entry into the study was to be based on the average (arithmetic mean) of the TG values from Visits 3 and 3.1.

Double-Blind Treatment Period

After confirmation of qualifying fasting TG values, eligible patients were to enter a 12-week randomized, double-blind treatment period. At Visit 4 (Week 0), patients were randomly assigned to 1 of the following treatment groups: AMR101 2 g daily, AMR101 4 g daily, or placebo.

Approximately 80 patients per treatment group were to be randomized in this study. Stratification was by baseline TG level (≤750 mg/dL or >750 mg/dL [≤8.5 mmol/L or >8.5 mmol/L), gender, and the use of statin therapy at randomization (currently treated or not currently treated with statin therapy).

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

Open-Label Extension Period

Patients who completed the 12-week double-blind treatment period were eligible to enter a 40-week open-label extension period at Visit 7 (Week 12). All patients were to receive open-label AMR101 4 g daily. From Visit 7 (Week 12) until the end of the study, changes to the lipid-altering regimen were permitted (e.g., initiating, restarting,

or increasing the dose of statin or adding/restarting non-statin, lipid-altering medications), as guided by standard practice and prescribing information.

After Visit 8 (Week 16), patients were to return to the site every 12 weeks until the last visit at Visit 11 (Week 52).

Duration of Treatment: 52 weeks: 12 weeks of double-blind treatment followed by 40 weeks of open-label treatment

Number of Patients:

Planned (randomized): 240

Screened: 610

Randomized: 229

Completed double-blind period: 215 (94% of randomized patients)

Discontinued from double-blind period: 14 (6% of randomized patients)

Diagnosis and Main Criteria for Inclusion: The population for this study was men and women >18 years of age with a body mass index (BMI) ≤45 kg/m^2. Patients on lipid-lowering therapy and patients not on lipid-lowering therapy were eligible to enroll in the study. Patients had to have an average TG level ≥500 mg/dL and ≤2000 mg/dL from Visit 2 and Visit 3 or Visit 3 and Visit 3.1 to be eligible for randomization.

Investigational Product and Comparator Information:

AMR101 1 g capsules: lot numbers XI07B2 and XI07B3

Placebo capsules to match AMR101 capsules: lot numbers XI07A1 and XI07A2

Criteria for Evaluation:

Efficacy: The primary efficacy variable for the double-blind treatment period was percent change in TG from baseline to Week 12 endpoint.

The secondary efficacy variable for the double-blind treatment period included the following:

- Percent changes in VLDL-C, Lp-PLA_2, and apo B from baseline to Week 12 endpoint.

The exploratory efficacy variables for the double-blind treatment period included the following:

- Percent changes in TC, HDL-C, LDL-C, and non-HDL-C from baseline to Week 12 endpoint;
- Percent change in VLDL-TG from baseline to Week 12;
- Percent changes in apo A-I and apo B/apo A-I ratio from baseline to Week 12;
- Percent change in Lp(a) from baseline to Week 12;

- Percent changes in LDL particle number and size, measured by nuclear magnetic resonance, from baseline to Week 12;
- Percent change in RLP-C from baseline to Week 12;
- Percent change in oxidized LDL from baseline to Week 12;
- Changes in FPG and HbA_{1c} from baseline to Week 12;
- Change in insulin resistance, as assessed by the homeostasis model index insulin resistance (HOMA-IR), from baseline to Week 12;
- Change in ICAM-1 from baseline to Week 12;
- Change in IL-6 from baseline to Week 12;
- Change in PAI-1 from baseline to Week 12 (Note: This parameter was only collected at sites with proper storage conditions);
- Change in hsCRP from baseline to Week 12;
- Change in plasma and red blood cell EPA concentrations from baseline to Week 12; and
- Change in plasma and red blood cell concentrations of 28 fatty acids, including EPA, docosapentaenoic acid (n-3) (DPAn-3), docosahexaenoic acid (DHA), and the arachidonic acid/EPA (AA/EPA) ratio from baseline to Week 12.

Safety: Safety assessments included adverse events, clinical laboratory measurements (chemistry, hematology, and urinalysis), 12-lead electrocardiograms (ECGs), blood pressure, and physical examinations.

Statistical Methods: Efficacy evaluations were performed on the intent-to-treat (ITT) population. The primary efficacy analysis was also repeated on the per-protocol population. All efficacy statistical assessments are presented by randomized treatment group.

Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum or first and third quartile for non-parametric statistics) for the baseline and post-baseline measurements, the percent changes, or changes from baseline are presented by treatment group and by visit for all efficacy variables.

The primary efficacy analysis was performed using an analysis of covariance (ANCOVA) model with treatment, gender, and the use of statin therapy at randomization as factors and baseline TG value as a covariate. The statistical modeling assumptions were examined. Since significant departures from normality were observed, the alternative non-parametric analysis was performed. The Wilcoxon rank-sum test was used for the treatment comparisons and medians and quartiles were provided for each treatment group. Estimates for the median of the treatment differences and Hodges-Lehmann 2-tailed 95% and 99% confidence intervals were provided for each treatment comparison.

A step-down testing procedure (also called fixed-sequence testing) was to be performed. That is, only in the case in which AMR101 4 g daily was shown to have a greater TG reducing effect compared to placebo was the AMR101 2 g daily group to be tested as a primary endpoint. The principle of step-down testing procedures guaranteed that the family-wise error rate was properly controlled.

For the analysis of secondary efficacy parameters, ANCOVA models were used with treatment, gender, baseline TG category (≤750 mg/dL or >750 mg/dL [≤8.5 mmol/L or >8.5 mmol/L]), and the use of statin therapy at randomization as factors and the baseline value of the tested parameter as a covariate. For the analysis of exploratory efficacy parameters, an ANCOVA model was used with treatment as a factor and the baseline value of the tested parameter as a covariate. For the exploratory efficacy parameters, multiple comparisons were not used and the ANCOVA output was considered descriptive. For the analysis of the secondary and selected exploratory efficacy variables, the statistical modeling assumptions were examined. When significant departures from normality were observed, the alternative non-parametric analysis was performed.

When the parametric analysis was performed, the least-squares (LS) means, standard errors, and 2-tailed 95% confidence intervals for each treatment group and for the comparisons between each AMR101 group and placebo were provided. When the non-parametric analysis was performed, the Wilcoxon rank-sum test was used for the treatment comparisons and medians and quartiles were provided for each treatment group. Estimates for the median of the treatment differences and Hodges-Lehmann 2-tailed 95% and 99% confidence intervals were provided for each treatment comparison.

Safety analyses during the double-blind treatment period were conducted on the safety population with the actual treatment patients received. The evaluation of safety during the double-blind treatment period was based primarily on adverse events, clinical laboratory assessments, 12-lead ECGs, physical examinations, weight and BMI, and vital signs (heart rate and blood pressures). Other safety data were summarized, as appropriate.

Summary of Results: The population recruited for the current study included males (76.4%) and females (23.6%) with a mean age of 53 years. Approximately 25% of patients in each treatment group received statin therapy throughout the study. The percentage of patients in each treatment group with type 2 diabetes was 27.6% in the placebo group, 26.3% in the AMR101 2 g group, and 28.6% in the AMR101 4 g group. Mean compliance with study drug during the double-blind treatment period was 96.8% for the placebo group, 95.4% for the AMR101 2 g group, and 98.2% for the AMR101 4 g group.

Efficacy: In the ITT population, treatment with 4 g or 2 g per day of AMR101 for 12 weeks reduced fasting median TG levels to a greater extent than placebo by 33.1% ($p<0.0001$) and 19.7% ($p=0.0051$), respectively. The baseline median TG level for the total study population was 679.5 mg/dL. For both the AMR101 4 g and 2 g treatment groups, the maximum effect on fasting TG reduction occurred by Week 4 of the 12-week treatment period. Approximately 40% of patients in each treatment group

had median baseline TG levels >750 mg/dL. The median baseline TG level for this subgroup of patients was 1052 mg/dL in the placebo group, 947.5 mg/dL in the AMR101 2 g group, and 902.0 mg/dL in the AMR101 4 g group. As has been demonstrated previously in other TG-lowering agents in this subgroup of patients with higher median baseline TG levels, treatment with 4 g or 2 g per day of AMR101 reduced fasting median TG levels to a greater extent compared to the overall population (45.4% [p=0.0001] and 32.9% [p=0.0016], respectively). In patients with baseline TG levels ≤750 mg/dL, the median baseline TG level was 564.5 mg/dL in the placebo group, 568.0 mg/dL in the AMR101 2 g group, and 613.8 mg/dL in the AMR101 4 g group. Treatment with AMR101 reduced fasting median TG levels to a greater extent than placebo by 26.6% (p=0.0006) in the 4 g group. The reduction in fasting TG in the 2 g group compared to placebo (-7.0%) was not statistically significant.

In the subgroup of patients on statin therapy at baseline, AMR101 significantly reduced placebo-corrected median TG levels by 65.0% in the 4 g group and 40.7% in the 2 g group. The median-TG lowering effect with AMR101 appeared to be much higher in the statin-treated subgroup versus patients not on statins. In the subgroup of patients not on statin therapy at baseline, AMR101 significantly reduced placebo-corrected median TG levels by 25.8% in the 4 g group and 16.4% in the 2 g group.

The reduction in TG observed in this study with either dosage regimen of AMR101 was not associated with significant elevations in LDL-C. The estimate of the median of the treatment difference between the AMR101 4 g group and the placebo group was -2.3%. The estimate of the median of the treatment difference between the AMR101 2 g group and the placebo group was 5.2%. The treatment differences between each AMR101 treatment group and the placebo group were not statistically significant.

For the secondary efficacy parameters, 12 weeks of treatment with AMR101 4 g per day reduced median levels of VLDL-C, Lp-PLA_2, and apo B compared to placebo by 28.6% (adjusted p-value=0.0005), 13.6% (adjusted p-value=0.0006), and 8.5% (adjusted p-value=0.0019), respectively. A statistically significant percent reduction with AMR101 2 g compared to placebo was observed for VLDL-C; the placebo-corrected change in VLDL-C for the AMR101 2 g group (-15.3%) was not statistically significant after applying Hommel's multiple comparison procedure (adjusted p-value=0.1152).

Treatment with 4 g or 2 g per day of AMR101 for 12 weeks reduced median non-HDL-C levels compared to placebo by 17.7% (p<0.0001) and 8.1% (p=0.0182), respectively. The treatment differences in TC between the AMR101 4 g group and the placebo group (-16.3%; p<0.0001) and between the AMR101 2 g group and the placebo group (-6.8%; p=0.0148) were statistically significant.

In addition, compared to placebo, statistically significant percent reductions in VLDL-TG (-25.8%), apo A-I (-4.2%), LDL particle number (-16.3%), RLP-C (-29.8%), and hsCRP (-0.7 mg/L) were observed in the AMR101 4 g group.

The placebo-corrected changes in these exploratory parameters were not statistically significant in the AMR101 2 g group.

Treatment with 4 g or 2 g per day of AMR101 for 12 weeks statistically significantly increased EPA concentration (in both plasma and red blood cells) in a dose-dependent manner compared to placebo. The LS mean change in plasma EPA concentration from baseline to Week 12 endpoint was 269.2 μg/mL (LS mean percent change, 679.6%) for the AMR101 4 g group, 124.2 μg/mL (LS mean percent change, 308.9%) for the AMR101 2 g group, and -0.2 μg/mL (LS mean percent change, 12.7%) for the placebo group. The LS mean change in red blood cell EPA concentration from baseline to Week 12 endpoint was 57.0 μg/mL (LS mean percent change, 480.9%) for the AMR101 4 g group, 30.6 μg/mL (LS mean percent change, 270.0%) for the AMR101 2 g group, and -1.4 μg/mL (LS mean percent change, -3.5%) for the placebo group.

A linear relationship between EPA levels (in plasma and red blood cells) and TG reduction was observed. Patients in the AMR101 4 g group had a larger mean percent increase in EPA concentration (in plasma and in red blood cells) and a larger median percent decrease in TG from baseline than patients in the AMR101 2 g group and the placebo group.

From baseline to Week 12 endpoint, mean levels of plasma and red blood cell fatty acid parameters EPA and DPAn-3 (a metabolite of EPA) also increased in a dose-dependent manner. Small mean reductions in DHA in plasma and red blood cells were observed in each treatment group.

Safety: During the double-blind treatment period, 82 (35.8%) patients had at least 1 treatment-emergent adverse event (TEAE): 28 (36.8%) patients in the placebo group, 27 (35.5%) patients in the AMR101 2 g group, and 27 (35.1%) patients in the AMR101 4 g group. Twenty-seven (11.8%) patients had a TEAE that was considered by investigators to be related to study drug: 11 (14.5%) patients in the placebo group, 8 (10.5%) patients in the AMR101 2 g group, and 8 (10.4%) patients in the AMR101 4 g group. Most TEAEs during the double-blind treatment period were mild or moderate in severity.

Two patients had a treatment-emergent serious adverse event (SAE): 1 patient in the AMR101 2 g group (non-cardiac chest pain) and 1 patient in the AMR101 4 g group (coronary artery disease). Neither SAE was assessed by investigators as being related to study drug.

Four patients discontinued from the double-blind treatment period due to an adverse event: 3 patients in the placebo group and 1 patient in the AMR101 2 g group. Three of the 4 patients had an adverse event that was considered by investigators to be related to study drug: 2 patients in the placebo group (arthralgia and nausea) and 1 patient in the AMR101 2 g group (diarrhea). The 4th patient in the placebo group whose adverse event was not related to study drug discontinued from the study due to gout.

The most common system organ class of TEAEs in each treatment group was gastrointestinal disorders: 14 (18.4%) patients in the placebo group, 12 (15.8%) patients in the AMR101 2 g group, and 8 (10.4%) patients in the AMR101 4 g group.

Patients in the AMR101 4 g group had the lowest incidence of diarrhea (1.3%), nausea (1.3%), and eructation (0.0%). The incidence of diarrhea was 5.3% in the AMR101 2 g group and 6.6% in the placebo group. The incidence of nausea was 6.6% in the AMR101 2 g group and 5.3% in the placebo group. The incidence of eructation was 1.3% in the AMR101 2 g group and 3.9% in the placebo group.

No clinically meaningful changes in safety laboratory parameters, ECG parameters, vital signs, or physical examination findings were noted.

Conclusions: In a population of patients with very high TG levels who are at risk for pancreatitis, treatment with 4 g or 2 g per day of AMR101 resulted in reductions in TG levels compared to placebo that were statistically significant and clinically meaningful. As has been demonstrated previously, the percent reduction in TG levels was greater in those patients with higher baseline TG levels. In addition, compared to placebo, statistically and clinically significant percent reductions in VLDL-C, Lp-PLA_2, apo B, TC, non-HDL-C, VLDL-TG, apo A-I, LDL particle number, RLP-C, and hsCRP were observed in the AMR101 4 g group. In contrast to other TG-lowering agents, the reduction in TG levels was not associated with an elevation in LDL-C levels compared to placebo.

Treatment with AMR101 was well tolerated and no safety concerns emerged in this study.

Date of the Report: 15 June 2011