AMR101: Effects of a Pure EPA Omega-3 Fatty Acid on the Fatty Acid Profile in Plasma and Red Blood Cells in Patients With Very High Triglycerides (Results from the MARINE Study)

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INTRODUCTION

• AMR101 is a EPA fatty acid for 100% pure EPA omega-3, the only EPA omega-3.
• The MARINE study demonstrated that AMR101 significantly reduced plasma and RBC fatty acid levels compared with placebo in patients with high triglycerides, primarily by lowering arachidonic acid (AA) but no other fatty acid.
• EPA, an omega-3 fatty acid, has been shown to act as a proinflammatory mediator, with a potential role in cardiovascular disease.
• AMR101 was shown to be safe and well tolerated, with no serious adverse events (AEs).

METHODS

• Study Design

- Randomized, placebo-controlled, double-blind, parallel-group, and 4-arm design (Fig. 1).
- 10-week lead-in period and 12-week randomized period.
- Participants were randomized to 1 of 4 treatment groups: placebo (P); AMR101, 2 g/day; AMR101, 4 g/day; or matching placebo twice daily.
- AMR101 was administered for 4 weeks before the randomized period to achieve stabilization.
- Participants underwent a 1-week washout period before entering the randomized period.
- Baseline samples were collected at Week 0 and Week 12.
- AMR101 2 g/day; AMR101 4 g/day; or matching placebo administered twice daily.
- Participants were instructed to remain on their stable diets and no changes in normal physical activity level during the study.
- Participants were instructed to maintain weight, recruit stable physical activity level during the study.
- Participants were instructed to avoid consuming alcohol or other dietary supplements.
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RESULTS

• Twenty-five patients were included in the lead-in period (7, 7, and 11 patients are in the AMR101 2 g/day, 4 g/day, and placebo groups, respectively).
• Plasma lipids were measured at Week 0 and Week 12.
• Plasma and RBC samples were collected at baseline and Week 12.
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CONCLUSION

• AMR101 significantly reduced plasma and RBC fatty acid levels compared with placebo in patients with high triglycerides, primarily by lowering arachidonic acid (AA) but no other fatty acid.
• AMR101 was shown to be safe and well tolerated, with no serious adverse events (AEs).
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REFERENCES

AMR101 is an OM-3 fatty acid agent containing ≥96% pure icosapent ethyl, the ethyl ester of

Palmitic acid, μg/g (n=48, 53, 44) 346.1 (44.5) -5.8 (5.7) 344.1 (45.1) -2.9 (5.4) 341.5 (37.7) -1.4 (6.0) -0.7

Linoleic acid, μg/g (n=47, 54, 48) 76.8

The AA/EPA ratio, which shows the balance of each polyunsaturated fatty acid, has been

AMR101 4 g/day; RBC Effects

AMR101 decreased the concentrations of key fatty acids including arachidonic, palmitic,

Overall, AMR101 increased EPA concentrations in a linear dose-dependent fashion,

Lipids were extracted from plasma and RBC suspensions and converted into fatty acid

Percent Mean Change in Plasma Fatty Acid Concentrations and Ratios (95% CI)

Percent Mean Change in EPA Concentrations in Plasma and Red Blood Cells (95% CI)

AMR101 2 g/day; Plasma Effects

AMR101 2 g/day significantly decreased placebo-adjusted mean plasma AA to EPA ratio as

The dose-dependent increase in EPA concentrations was consistent with the previously

Stable diet and no alterations in normal physical activity level during study

AMR101 2 g/day; RBC Effects

AMR101 significantly increased DHA in plasma and decreased the proportion of OM-6 fatty acids in RBCs. AMR101 significantly increased EPA and DPAn-3, as well as the ratio of total OM-3 to total OM-6 in RBCs

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AMR101 from Baseline to Week 12: Placebo-Adjusted

Double-Blind Period

Open-Label Extension

Study Design

Assessments

Concentrations (95% CI) from Baseline to Week 12

Mean and SD are reported for baseline values; LS mean and SE are reported for changes from baseline and placebo-adjusted changes from baseline.

a

‰OM-6 fatty acids = sum of linoleic,:

Figure 2.  AMR101 from Baseline to Week 12: Placebo-Adjusted

1 wk6 wks

AMR101 2 g/day

0

1 wk

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INTRODUCTION

- AMR101 is an OM-3 fatty acid agent containing ≥96% pure icosapent ethyl, the ethyl ester of EPA.
- The MARINE study demonstrated that AMR101 significantly reduced placebo-adjusted TG levels and significantly improved other lipid parameters without significantly increasing LDL-C levels in patients with very high TG levels (>500 and ≤2000 mg/dL).
- EPA may potentially reduce cardiovascular disease risk via anti-inflammatory properties, antithrombotic effects, inhibition of platelet aggregation, vasodilatory activity, increasing circulating adiponectin level, triglyceride-lowering effect, and induction of plaque stabilization.
- Variations in fatty acid levels and their relative proportions to one another in plasma and/or RBC membranes are correlated with cardiovascular risk as well as the production of proinflammatory/anti-inflammatory mediators.
- This analysis evaluated the effects of AMR101 on plasma and RBC fatty acid profiles in patients from the MARINE study, and assessed the relationship of the fatty acid profiles to the TG-lowering effects of AMR101.

METHODS

Figure 1. Study Design

Study Design

- The previously reported MARINE study was a 12-week, phase 3, multicenter, international trial; the study design is summarized below (Figure 1).
- Patients entered a 4- to 6-week lead-in period of diet and lifestyle stabilization and non-statin lipid-altering drug washout, possible statin washout, and medication washout.
- AMR101 had no significant change on the proportion of saturated fatty acids in plasma and RBCs.
- AMR101 increased the proportion of OM-3 fatty acids in plasma and RBCs.
- Overall, AMR101 increased EPA concentrations in a linear dose-dependent fashion, indicating that its metabolic effects (including TG-lowering) are not due to changes in DHA levels.
- AMR101 did not significantly affect the concentrations of DHA in plasma or RBCs, indicating that its metabolic effects (including TG-lowering) are not due to changes in DHA levels.

Assessments

- In this exploratory analysis of the MARINE study, efficacy endpoints included percent change in plasma concentration and RBC membrane content of fatty acids from baseline to Week 12 for AMR101 versus placebo.
- Fatty Acid Measurement
  - The fatty acid profile of plasma and RBCs included adventic acid, arachidonic acid, and stearic acid (saturated).
  - Fatty acids at lower concentrations but with important biological roles: the OM-3 fatty acids EPA (present in AMR101 as ethyl-EPA) and DHA.
  - Lipids were extracted from plasma and RBC suspensions and converted into fatty acid methyl esters for analysis using a validated GC/FID.
- Statistical Analysis
  - Patients from the intent-to-treat population (all randomized patients who had a baseline TG primary efficacy and point measurement, received ≥1 dose of study drug, and had ≥1 postrandomization efficacy measurement) with non-missing baseline and Week 12 and point plasma or RBC values were included in analyses; outliers were detected for each parameter and excluded from analyses.
  - Outliers were defined as data points (baseline and on-treatment fatty acid parameter values) for which the percent change from baseline fell outside the range defined by the IQR (1st and 3rd quartile) ± 1.5 * IQR.
  - Fatty acid parameters were compared between AMR101 and placebo using an ANCOVA model with treatment, gender, and statin use at randomization as factors, and the baseline parameter value as a covariate.
  - LSMs, SDs, SEs, and 2-tailed 95% CIs for each treatment group and for each comparison are reported (α = 0.05).

RESULTS

- 224 patients were in the intent-to-treat population (76, 73, and 75 patients in the AMR101 4 g/day, 2 g/day, and placebo groups, respectively); some patients had missing fatty acid data at baseline and/or Week 12, and are therefore not included (as reflected in the n values in the results).
- Baseline characteristics were comparable between treatment groups; total ITT population: 76.4% male, 88.2% white, mean age 52.9 years, weight 82.8 kg, BMI 30.8 kg/m².

- The MARINE study demonstrated that AMR101 significantly reduced placebo-adjusted TG levels and significantly improved other lipid parameters without significantly increasing LDL-C levels in patients with very high TG levels (>500 and ≤2000 mg/dL).
- EPA may potentially reduce cardiovascular disease risk via anti-inflammatory properties, antithrombotic effects, inhibition of platelet aggregation, vasodilatory activity, increasing circulating adiponectin level, triglyceride-lowering effect, and induction of plaque stabilization.
- Variations in fatty acid levels and their relative proportions to one another in plasma and/or RBC membranes are correlated with cardiovascular risk as well as the production of proinflammatory/anti-inflammatory mediators.
- This analysis evaluated the effects of AMR101 on plasma and RBC fatty acid profiles in patients from the MARINE study, and assessed the relationship of the fatty acid profiles to the TG-lowering effects of AMR101.
In the MARINE study, AMR101 (≥96% pure icosapent ethyl, the ethyl ester of EPA) did not significantly affect the concentrations of DHA in plasma or RBCs, indicating that AMR101 did not change the ratio of DHA to EPA. However, AMR101 significantly increased the concentrations of EPA and its metabolite, DPAn-3, in plasma and RBCs. AMR101 significantly reduced the AA/EPA ratio in plasma and RBCs; the AA concentration in RBCs decreased significantly relative to the total of OM-3, OM-6, saturated, and monounsaturated fatty acids. AMR101 increased the ratio of total OM-3 to total OM-6 in RBCs.

Fatty Acid Concentrations in Plasma (Figure 2, Figure 3, Table 1)
- Both doses of AMR101 (4 g/day and 2 g/day) significantly increased the placebo-adjusted mean concentrations of EPA and DPAn-3 and increased the ratio of total OM-3 to total OM-6 in plasma.
- AMR101 4 g/day significantly decreased placebo-adjusted mean plasma AA to EPA ratio as well as the plasma concentrations of arachidonic, palmitic, stearic, oleic, and linoleic acids.
- Neither dose of AMR101 had a significant effect on placebo-adjusted mean concentration of DHA in plasma.

Fatty Acid Concentrations in RBCs (Figure 2, Figure 4, Table 2)
- Both doses of AMR101 significantly increased the placebo-adjusted mean concentrations of EPA and DPAn-3, as well as the ratio of total OM-3 to total OM-6 in RBCs.
- Both doses of AMR101 significantly decreased the placebo-adjusted mean concentration of AA and the ratio of AA to EPA in RBCs, and AMR101 4 g/day significantly reduced the placebo-adjusted mean concentration of linoleic acid in RBCs.
- Neither dose of AMR101 had a significant effect on the placebo-adjusted mean concentration of DHA in RBCs.

Figure 5. AMR101: Dose-dependent Mean Change in EPA Concentrations (95% CI) from Baseline to Week 12
- Increasing doses of AMR101 increased both plasma and RBC EPA concentrations (Figure 5).

Table 1. AMR101: Change from Baseline to Week 12 in Plasma Fatty Acid Concentrations and Ratios

<table>
<thead>
<tr>
<th>AMR101 4 g/day (n=76)</th>
<th>AMR101 2 g/day (n=75)</th>
<th>Placebo (n=75)</th>
<th>Placebo-adjusted Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean Change in EPA Concentration from Baseline (/μg/g)</strong></td>
<td><strong>Mean Change in EPA Concentration from Baseline (/μg/g)</strong></td>
<td><strong>Mean Change in EPA Concentration from Baseline (/μg/g)</strong></td>
<td><strong>Mean Change in EPA Concentration from Baseline (/μg/g)</strong></td>
</tr>
<tr>
<td>Linoleic acid, μg/g</td>
<td>188.7 (40.6)</td>
<td>150.5 (35.0)</td>
<td>128.8 (32.0)</td>
</tr>
<tr>
<td>Stearic acid, μg/g</td>
<td>21.6 (1.4)</td>
<td>27.7 (1.5)</td>
<td>28.7 (2.0)</td>
</tr>
<tr>
<td>EPA, μg/g</td>
<td>50.8 (2.5)</td>
<td>107.2 (6.9)</td>
<td>107.2 (7.0)</td>
</tr>
<tr>
<td>DPAn-3, μg/g</td>
<td>1.9 (0.3)</td>
<td>0.8846</td>
<td>0.0435</td>
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<tr>
<td><strong>Ratio of total OM-3 to total OM-6</strong></td>
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</tr>
<tr>
<td>Placebo</td>
<td>0.45 (0.02)</td>
<td>0.3278</td>
<td>0.8076</td>
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<tr>
<td>AMR101 2 g/day</td>
<td>0.30 (0.03)</td>
<td>0.0001</td>
<td>0.0001</td>
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<tr>
<td>AMR101 4 g/day</td>
<td>0.30 (0.03)</td>
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</table>

Mean and SD are reported for baseline values; LS mean and SE are reported for changes from baseline and placebo-adjusted changes from baseline.
AMR101: Effects of a Pure EPA Omega-3 Fatty Acid on the Fatty Acid Profile in Plasma and RBCs

Qualifying patients entered the double-blind 12-week safety and efficacy period (Visit 4) and were randomized to 1 of 3 blinded treatment groups: AMR101 4 g/day, AMR101 2 g/day, or matching placebo administered twice daily. AMR101 significantly reduced placebo-adjusted TG concentrations compared to placebo (Visit 4 vs Visit 0).

Figure 1

Figure 2

Figure 3

Figure 4

Figure 5

Figure 6

Table 2. AMR101: Change from Baseline to Week 12 in RBC Fatty Acid Concentrations and Ratios

<table>
<thead>
<tr>
<th>AMR101 4 g/day (n=76)</th>
<th>AMR101 2 g/day (n=73)</th>
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</thead>
<tbody>
<tr>
<td><strong>EPA, μg/g</strong></td>
<td><strong>Change from baseline, μg/g</strong></td>
<td><strong>Baseline value, μg/g</strong></td>
<td><strong>Change from baseline, μg/g</strong></td>
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<td>n=76</td>
<td>n=73</td>
<td>n=75</td>
<td>n=76</td>
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<tr>
<td>Oleic Acid, μg/g</td>
<td>-0.1278</td>
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<td>Palmitic Acid, μg/g</td>
<td>0.0072</td>
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<td>Stearic Acid, μg/g</td>
<td>0.3044</td>
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<td><strong>AA, μg/g</strong></td>
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Mean and SD are reported for changes from baseline and placebo-adjusted changes from baseline.

Figure 1: AMR101 from Baseline to Week 12: Placebo-Adjusted Percent Mean Change in Plasma Fatty Acid Concentrations and Ratios (95% CI)

Figure 2: AMR101 from Baseline to Week 12: Placebo-Adjusted Percent Mean Change in RBC Fatty Acid Concentrations and Ratios (95% CI)

Figure 3: AMR101 from Baseline to Week 12: Placebo-Adjusted Percent Mean Change in Plasma Fatty Acid Concentrations and Ratios (95% CI)

Figure 4: AMR101 from Baseline to Week 12: Placebo-Adjusted Percent Mean Change in RBC Fatty Acid Concentrations and Ratios (95% CI)

Figure 5: AMR101: Relationship Between Plasma TG-lowering Effect and EPA Concentrations in Plasma and RBCs (PK/PD Relationship)

Figure 6: AMR101: Relationship Between Plasma TG-lowering Effect and EPA Concentrations in Plasma and RBCs (PK/PD Relationship)

AMR101: Relationship Between Plasma and RBC EPA Concentration and TG-lowering

- Increased plasma and RBC concentrations of EPA were accompanied by greater reductions in plasma TGs (Figure 6)
The most abundant fatty acids in plasma and RBCs: linoleic and arachidonic acids

Fatty Acid Measurement

INTRODUCTION

RESULTS

METHODS

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Patients from the intent-to-treat population (all randomized patients who had a baseline

esters

GC/FID measures total fatty acid concentrations, including unesterified fatty acids and fatty

methyl esters for analysis using a validated GC/FID

Qualifying patients entered the double-blind 12-week safety and efficacy period (Visit 4) and

week was allowed for another measurement (adjunct Visit 3.1) and Visits 3 and 3.1 were used

trial1; the study design is summarized below (V3

V5

40-Week

Table 1. AMR101: Change from Baseline to Week 12 in Plasma Fatty Acid Concentrations

Baseline value (SD)

Placebo-adjusted Mean Change from Baseline (%)

Saturated

Palmitic acid, μg/g

Stearic acid, μg/g

OM-3 fatty acids generally exert anti-inflammatory effects while OM-6 fatty acids may

OM-6 fatty acids; PD = pharmacodynamics; PK = pharmacokinetics; RBC = red blood cell; SD

immunodeficiency virus; IQR = interquartile range; LDL-C = low-density lipoprotein cholesterol;

kinase; DHA = docosahexaenoic acid; DPA = docosapentaenoic acid; EPA = eicosapentaenoic

aspartate aminotransferase; BMI = body mass index; CI = confidence interval; CK = creatine

AA/EP A ****

AA ****

Oleic Acid **

Palmitic Acid ****

DHA NS

Percent Mean Change in Plasma Fatty Acid Concentrations from Baseline (/μg/g)

AMR101 4 g/day vs

AMR101 2 g/day vs

Placebo (n=75)

Placebo-adjusted Mean Change from Baseline (95% CI)

Baseline value (SD)

Placebo-adjusted Mean Change from Baseline (%)

Median Change in Plasma TG (μg/dl)

Figure 4. AMR101 from Baseline to Week 12: Placebo-Adjusted

Placebo-adjusted change from baseline (SE) Baseline value (SD)

CONCLUSION

Overall, AMR101 increased EPA concentrations in a linear dose-dependent fashion, lowered TG linearly related to EPA concentrations, caused beneficial shifts in the fatty acid profile, and significantly decreased the AA/EPA ratio in plasma and RBCs, which could help reduce cardiovascular risk.4,5

ABBREVIATIONS

AA = arachidonic acid; ALT = alanine transaminase; ANCOVA = analysis of covariance; AST = aspartate aminotransferase; BMI = body mass index; CI = confidence interval; CK = creatine kinase; DHA = docosahexaenoic acid; DPA = docosapentaenoic acid; EPA = eicosapentaenoic acid; GC/FID = gas chromatograph assay method with flame ionization detector; HIV = human immunodeficiency virus; IQR = interquartile range; LDL-C = low-density lipoprotein cholesterol; LUM = least squares means; MARINE = Multi-Center, Placebo-Controlled, Randomized, Double-Blind, 12-week study with an open-label extension; OM-3 = omega-3 fatty acids; OM-6 = omega-6 fatty acids; PD = pharmacodynamics; PK = pharmacokinetics; RBC = red blood cell; SD = standard deviation; SE = standard error; TG = triglycerides; ULN = upper limit of normal

REFERENCES