AMR101, a Pure-EPA Omega-3 Fatty Acid, Lowers Triglycerides in Patients with Very High Triglycerides Without Raising LDL-C: The MARINE Study

HE Bays,¹ CM Ballantyne,² JJ Kastelein,³ E Stein,⁴ JL Isaacsohn,⁴ RA Braeckman,⁵ and PN Soni⁵

¹Louisville, KY, USA; ²Houston, TX, USA; ³Amsterdam, The Netherlands; ⁴Cincinnati, OH, USA; ⁵Mystic, CT, USA
Declaration of Interest

Dr. Bays reports research grants for the conduct of the MARINE study and other Amarin trials, and has served as an advisor to Amarin Pharma Inc. He has also received research grants from GlaxoSmithKline, Omthera, and Trygg, and in more than 20 years of clinical research, has received research grants and served as an advisor, consultant, and speaker to other pharmaceutical companies.
Introduction

- Fish oil therapies rich in OM-3 fatty acids (EPA and DHA) and fibrates effectively lower TG in hypertriglyceridemic patients; however, these agents may substantially increase LDL-C levels, especially in patients with very high TG levels\(^1\-3\)
- Pure EPA may reduce TG levels without raising LDL-C levels\(^4\-8\)
- AMR101 is an OM-3 agent containing ≥96% pure icosapent ethyl EPA (the ethyl ester of EPA)


DHA=docosahexaenoic acid; EPA=eicosapentaenoic acid; LDL-C=low-density lipoprotein cholesterol; OM-3=omega-3; TG=triglycerides.
The MARINE Study

Objective

• The MARINE study (Multi-Center, PIAcebo-Controlled, Randomized, Double-Bl/InD, 12-week study with an open-label Extension) investigated the efficacy and safety of AMR101 in reducing TG levels in patients with very high TG (≥500 mg/dL) and evaluated the effect of AMR101 on other lipid and lipoprotein parameters.
The MARINE Study

Inclusion Criteria

- Men or women >18 years of age
- Stable diet
- No alterations in physical activity level during study
- TG $\geq 500$ mg/dL and $\leq 2000$ mg/dL
- If on background statin therapy, study participants were to remain on the same statin at the same dose through the duration of the study.
The MARINE Study

Study Design

- 12-week, phase 3, multicenter study conducted in the US, South Africa, India, Ukraine, Finland, Germany, Italy, and Netherlands

- Patients with TG ≥500 mg/dL and ≤2000 mg/dL, with or without background statin therapy
The MARINE Study

Disposition of Patients

610 Patients Screened

381 (62.5%) Screen Failed:
- 333 Did not satisfy inclusion/exclusion criteria
- 32 Withdrew consent
- 5 Lost to follow-up
- 1 Protocol violation
- 3 Adverse event
- 7 Other

229 Patients Randomized

Randomized
- AMR101 4 g/day
  77 Patients
- AMR101 2 g/day
  76 Patients
- Placebo
  76 Patients

Completed 4 weeks
- AMR101 4 g/day
  75 (97.4%)
- AMR101 2 g/day
  73 (96.1%)
- Placebo
  74 (97.4%)

Completed 12 weeks
- AMR101 4 g/day
  74 (96.1%)
- AMR101 2 g/day
  70 (92.1%)
- Placebo
  71 (93.4%)

Discontinued*
- Adverse event
  3 (3.9%)
- Withdrew consent
  0
- Lost to follow-up
  0
- TG >2000 mg/dL
  1

*Of the 4 patients who discontinued the study due to adverse events, 1 patient in the AMR101 2-g/day group discontinued due to diarrhea and 3 patients in the placebo group discontinued due to arthralgia, gout, and nausea, respectively.
### The MARINE Study

#### Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>AMR101 4 g/day (n=77)</th>
<th>AMR101 2 g/day (n=76)</th>
<th>Placebo (n=76)</th>
<th>Total (n=229)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean y (SD)</strong></td>
<td>51.9 (10.3)</td>
<td>53.4 (9.3)</td>
<td>53.4 (8.3)</td>
<td>52.9 (9.3)</td>
</tr>
<tr>
<td><strong>Age ≤65 y, n (%)</strong></td>
<td>70 (90.9)</td>
<td>70 (92.1)</td>
<td>71 (93.4)</td>
<td>211 (92.1)</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>59 (76.6)</td>
<td>58 (76.3)</td>
<td>58 (76.3)</td>
<td>175 (76.4)</td>
</tr>
<tr>
<td><strong>White, n (%)</strong></td>
<td>67 (87.0)</td>
<td>67 (88.2)</td>
<td>68 (89.5)</td>
<td>202 (88.2)</td>
</tr>
<tr>
<td><strong>Weight, mean kg (SD)</strong></td>
<td>93.2 (18.3)</td>
<td>92.1 (15.6)</td>
<td>93.0 (16.9)</td>
<td>92.8 (16.9)</td>
</tr>
<tr>
<td><strong>BMI, mean kg/m² (SD)</strong></td>
<td>30.4 (4.3)</td>
<td>30.8 (4.2)</td>
<td>31.0 (4.3)</td>
<td>30.8 (4.3)</td>
</tr>
</tbody>
</table>

- 25% on background statin therapy
- 39% with baseline TG >750 mg/dL
- Median baseline TG: 680 mg/dL

BMI = body mass index.
Primary End Point

- AMR101 significantly reduced median placebo-adjusted TG levels from baseline to study end
  - 4 g/day, 33.1% ($P<0.0001$)
  - 2 g/day, 19.7% ($P=0.0051$)
- Significant reductions in sub-populations
  - Patients with baseline TG >500 mg/dL
  - Patients with baseline TG >750 mg/dL
  - Statin-treated patients
The MARINE Study
Median Percent Change (IQR) in TG from Baseline (ITT population)

ITT=intent-to-treat; IQR=interquartile range.
The MARINE Study
Change in Median Placebo-adjusted TG Levels from Baseline to Study End by Baseline TG (ITT population)

The chart shows the change in median placebo-adjusted TG levels from baseline to study end by baseline TG levels for the ITT population. The chart is divided into three groups:

1. Baseline TG ≤750 mg/dL
   - 4 g/day: Median change of -25.1%, n=48
   - 2 g/day: Median change of -9.1%, n=45
   - P-value: NS

2. Baseline TG >750 mg/dL
   - 4 g/day: Median change of -45.4%, n=28
   - 2 g/day: Median change of -32.9%, n=28
   - P-value: *P<0.05

3. All Patients
   - 4 g/day: Median change of -33.1%, n=76
   - 2 g/day: Median change of -19.7%, n=73
   - P-values: ****P<0.0001, ***P<0.001, **P<0.01, *P<0.05

The chart indicates that patients who started with higher baseline TG levels had a greater reduction in TG levels compared to those with lower baseline TG levels, with statistically significant differences noted in all groups.

P-values reflect differences between AMR101 versus placebo.
The MARINE Study
Change in Median Placebo-adjusted TG Levels from Baseline to Study End by Statin Use (ITT population)

Baseline TG (mg/dL)

With Statin
650 592
No Statin
680 673
All Patients
680 657

Median Change (%)

4 g/day
2 g/day
-65.0
-40.7
-60.0
-50.0
-40.0
-30.0
-20.0
-10.0
0

-19.7
n=73
***

-33.1
n=76
****

-25.8
n=57
*

-16.4
n=54

-40.7
n=19
*

****P<0.0001; ***P<0.001; **P<0.01; *P<0.05; NS=Not Significant (P≥0.05)
P-values reflect differences between AMR101 versus placebo
The MARINE Study
Median Placebo-Adjusted Change from Baseline for Efficacy End Points (ITT population)

Apo B=apolipoprotein B; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; Lp-PLA2=lipoprotein-associated phospholipase A2; TC=total cholesterol; VLDL-C=very–low-density lipoprotein cholesterol; VLDL-TG=very–low-density lipoprotein triglycerides.

****P<0.0001; ***P<0.001; **P<0.01; *P<0.05; NS=Not Significant (P≥0.05)
P-values reflect differences between AMR101 versus placebo
The MARINE Study
Change in Median Placebo-adjusted hsCRP Levels from Baseline to Study End by Statin Use (ITT population)

Median Change (%)

<table>
<thead>
<tr>
<th></th>
<th>With Statin</th>
<th>No Statin</th>
<th>All Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 g/day</td>
<td>-67.9 n=19</td>
<td>-33.2 n=18 NS</td>
<td>-36.0 n=75 **</td>
</tr>
<tr>
<td>2 g/day</td>
<td></td>
<td>-27.4 n=56 *</td>
<td>-10.1 n=70 NS</td>
</tr>
</tbody>
</table>

**P<0.01; *P<0.05; NS=Not Significant (P≥0.05)
P-values reflect differences between AMR101 versus placebo
The MARINE Study

Safety Assessments

• Treatment-emergent adverse events (TEAEs) similar across treatment groups
  – Most were mild to moderate and deemed not related to study drug
• 2 SAEs deemed unrelated to study drug
  – Noncardiac chest pain (AMR101 2 g/day)
  – Coronary artery disease (AMR101 4 g/day)
• 4 discontinuations due to TEAEs (3 placebo; 1 AMR101 2 g/day)
• No deaths occurred during the study
• No significant changes in fasting blood glucose, HBA$_{1C}$, vital signs, electrocardiograms, or liver or kidney function with either AMR101 dose

A$_{1C}$=hemoglobin A1C; CAD=coronary artery disease; ECG=electrocardiogram; FBG=fasting blood glucose; SAE=serious adverse event; TEAE=treatment-emergent adverse event.
### The MARINE Study

#### TEAEs Occurring in >3% of Patients (Safety Population)

<table>
<thead>
<tr>
<th></th>
<th>AMR101 4 g/day (n=77)</th>
<th>AMR101 2 g/day (n=76)</th>
<th>Placebo (n=76)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any TEAE</strong></td>
<td>27 (35.1)</td>
<td>26 (34.2)</td>
<td>28 (36.8)</td>
</tr>
<tr>
<td><strong>Diarrhea</strong></td>
<td>1 (1.3)</td>
<td>4 (5.3)</td>
<td>5 (6.6)</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>1 (1.3)</td>
<td>5 (6.6)</td>
<td>4 (5.3)</td>
</tr>
<tr>
<td><strong>Eructation</strong></td>
<td>0</td>
<td>1 (1.3)</td>
<td>3 (3.9)</td>
</tr>
</tbody>
</table>
The MARINE Study

Conclusions

• AMR101 (pure EPA) significantly reduced TG at both the 4 g/day and 2 g/day doses in patients with very high TG levels
• AMR101 had no significant effect on LDL-C
• AMR101 4 g/day significantly reduced non–HDL-C, Apo B, Lp-PLA₂, TC, VLDL-C, VLDL-TG, and hsCRP, with no significant effect on HDL-C
• AMR101 4 g/day reduced CRP to a degree often reported with statins¹,²
• AMR101 was effective when administered with or without statins
  – AMR101 appeared to reduce TG more in the statin-treated subgroup than in patients not on statins, suggesting AMR101 may have synergistic effects when administered with statins
• AMR101 was generally well tolerated, with incidence and severity of TEAEs similar to placebo
• AMR101 is a novel TG lowering-agent that significantly reduces TG levels without significantly increasing LDL-C levels

Thank You