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

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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\textsuperscript{1-3}
• Pure EPA may reduce TG levels without raising LDL-C levels\textsuperscript{4-8}
• AMR101 is an OM-3 agent containing ≥96% pure icosapent ethyl EPA (the ethyl ester of EPA)

Objective

- The MARINE study (Multi-Center, Placebo-Controlled, Randomized, Double-Blinded, 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.
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.
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
- 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

Randomized
- AMR101 4 g/day
  - 77 Patients
  - Completed 4 weeks: 75 (97.4%)
  - Completed 12 weeks: 74 (96.1%)
  - Discontinued:
    - Adverse event: 3 (3.9%)
    - Withdrew consent: 2
    - Lost to follow-up: 0
    - TG >2000 mg/dL: 1

- AMR101 2 g/day
  - 76 Patients
  - Completed 4 weeks: 73 (96.1%)
  - Completed 12 weeks: 70 (92.1%)
  - Discontinued:
    - Adverse event: 6 (7.9%)
    - Withdrew consent: 1
    - Lost to follow-up: 1
    - TG >2000 mg/dL: 0

- Placebo
  - 76 Patients
  - Completed 4 weeks: 74 (97.4%)
  - Completed 12 weeks: 71 (93.4%)
  - Discontinued:
    - Adverse event: 5 (6.6%)
    - Withdrew consent: 3
    - Lost to follow-up: 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
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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)

<table>
<thead>
<tr>
<th>Baseline TG (mg/dL)</th>
<th>Median Change (%)</th>
<th>P-value</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤750</td>
<td>-25.1***</td>
<td>&lt;0.0001</td>
<td>48</td>
</tr>
<tr>
<td>&gt;750</td>
<td>-32.9**</td>
<td>&lt;0.001</td>
<td>28</td>
</tr>
<tr>
<td>All Patients</td>
<td>-33.1****</td>
<td>&lt;0.0001</td>
<td>76</td>
</tr>
</tbody>
</table>

P-values reflect differences between AMR101 versus placebo

****P<0.0001; ***P<0.001; **P<0.01; *P<0.05; NS=Not Significant (P≥0.05)
**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 (%)**

- **With Statin**
  - 4 g/day: -65.0, n=19
  - 2 g/day: -40.7, n=19

- **No Statin**
  - 4 g/day: -25.8, n=57
  - 2 g/day: -16.4, n=54

- **All Patients**
  - 4 g/day: -33.1, n=76
  - 2 g/day: -19.7, n=73

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**P-values**

- **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)**

<table>
<thead>
<tr>
<th></th>
<th>4 g/day</th>
<th>2 g/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG</td>
<td>-33.1</td>
<td>5.2</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>-36.0</td>
<td>-10.1</td>
</tr>
<tr>
<td>VLDL-C</td>
<td>-28.6</td>
<td>-25.8</td>
</tr>
<tr>
<td>Lp-PLA₂</td>
<td>-19.7</td>
<td>-17.3</td>
</tr>
<tr>
<td>Apo B</td>
<td>-13.6</td>
<td>-16.3</td>
</tr>
<tr>
<td>TC</td>
<td>-5.1</td>
<td>NS</td>
</tr>
<tr>
<td>LDL-C</td>
<td>-2.6</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-C</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>VLDL-TG</td>
<td>-3.6</td>
<td>NS</td>
</tr>
<tr>
<td>hsCRP</td>
<td>-28.6</td>
<td>NS</td>
</tr>
</tbody>
</table>

**P-values reflect differences between AMR101 versus placebo**

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<0.01; *P<0.05; NS=Not Significant (P≥0.05)**
**The MARINE Study**

Change in Median Placebo-adjusted hsCRP Levels from Baseline to Study End by Statin Use (ITT population)

**P**<0.01; *P*<0.05; NS=Not Significant (P≥0.05)

P-values reflect differences between AMR101 versus placebo
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>Any TEAE</td>
<td>27 (35.1)</td>
<td>26 (34.2)</td>
<td>28 (36.8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (1.3)</td>
<td>4 (5.3)</td>
<td>5 (6.6)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (1.3)</td>
<td>5 (6.6)</td>
<td>4 (5.3)</td>
</tr>
<tr>
<td>Eructation</td>
<td>0</td>
<td>1 (1.3)</td>
<td>3 (3.9)</td>
</tr>
</tbody>
</table>
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.

The MARINE Study

Thank You
Back up
Exclusion Criteria

• History of pancreatitis, untreated hypothyroidism, known nephrotic syndrome or >3 g/day proteinuria; history of stroke, MI, life-threatening arrhythmia, or coronary vascularization within 6 months of screening
• BMI >45 kg/m²; weight change >3 kg during the lead-in period
• $A_1C > 9.5\%$; TSH >1.5 x ULN; thyroid hormone therapy not stable for ≥6 weeks prior to screening; ALT or AST >3 x ULN; unexplained CK concentration >3 x ULN or CK elevation due to known muscle disease
• Prohibited drugs; non-statin lipid-altering medications; weight loss agents; HIV protease inhibitors; cyclophosphamide; isotretinoin; ongoing or anticipated use of systemic corticosteroids

$A_1C=$ hemoglobin A1c; ALT=alanine transaminase; AST=aspartate aminotransferase; BMI=body mass index; CK=creatine kinase; HIV=human immunodeficiency virus; MI=myocardial infarction; TSH=thyroid stimulating hormone; ULN=upper limit of normal.
Study End Points

• Primary end point
  – Median placebo-adjusted percent change in TG from baseline to study end

• Secondary efficacy end points
  – Median placebo-adjusted percent change from baseline to study end in VLDL-C, Apo B, and Lp-PLA₂

• Exploratory end points
  – Median placebo-adjusted percent change from baseline to study end in TC, LDL-C, HDL-C, VLDL-TG, and non-HDL-C
  – Median placebo-adjusted percent change from baseline to study end in hsCRP

• Safety end points

Apo B=apolipoprotein B; HDL-C=high-density lipoprotein cholesterol; hsCRP=high-sensitivity C-reactive protein; 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 cholesterol triglycerides.
The MARINE Study

Placebos used in Prescription OM-3 Clinical Trials

<table>
<thead>
<tr>
<th></th>
<th>LOVAZA® Placebo* (TG&gt;500 mg/dL)</th>
<th>AMR101 Placebo (TG&gt;500 mg/dL MARINE study)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>% Change</td>
</tr>
<tr>
<td>TG</td>
<td>788</td>
<td>+6.7</td>
</tr>
<tr>
<td>LDL-C</td>
<td>108</td>
<td>-4.8</td>
</tr>
</tbody>
</table>

- TG and LDL-C effects of placebos used for LOVAZA and MARINE studies were similar
- MARINE placebo
  - Light liquid paraffin
  - Paraffin is an inert substance
  - No absorption expected

* LOVAZA US Prescribing Information, 2010