The LAPLACE-2 Trial: A Phase 3, Double-blind, Randomized, Placebo and Ezetimibe Controlled, Multicenter Study to Evaluate Safety, Tolerability and Efficacy of Evolocumab (AMG 145) in Combination With Statin Therapy in Subjects With Primary Hypercholesterolemia and Mixed Dyslipidemia

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Statins are the first-line therapy for reducing atherosclerotic cardiovascular disease (ASCVD).

2013 ACC/AHA Cholesterol Guidelines\(^1\)

- A high-intensity statin (≥ 50% LDL-C lowering) is recommended for high-risk patients.
  - Clinical ASCVD; aged ≤ 75 y
  - LDL-C ≥ 190 mg/dL (4.9 mmol/L)
  - Diabetes; aged 40-75 years with ≥ 7.5% 10-y ASCVD risk
- A moderate-intensity statin (30-< 50% LDL-C lowering) is otherwise recommended.
- Non-statin therapy is recommended for high-risk patients who cannot tolerate a high-intensity statin, have a less than anticipated therapeutic response, or have genetic hypercholesterolemia.

\(^1\)Circulation. Online ahead of print November 2013.
Outside of the USA, guidelines recommend an LDL-C <100 mg/dL or <70 mg/dL, depending on the level of risk.1-3

Many patients receiving moderate- or high-intensity statin therapy will require addition of another LDL-C lowering drug.4-5

Evolocumab (AMG 145) is a human monoclonal antibody to PCSK9.

Evolocumab was well tolerated and showed robust LDL-C lowering in phase 2 trials,6-9 including a longer-term, 52-week study.10

**The LAPLACE-2 Study**

**LDL-C Assessment with PCSK9 Monoclonal Antibody Inhibition Combined With Statin Therapy – 2 (NCT01763866)**

**Design:**
A 12-week, randomized, double-blind, placebo- and ezetimibe-controlled, phase III study

**Objective:**
To evaluate the efficacy and safety of evolocumab administered biweekly (140 mg) or monthly (420 mg) in combination with a statin in hypercholesterolemic patients
LAPLACE-2: Study Design

Eligibility: LDL-C at screening
- ≥150 mg/dL (4.0 mmol/L): no statin
- ≥100 mg/dL (2.6 mmol/L): non-intensive statin
- ≥80 mg/dL (2.1 mmol/L): intensive statin

Total N = 1896

*1896 patients were randomized and received at least one dose of study drug. LDL-C, low-density lipoprotein cholesterol; PBO, placebo; EvoMab, evolocumab; EZE, ezetimibe; PO, oral; Q2W, biweekly; QM, monthly; QD, daily; SC, subcutaneous; W, week.

Clinical Cardiology. Online ahead of print January 2014.
### LAPLACE-2: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Any Statin + Placebo (N = 558)</th>
<th>Atorvastatin + Ezetimibe (N = 221)</th>
<th>Any Statin + Evolocumab (N = 1117)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>60 (10)</td>
<td>61 (9)</td>
<td>60 (10)</td>
</tr>
<tr>
<td>Female, %</td>
<td>48</td>
<td>49</td>
<td>44</td>
</tr>
<tr>
<td>Coronary artery disease, %</td>
<td>22</td>
<td>17</td>
<td>24</td>
</tr>
<tr>
<td>Peripheral arterial disease or cerebrovascular disease, %</td>
<td>10</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Diabetes mellitus, Type 2, %</td>
<td>13</td>
<td>20</td>
<td>16</td>
</tr>
</tbody>
</table>

**Total N = 1896***

*1896 patients were randomized and received at least one dose of study drug. Baseline characteristics were collected at randomization to statin. SD, standard deviation.
### LAPLACE-2: Baseline Lipids

<table>
<thead>
<tr>
<th></th>
<th>Any Statin + Placebo (N = 558)</th>
<th>Atorvastatin + Ezetimibe (N = 221)</th>
<th>Any Statin + Evolocumab (N = 1117)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LDL-C, mg/dL, mean (SD)</strong></td>
<td>108 (40)</td>
<td>109 (37)</td>
<td>110 (42)</td>
</tr>
<tr>
<td><strong>ApoB, g/L, mean (SD)</strong></td>
<td>88 (25)</td>
<td>90 (25)</td>
<td>90 (27)</td>
</tr>
<tr>
<td><strong>TG, mg/dL, mean (SD)</strong></td>
<td>129 (66)</td>
<td>136 (77)</td>
<td>137 (82)</td>
</tr>
<tr>
<td><strong>HDL-C, mg/dL, mean (SD)</strong></td>
<td>55 (17)</td>
<td>52 (15)</td>
<td>53 (16)</td>
</tr>
<tr>
<td><strong>Lp(a), mg/dL, mean (SD)</strong></td>
<td>86 (100)</td>
<td>92 (104)</td>
<td>91 (113)</td>
</tr>
<tr>
<td><strong>PCSK9, ng/mL, mean (SD)</strong></td>
<td>353 (114)</td>
<td>351 (112)</td>
<td>355 (111)</td>
</tr>
</tbody>
</table>

Baseline characteristics were collected at randomization to statin.

*Determined by the Friedewald formula with reflexive testing via preparative ultracentrifugation when calculated LDL-C was < 40 mg/dL or triglycerides were > 400 mg/dL.

LDL-C, low-density lipoprotein cholesterol; ApoB, apolipoprotein B; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; Lp(a), lipoprotein (a); PCSK9, proprotein convertase subtilisin/kexin type 9.
All treatment differences versus placebo and ezetimibe were statistically significant (P<0.001).
No notable differences were observed between the mean of weeks 10 and 12 and week 12 alone.
LDL-C, low-density lipoprotein cholesterol; Q2W, biweekly; QM, monthly. Vertical lines represent 95% CIs.
LAPLACE-2: Screening, Baseline, and On-treatment LDL-C

LDL-C < 70 mg/dL: High-intensity statin Q2W 94%; QM 93 to 95%

LDL-C < 70 mg/dL: Moderate-intensity statin Q2W 88 to 94%; QM 86 to 90%

Mean of weeks 10 and 12. No notable differences were observed between the mean of weeks 10 and 12 and week 12 alone.

LDL-C, low-density lipoprotein cholesterol; ISP, lipid-stabilization period; Q2W, biweekly; QM, monthly.
All treatment differences vs placebo and ezetimibe were statistically significant (P<0.05). Vertical lines represent 95% CIs. No notable differences were observed between the mean of weeks 10 and 12 and week 12 alone. Non-HDL-C, non high-density lipoprotein cholesterol; ApoB, apolipoprotein B; Q2W, biweekly; QM, monthly.
LAPLACE-2: Other Lipids at Mean Weeks 10/12

All treatment differences vs placebo and ezetimibe were statistically significant (P<0.05).
No notable differences were observed between the mean of weeks 10 and 12 and week 12 alone.
Vertical lines represent 95% CIs. Q2W, biweekly; QM, monthly.
# LAPLACE-2: Safety and Tolerability

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Any Statin + Placebo (N = 558)</th>
<th>Atorvastatin + Ezetimibe (N = 221)</th>
<th>Any Statin + Evolocumab (N = 1117)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment-emergent AEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>219 (39)</td>
<td>89 (40)</td>
<td>406 (36)</td>
</tr>
<tr>
<td>Most common AEs&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>14 (3)</td>
<td>7 (3)</td>
<td>20 (2)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>9 (2)</td>
<td>4 (2)</td>
<td>19 (2)</td>
</tr>
<tr>
<td>Headache</td>
<td>15 (3)</td>
<td>5 (2)</td>
<td>19 (2)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>6 (1)</td>
<td>6 (3)</td>
<td>17 (2)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>7 (1)</td>
<td>3 (1)</td>
<td>17 (2)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>13 (2)</td>
<td>2 (1)</td>
<td>23 (2)</td>
</tr>
<tr>
<td>AEs leading to study drug discontinuation</td>
<td>12 (2)</td>
<td>4 (2)</td>
<td>21 (2)</td>
</tr>
<tr>
<td>Deaths</td>
<td>1 (0.2)</td>
<td>0 (0)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0 (0)</td>
</tr>
<tr>
<td>CK &gt; 5 x ULN</td>
<td>2 (0.4)</td>
<td>0 (0)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>ALT or AST &gt; 3 x ULN</td>
<td>6 (1)</td>
<td>3 (1)</td>
<td>4 (0.4)</td>
</tr>
<tr>
<td>Potential injection site reactions&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8 (1)</td>
<td>2 (1)</td>
<td>15 (1)</td>
</tr>
<tr>
<td>Neurocognitive AEs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive deterioration</td>
<td>0 (0)</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Disorientation</td>
<td>0 (0)</td>
<td>1 (0.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Post-baseline binding antibodies</td>
<td>NA</td>
<td>NA</td>
<td>1 (0.1)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Top 5 in evolocumab treatment group. <sup>b</sup> One subject died after the end of study. <sup>c</sup> Reported using high-level term groupings which included injection site (IS) rash, IS inflammation, IS pruritus, IS reaction, and IS urticaria.<br><sup>d</sup> Binding antibody was present at baseline and at the end of study. No neutralizing antibodies were detected.

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.
LAPLACE-2: Conclusions

- Evolocumab significantly lowered LDL-C at the mean of weeks 10/12 in patients with hypercholesterolemia on background statin therapy.
  - There were no notable differences in percent reductions for moderate and high-intensity background statin therapies.

- Evolocumab 140 mg biweekly and 420 mg monthly dosing regimens are clinically equivalent.

- When combined with atorvastatin, LDL-C lowering was significantly greater in patients receiving evolocumab (63-75%) versus those receiving ezetimibe (19-32%).

- LDL-C < 70 mg/dL was achieved in most patients on evolocumab.
  - 86-94% (moderate-intensity statin)
  - 93-95% (high-intensity statin)

- There were no notable differences in safety & tolerability in evolocumab-, placebo-, and ezetimibe-treated patients.
An ASCVD outcomes trial is underway

- Evolocumab Q2W or QM added to moderate or high intensity statin therapy
- Patients are those with clinical ASCVD (N = 22,500)
- The trial is evaluating atherosclerotic cardiovascular disease (ASCVD) event reduction and safety

Disclosures

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