Lipid-Modulating Effects of Evacetrapib, a Novel CETP Inhibitor, Administered as Monotherapy or in Combination with the Most Commonly-Used Statins

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Disclosures

• Research support: AstraZeneca, Anthera, Eli Lilly, Novartis, Resverlogix, Roche and LipoScience

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• The study was sponsored by Eli Lilly
Steering Committee

• Steven Nissen (Chair)
• Stephen Nicholls (Principal Investigator)
• Bryan Brewer
• John Kastelein
• Holger Schilske (non-voting)
Background

- Cholesteryl ester transfer protein (CETP) inhibition represents a potentially useful strategy to raise HDL-C and lower LDL-C.

- Despite the failure of torcetrapib, interest in CETP inhibitors remains strong.

- Evacetrapib is a novel CETP inhibitor without adverse effects on blood pressure or mineralocorticoid activity in preclinical studies.

- The lipid effects of evacetrapib in combination with statins and in dyslipidemia remain unknown.
Objective

To characterize the efficacy, safety and tolerability of evacetrapib as monotherapy and in combination with commonly-used statins in patients with low HDL-C or high LDL-C
Study Design

• Subjects with elevated LDL-C or low HDL-C

• Up to 8 week dietary lead-in period and withdrawal of lipid-modifying therapies

• 12 week treatment period
  
  – Evacetrapib (30, 100 or 500 mg) or placebo
  
  – Evacetrapib 100 mg or placebo in combination with statin therapy (simvastatin 40 mg, atorvastatin 20 mg, rosvuastatin 10 mg)

• Co-primary endpoints: Percent change in HDL-C and LDL-C
1154 patients screened at 70 centers in US and Europe

826 patients entered dietary lead-in period and withdrawal of lipid-modifying therapies

398 patients randomized to treatment groups

393 patients received study drug

382 patients with follow up lipid data for primary analysis
## Demographic Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cohort (n=393)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>58.3</td>
</tr>
<tr>
<td>Females</td>
<td>56%</td>
</tr>
<tr>
<td>Mean body mass index (kg/m(^2))</td>
<td>29.0</td>
</tr>
<tr>
<td>Metabolic Syndrome</td>
<td>25.7%</td>
</tr>
<tr>
<td>History of Hypertension</td>
<td>35.1%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4.1%</td>
</tr>
<tr>
<td>Smoker</td>
<td>14.8%</td>
</tr>
<tr>
<td>Mean systolic BP (mmHg)</td>
<td>122.8</td>
</tr>
<tr>
<td>Mean diastolic BP (mmHg)</td>
<td>77.5</td>
</tr>
</tbody>
</table>
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cohort (n=393)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C (mg/dL)</td>
<td>144.3</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>55.1</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)*</td>
<td>121.3</td>
</tr>
<tr>
<td>Non-HDL C (mg/dL)</td>
<td>170.7</td>
</tr>
<tr>
<td>ApoB (mg/dL)</td>
<td>107.1</td>
</tr>
<tr>
<td>ApoA-I (mg/dL)</td>
<td>156.8</td>
</tr>
<tr>
<td>ApoA-II (mg/dL)</td>
<td>39.3</td>
</tr>
<tr>
<td>hsCRP (mg/L)*</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Presented as mean values. *median values
Percent Changes in HDL-C and LDL-C

HDL-C
- Placebo: -3.0%
- 30 mg: 53.6%
- 100 mg: 94.6%
- 500 mg: 128.8%

LDL-C
- Placebo: 3.9%
- 30 mg: -13.6%
- 100 mg: -22.3%
- 500 mg: -35.9%

* P<0.001 compared with placebo
Percent Change HDL-C: Evacetrapib 100 mg Combined with Statin Therapy

- **Simvastatin 40 mg**: 86.6% (P<0.001)
- **Atorvastatin 20 mg**: 79.9% (P<0.001)
- **Rosuvastatin 10 mg**: 94.0% (P<0.001)

**Statin + Placebo**
- **Simvastatin 40 mg**: 7.3%
- **Atorvastatin 20 mg**: 1.4%
- **Rosuvastatin 10 mg**: 5.5%
Percent Change LDL-C: Evacetrapib 100 mg Combined with Statin Therapy

- Simvastatin 40 mg: -34.9% (P<0.01)
- Atorvastatin 20 mg: -33.6% (P<0.01)
- Rosuvastatin 10 mg: -38.8% (P<0.01)

Statin + Placebo

Statin + Evacetrapib 100 mg
Subgroup Heterogeneity: Percent Change HDL-C with Evacetrapib

<table>
<thead>
<tr>
<th></th>
<th>&lt;Mean &gt;Mean Age</th>
<th>&lt;Mean &gt;Mean Baseline HDL-C</th>
<th>&lt;Mean &gt;Mean Baseline Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent Change HDL-C</td>
<td>149.2%</td>
<td>148.6%</td>
<td>153.1%</td>
</tr>
<tr>
<td>Percent Change</td>
<td>118.0%</td>
<td>110.8%</td>
<td>106.3%</td>
</tr>
<tr>
<td>P&lt;0.01</td>
<td>P&lt;0.001</td>
<td>P&lt;0.01</td>
<td></td>
</tr>
</tbody>
</table>
Subgroup Heterogeneity: Percent Change LDL-C with Evacetrapib

- Age <Mean: -41.0% (P=0.03), >Mean: -32.4%
- Baseline LDL-C <Mean: -40.2% (P=0.03), >Mean: -29.1%
Blood Pressure

Systolic Blood Pressure

Diastolic Blood Pressure

Week

Baseline  2  4  8  12

Baseline  2  4  8  12

mmHg

Placebo  30 mg  100 mg  500 mg
## Safety Evaluation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo (n=38)</th>
<th>Eva 30 mg (n=40)</th>
<th>Eva 100 mg (n=38)</th>
<th>Eva 500 mg (n=40)</th>
<th>Statin (n=121)</th>
<th>Statin + Eva 100 mg (n=116)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-related AE</td>
<td>18.4%</td>
<td>20.0%</td>
<td>13.2%</td>
<td>25.0%</td>
<td>18.2%</td>
<td>26.7%</td>
</tr>
<tr>
<td>AE leading to discontinuation</td>
<td>2.6%</td>
<td>5.0%</td>
<td>2.6%</td>
<td>12.5%</td>
<td>2.5%</td>
<td>7.8%</td>
</tr>
<tr>
<td>SAE</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>2.5%</td>
<td>0.8%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Creatinine &gt;ULN</td>
<td>2.6%</td>
<td>2.6%</td>
<td>5.2%</td>
<td>10.0%</td>
<td>7.6%</td>
<td>5.2%</td>
</tr>
<tr>
<td>CK &gt; 5 X ULN</td>
<td>2.6%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>1.7%</td>
<td>1.7%</td>
</tr>
<tr>
<td>ALT &gt; 3 X ULN</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Aldosterone (ng/dL)*</td>
<td>-1.00</td>
<td>-0.45</td>
<td>0.96</td>
<td>-0.30</td>
<td>-1.12</td>
<td>-0.45</td>
</tr>
<tr>
<td>Salivary Cortisol (μg/dL)*</td>
<td>-0.003</td>
<td>-0.03</td>
<td>0.002</td>
<td>0.004</td>
<td>0.03</td>
<td>0.01</td>
</tr>
</tbody>
</table>

* Absolute change
Conclusions

• Evacetrapib monotherapy produced a dose-dependent increase in HDL-C up to 128.8% and decrease in LDL-C up to 35.9%.

• Significant incremental HDL-C and LDL-C changes were observed when evacetrapib 100 mg was administered in combination with statins.

• Evacetrapib was well tolerated with no evidence of adverse blood pressure or mineralocorticoid effects.

• The impact of evacetrapib on cardiovascular events remains to be determined.
Effects of the CETP Inhibitor Evacetrapib Administered as Monotherapy or in Combination With Statins on HDL and LDL Cholesterol: A Randomized Controlled Trial

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The development of statins for reducing low-density lipoprotein cholesterol (LDL-C) has revolutionized cardiovascular disease prevention. Nonetheless, cardiovascular disease remains the number one cause of death. Accordingly, considerable efforts have focused on development of novel therapeutic agents designed to address residual cardiovascular risk. Because individuals from the general population with elevations of high-density lipoprotein cholesterol (HDL-C) have a reduced incidence of coronary heart disease, it has been assumed that finding an appropriate therapy to increase HDL-C levels would yield substantial clinical benefit.

However, development of drugs that increase HDL-C levels has been challenging and fraught with failures, including the premature termination of trials.

Available at www.jama.com
A Final Thought

• Substantial HDL-C raising, and with some agents incremental LDL-C lowering, has stimulated interest in the development of CETP inhibitors.

• Elucidating the off-target toxicities of torcetrapib has provided hope that CETP inhibition will be shown to be a cardioprotective strategy.

• Ultimately large cardiovascular outcome trials will determine whether CETP inhibitors will reduce the residual risk observed despite the use of existing therapies.