Clinical Efficacy and Safety of Achieving Very Low LDL-C Levels With the PCSK9 Inhibitor Evolocumab in the FOURIER Outcomes Trial

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Clinical Trial Update I
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Declaration of interest

- Consulting/Royalties/Owner/ Stockholder of a healthcare company (Amgen, Bristol Myers Squibb, Merck, Pfizer, Daiichi Sankyo, GlaxoSmithKline)
- Research contracts (Amgen)
Evolocumab SC 140 mg Q2W or 420 mg QM

Placebo SC Q2W or QM

Follow-up Q 12 weeks

27,564 stable patients with CV disease (prior MI, stroke or PAD) age 40-85 years; additional CV risk factor(s)

Screening, Placebo Run-in, & Lipid Stabilization

Effective statin therapy (atorva ≥20 mg or ≈ statin dose ± ezetimibe)

LDL-C ≥ 1.8 mM non-HDL-C ≥ 2.6 mM

RANDOMIZED DOUBLE BLIND

Summary of FOURIER

- ↓ LDL-C by 59% (from 2.4 -> 0.8 [0.5, 1.2] mM)
- ↓ CV outcomes in patients already on statin therapy
- Evolocumab was safe and well-tolerated

**Evolocumab was safe and well-tolerated**

**CV death, MI, stroke, UA, cor revasc**

**KM Rate (%) at 3 Years**

- Placebo: HR 0.80 (0.73-0.88), P<0.0001
- Evolocumab: HR 0.85 (0.79-0.92), P<0.00001

**Absolute ↓ 1.45 mM (1.42-1.47)**

**Median 0.78 mM, IQR [0.49-1.27]**

**59% mean decline, P<0.00001**

**Weekly LDL-C levels**

- Placebo: Median 0.78 mM, IQR [0.49-1.27]
- Evolocumab: Median 0.78 mM, IQR [0.49-1.27]
Aims

To explore the clinical efficacy and safety associated with progressively lower achieved LDL-C levels
Methods - 1

- LDL-C assessed at 4 wks (ultracentrifugation if <1 mM)

- Analyzed 5 groups by achieved LDL-C at 4 weeks
  1) <0.5mM (20 mg/dL)
  2) 0.5-1.3 mM (20-49 mg/dL)
  3) 1.3-1.8 mM (50-69 mg/dL)
  4) 1.8-2.6mM (70-99 mg/dL)
  5) ≥2.6 mM (≥100 mg/dL) was the referent group

- Pooled results across 2 Rx groups (evo, placebo)

1582 pts with events in first 4 wks or no LDL-C at week 4 were excluded
Methods - 2

– Prespecified 1° and 2° efficacy composite endpoints

– 10 safety adverse events evaluated:
  – Serious AE  - AE->drug discon  - AST/ALT>3x
  – Cancer  - cataracts AEs  - CK > 5x ULN
  – Hem stroke  - Neurocognitive  - Non-CV death
  – New onset diabetes (adjudicated by CEC)

– Cognition¹ assessed using CANTAB tool and pt survey of everyday cognition (ECog)

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Achieved LDL-C at 4 Weeks

Median [IQR] LDL-C at 4 Weeks

**Evo** 0.8 mM [0.5-1.2]  Pbo 2.2 mM [1.9-2.7]
32 mg/dL [21-45]  87 mg/dL [74-104]

**Percent of Patients**

**LDL-C at Week 4 (mM)**

**LDL (mM)**  
<0.8  0.8-1.3  1.3-1.8  1.8-2.6  $\geq$ 2.6

**%Evo**  
99.6%  96.5%  41%  10%  9.6%

**%Placebo**  
0.4%  3.5%  59%  90%  90.4%

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**Baseline Characteristics**

<table>
<thead>
<tr>
<th>Achieved LDL-C in mM at 4 Weeks</th>
<th>&lt;0.5 (N=2669)</th>
<th>0.5-1.3 (N=8003)</th>
<th>1.3-1.8 (N=3444)</th>
<th>1.8-2.6 (N=7471)</th>
<th>≥2.6 (N=4395)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (median), yrs</strong>*</td>
<td>64</td>
<td>63</td>
<td>62</td>
<td>63</td>
<td>61</td>
</tr>
<tr>
<td><strong>Females</strong>*</td>
<td>16</td>
<td>23</td>
<td>27</td>
<td>24</td>
<td>28</td>
</tr>
<tr>
<td><strong>Caucasian race</strong>*</td>
<td>80</td>
<td>86</td>
<td>84</td>
<td>85</td>
<td>88</td>
</tr>
<tr>
<td><strong>Current smoker</strong>*</td>
<td>26</td>
<td>27</td>
<td>29</td>
<td>28</td>
<td>32</td>
</tr>
<tr>
<td><strong>Prior MI</strong></td>
<td>81</td>
<td>81</td>
<td>80</td>
<td>82</td>
<td>81</td>
</tr>
<tr>
<td><strong>Prior stroke</strong></td>
<td>20</td>
<td>19</td>
<td>19</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td><strong>Prior PAD</strong></td>
<td>12</td>
<td>14</td>
<td>14</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>78</td>
<td>80</td>
<td>82</td>
<td>80</td>
<td>81</td>
</tr>
<tr>
<td><strong>TIMI Risk Score 2° Prevention</strong>*</td>
<td><strong>3.2</strong></td>
<td><strong>3.3</strong></td>
<td><strong>3.4</strong></td>
<td><strong>3.3</strong></td>
<td><strong>3.4</strong></td>
</tr>
</tbody>
</table>

Data shown are % patients unless otherwise specified

*P trend ≤0.0001

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# Lipids and Lipid Rx at Randomization

## Achieved LDL-C in mM at 4 Weeks

<table>
<thead>
<tr>
<th>At Randomization</th>
<th>&lt;0.5 (N=2669)</th>
<th>0.5-1.3 (N=8003)</th>
<th>1.3-1.8 (N=3444)</th>
<th>1.8-2.6 (N=7471)</th>
<th>≥2.6 (N=4395)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Lipid values</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C, mM</td>
<td>2.1</td>
<td>2.4</td>
<td>2.2</td>
<td>2.3</td>
<td>3.0</td>
</tr>
<tr>
<td>Total cholesterol, mM</td>
<td>4.0</td>
<td>4.3</td>
<td>4.2</td>
<td>4.2</td>
<td>5.0</td>
</tr>
<tr>
<td>Triglycerides, mM</td>
<td>1.5</td>
<td>1.5</td>
<td>1.6</td>
<td>1.4</td>
<td>1.6</td>
</tr>
<tr>
<td>HDL-C, mM</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
<td>1.1</td>
<td>1.2</td>
</tr>
<tr>
<td>Lipoprotein (a), nM</td>
<td>22</td>
<td>43</td>
<td>32</td>
<td>37</td>
<td>48</td>
</tr>
<tr>
<td>High potency statin, % (&gt; Atorvastatin 40 mg/d)</td>
<td>63</td>
<td>69</td>
<td>70</td>
<td>70</td>
<td>72</td>
</tr>
<tr>
<td>Ezetimibe, %</td>
<td>4.1</td>
<td>5.0</td>
<td>5.4</td>
<td>4.6</td>
<td>7.4</td>
</tr>
</tbody>
</table>

P\_trend ≤0.0001 for each
LDL-C Over Time

LDL-cholesterol at 4 weeks in mM

- <0.5
- 0.5-1.3
- 1.3-1.8
- 1.8-2.6
- ≥ 2.6

Mean LDL-C (mM)

Weeks After Randomization

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<table>
<thead>
<tr>
<th>LDL-C (mM)</th>
<th>Adj HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.5</td>
<td>0.76 (0.64-0.90)</td>
</tr>
<tr>
<td>0.5-1.3</td>
<td>0.85 (0.76-0.96)</td>
</tr>
<tr>
<td>1.3-1.8</td>
<td>0.94 (0.82-1.09)</td>
</tr>
<tr>
<td>1.8-2.6</td>
<td>0.97 (0.86-1.09)</td>
</tr>
<tr>
<td>≥ 2.6</td>
<td>referent</td>
</tr>
</tbody>
</table>

P = 0.0012
An Academic Research Organization of Brigham and Women's Hospital and Harvard Medical School

CV Death, MI, or Stroke

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<thead>
<tr>
<th>LDL-C (mM)</th>
<th>Adj HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.5</td>
<td>0.69 (0.56-0.85)</td>
</tr>
<tr>
<td>0.5-1.3</td>
<td>0.75 (0.64-0.86)</td>
</tr>
<tr>
<td>1.3-1.8</td>
<td>0.87 (0.73-1.04)</td>
</tr>
<tr>
<td>1.8-2.6</td>
<td>0.90 (0.78-1.04)</td>
</tr>
<tr>
<td>≥ 2.6</td>
<td>referent</td>
</tr>
</tbody>
</table>

P = 0.0001
Safety Events - 1

% pts

Adj P-values for trend >0.10 for each comparison

LDL-C (mM) at 4 wks
- <0.5
- 0.5-1.3
- 1.3-1.8
- 1.8-2.6
- ≥2.6

SAE
AE->Discon
New DM
Cancer
Cataract

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Safety Events - 2

Adj P-values for trend >0.10 for each comparison

% pts

LDL-C (mM) at 4wks
- <0.5
- 0.5-1.3
- 1.3-1.8
- 1.8-2.6
- ≥2.6

% pts
# Evaluation of Cognition

<table>
<thead>
<tr>
<th>CANTAB Tests</th>
<th>Adj $P_{\text{trend}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executive function</td>
<td>0.11</td>
</tr>
<tr>
<td>Working memory</td>
<td>0.61</td>
</tr>
<tr>
<td>Episodic memory</td>
<td>0.61</td>
</tr>
<tr>
<td>Reaction Time</td>
<td>0.47</td>
</tr>
<tr>
<td><strong>Global Score</strong></td>
<td><strong>0.30</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Everyday Cognition Self Survey</th>
<th>Adj $P_{\text{trend}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory</td>
<td>0.11</td>
</tr>
<tr>
<td>Executive function</td>
<td>0.12</td>
</tr>
<tr>
<td>Planning</td>
<td>0.27</td>
</tr>
<tr>
<td>Organization</td>
<td>0.98</td>
</tr>
<tr>
<td>Divided attention</td>
<td>0.038</td>
</tr>
<tr>
<td><strong>Total Score</strong></td>
<td><strong>0.017</strong></td>
</tr>
</tbody>
</table>

Better scores at lower achieved LDL-C

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Exploratory Analysis Pts with LDL-C <0.26 mM (<10 mg/dL) at 4 wks

N=504: Median [IQR] LDL-C 0.18 [0.13-0.23] mM = 7 [5-9] mg/dL

Cardiovascular Efficacy

- Adj HR 0.69 (0.49-0.97) P=0.03
- Adj HR 0.59 (0.37-0.92) P=0.02

Safety

- Adj HR 0.94 (0.74-1.20) P=0.61
- Adj HR 1.08 (0.63-1.85) P=0.78

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Conclusions

- LDL-C can now be reduced to unprecedented low levels with statin + PCSK9i (<< 1 mM)

- A strong progressive relationship of achieved LDL-C and CV events seen, down to LDL <0.26 mM (<10 mg/dL)

- No excess in safety events with very low achieved LDL-C <0.5 mM (<20 mg/dL) at 2.2 years

*These data suggest that we should target considerably lower LDL-C than is currently recommended for our patients with atherosclerotic CV disease*
Clinical efficacy and safety of achieving very low
LDL-cholesterol concentrations with the PCSK9 inhibitor
evolocumab: a prespecified secondary analysis of the
FOURIER trial

Robert P Giugliano, Terje R Pedersen, Jeong-Gun Park, Gaetano M De Ferrari, Zbigniew A Gaciong, Richard Ceska, Kalman Toth, Joanna Gouni-Berthold, Jose Lopez-Miranda, François Schiele, François Mach, Brian R Ott, Estella Kanovsky, Armando Lira Pineda, Ransi Somaratne, Scott M Wasserman, Anthony C Keech, Peter S Sever, Marc S Sabatine, on behalf of the FOURIER Investigators

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Slides available at www.TIMI.org