Long-Term Evolocumab in Patients with Established Atherosclerotic Cardiovascular Disease:

Primary Results of the FOURIER-OLE (Open-Label Extension) Studies

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On Behalf of the FOURIER-OLE Investigators

This study was funded by Amgen Inc.
Background

• In the FOURIER trial, 27,564 patients with stable ASCVD were randomized to the PCSK9 inhibitor evolocumab vs. placebo

• Evolocumab reduced the risk of MACE, but there was no observed effect on CV mortality

• However, the median follow-up was only 2.2 years
Background (2)

- Pivotal statin trials had median follow-up of 4-5 years and demonstrated both a lag effect (clinical benefit grew over time) and legacy effect (clinical benefit persisted in extended follow-up after the parent trial ended).

- Thus, very long-term data on safety and efficacy of LDL-C lowering with PCSK9 inhibition are needed.
Evolocumab: Evidence of Lag Effect for MACE

CV Death, MI, Stroke

16% RRR
HR 0.84 (95%CI 0.74-0.96)
P=0.008

25% RRR
HR 0.75 (95%CI 0.66-0.85)
P<0.00001

Sabatine MS et al. NEJM 2017;376:1713-22
Study Schema

Patients with stable ASCVD and LDL-C ≥70 mg/dl (~1.8mM) or non-HDL-C ≥100 mg/dl (~2.6mM) on optimized statin Rx

Evolocumab q2 or q4 wks

Matching placebo

Parent FOURIER Trial
Median follow-up 2.2 yrs
N=27,564

Open-Label Evolocumab q2 or q4 wks

FOURIER OLE Program
Median follow-up 5.0 yrs
N=6635

US & Eastern Europe: NCT02867813
Western Europe: NCT03080935
Methods

• Primary endpoint was incidence of adverse events
• MACE were prespecified exploratory endpoints and were reviewed by the TIMI Study Group Clinical Events Committee
• Safety evaluations included all patients in FOURIER-OLE who received ≥1 dose of study drug and for whom post-dose data were available. Patients were censored for safety analyses 30 days following permanent drug discontinuation or end-of-study (whichever was earlier).
• Analyses for major adverse cardiovascular events were conducted on an intention-to-treat basis and stratified by original treatment assignment at randomization
Baseline Characteristics of OLE Population at Randomization

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Placebo (N=3280)</th>
<th>Evolocumab (N=3355)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, years)</td>
<td>62</td>
<td>62</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>76</td>
<td>77</td>
</tr>
<tr>
<td>White race (%)</td>
<td>96</td>
<td>95</td>
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<tr>
<td>Region (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>66</td>
<td>67</td>
</tr>
<tr>
<td>United States</td>
<td>34</td>
<td>33</td>
</tr>
<tr>
<td>Type of athero (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>84</td>
<td>84</td>
</tr>
<tr>
<td>Non-hemorrhagic stroke</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>CV risk factors (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>85</td>
<td>82</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>35</td>
<td>33</td>
</tr>
<tr>
<td>Current cigarette use</td>
<td>27</td>
<td>26</td>
</tr>
<tr>
<td>Meds at time of enrollment in FOURIER (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-intensity statin use</td>
<td>76</td>
<td>77</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>5.5</td>
<td>6.0</td>
</tr>
<tr>
<td>LDL-C at randomization (median, IQR)</td>
<td>2.4 (2.1-2.8)</td>
<td>2.4 (2.1-2.8)</td>
</tr>
<tr>
<td>mg/dl</td>
<td>91 (80-109)</td>
<td>92 (80-108)</td>
</tr>
</tbody>
</table>

All comparisons P>0.05
Effect on LDL-C

Median LDL cholesterol (95% CI, mmol/L)

- Randomized to placebo
- Randomized to evolocumab

Placebo transition to evolocumab
Parent FOURIER
Evolocumab vs placebo
FOURIER-OLE
Open-label Evolocumab

Median LDL-C at Week 260:
0.75 mmol/L (IQR 0.44-1.29)
29 mg/dl (IQR 17-50)
Long-Term Safety

SERIOUS ADVERSE EVENTS

INJECTION SITE REACTIONS

DRUG-RELATED ALLERGIC RXN

MUSCLE-RELATED EVENT

NEW ONSET DIABETES

HEMORRHAGIC STROKE

- Placebo Phase FOURIER
- Evolocumab Phase FOURIER
- Evolocumab Phase FOURIER & OLE
Efficacy during FOURIER-OLE

Primary Endpoint: CV death, MI, stroke, unstable angina or coronary revascularization

HR 0.85
(95% CI 0.75-0.96)
P=0.008

15.4% reduction

Placebo → Evolocumab
Evolocumab → Evolocumab

Number at risk:

<table>
<thead>
<tr>
<th>Years</th>
<th>Placebo-Evolocumab</th>
<th>Evolocumab-Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3280</td>
<td>3355</td>
</tr>
<tr>
<td>1</td>
<td>3055</td>
<td>3186</td>
</tr>
<tr>
<td>2</td>
<td>2876</td>
<td>3033</td>
</tr>
<tr>
<td>3</td>
<td>2716</td>
<td>2890</td>
</tr>
<tr>
<td>4</td>
<td>2573</td>
<td>2716</td>
</tr>
<tr>
<td>5</td>
<td>1706</td>
<td>1754</td>
</tr>
</tbody>
</table>
Efficacy during FOURIER-OLE

Key Secondary Endpoint: CV death, MI or stroke

HR 0.80
(95% CI 0.68-0.93)
P=0.003

20% reduction

9.7% reduction

Placebo → Evolocumab
Evolocumab → Evolocumab

Number at risk:
Placebo-Evolocumab: 3280, 3128, 2987, 2857, 2729, 1809
Evolocumab-Evolocumab: 3355, 3247, 3123, 3012, 2870, 1862

Years in OLE
Efficacy during FOURIER-OLE Time Period

- **HR 0.77**
  - (95% CI 0.60-0.99)
  - P=0.04

23% reduction

CV death

<table>
<thead>
<tr>
<th>Years in OLE</th>
<th>Placebo-Evolocumab</th>
<th>Evolocumab-Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3280</td>
<td>3355</td>
</tr>
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<td>1</td>
<td>3223</td>
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<td>2991</td>
<td>3080</td>
</tr>
<tr>
<td>5</td>
<td>2049</td>
<td>2069</td>
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</table>

Number at risk:

- Placebo-Evolocumab: 3280
- Evolocumab-Evolocumab: 3355

Increase in CV death: 3.32% to 4.45%
Efficacy during FOURIER & FOURIER-OLE

**FOURIER Primary Endpoint**

- CV death, MI, stroke, UA, or coronary revascularization (%)

<table>
<thead>
<tr>
<th>Years</th>
<th>Placebo</th>
<th>Evolocumab</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>13784</td>
<td>12937</td>
</tr>
<tr>
<td>1</td>
<td>13780</td>
<td>12822</td>
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<tr>
<td>2</td>
<td>8467</td>
<td>8683</td>
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<tr>
<td>3</td>
<td>3260</td>
<td>3389</td>
</tr>
<tr>
<td>4</td>
<td>2654</td>
<td>2814</td>
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<tr>
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<td>1569</td>
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<tr>
<td>8</td>
<td>189</td>
<td>165</td>
</tr>
</tbody>
</table>

**Median**
- Parent FOURIER: 2.2 yrs
- FOURIER-OLE: 5 yrs

**Efficacy during FOURIER & FOURIER-OLE**
Efficacy during FOURIER & FOURIER-OLE

FOURIER Key Secondary Endpoint

Parent FOURIER Median 2.2 yrs

FOURIER-OLE Median 5 yrs

CV death, MI or stroke (%)

Years

Number at risk:

Placebo-Evocumab 13780 13140 8846 3470 2861 2757 2621 1664 216
Evocumab-Evocumab 13784 13240 9051 3617 2946 2810 1746 185

0% 10% 20%

Placebo → Evocumab
Evocumab → Evocumab

An Academic Research Organization of Brigham and Women’s Hospital and Harvard Medical School
Efficacy during FOURIER & FOURIER-OLE

CV Death

- Placebo
- Evolocumab

Parent FOURIER Median 2.2 yrs
FOURIER-OLE Median 5 yrs

Number at risk:

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<tr>
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<td>7</td>
<td>1965</td>
<td>1988</td>
</tr>
<tr>
<td>8</td>
<td>268</td>
<td>237</td>
</tr>
</tbody>
</table>
MACE by Year of Study

CV death, MI, stroke, hosp for UA, or coronary revascularization

Hazard ratio (95% CI)

- **Year 1**: 0.88 (0.80-0.97), Favors evolocumab-
evolocumab
- **Year 2**: 0.81 (0.73-0.89), Favors evolocumab-
evolocumab
- **Year 2+**: 0.81 (0.73-0.89), Favors evolocumab-
evolocumab
- **Year 3**: 0.71 (0.57-0.89), Favors evolocumab-
evolocumab
- **Year 4**: 1.21 (0.94-1.56), Favors evolocumab-
evolocumab
- **Year 5+**: 1.06 (0.80-1.40), Favors evolocumab-
evolocumab

CV death, MI or stroke

Hazard ratio (95% CI)

- **Year 1**: 0.88 (0.80-0.97), Favors evolocumab-
evolocumab
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evolocumab
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evolocumab
- **Year 3**: 0.71 (0.57-0.89), Favors evolocumab-
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- **Year 4**: 1.21 (0.94-1.56), Favors evolocumab-
evolocumab
- **Year 5+**: 1.06 (0.80-1.40), Favors evolocumab-
evolocumab

**LDL-C △** between arms

- **1.6 mM (62 mg/dl)**
- **0.0 mM**

**Fourier-Ole Fourier**

- Year 1
- Year 2+
- Year 1
- Year 2
- Year 3
- Year 4
- Year 5+

Lag

- **Legacy**

**Hazard ratio (95% CI)**

- **Year 1**: 0.88 (0.80-0.97)
- **Year 2**: 0.81 (0.73-0.89)
- **Year 2+**: 0.81 (0.73-0.89)
- **Year 3**: 0.71 (0.57-0.89)
- **Year 4**: 1.21 (0.94-1.56)
- **Year 5+**: 1.06 (0.80-1.40)
Summary

- Long-term use of evolocumab with median follow-up of more than 7 years appears both safe and well-tolerated.
- Earlier initiation of evolocumab is associated with continued accrual of cardiovascular benefit, including cardiovascular mortality, over the next several years.
- These findings argue for early initiation of a marked and sustained LDL-C reduction to maximize clinical benefit.
LONG-TERM EVOLOCUMAB IN PATIENTS WITH ESTABLISHED ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

MICHELLE L. O’DONOGHUE, MD, MPH; ROBERT P. GIUGLIANO, MD, SM; STEPHEN D. WIVIOTT, MD; DAN ATAR, MD; ANTHONY KEECH, MBBS; JULIA F. KUDER, MA; KYUNGAH IM, PHD; SABINA A. MURPHY, MPH; JOSE H. FLORES-ARREDONDO, MD; J. ANTONIO G. LÓPEZ, MD; MARY ELLIOTT-DAVEY, MSC; BEI WANG, PHD; MARIA LAURA MONSALVO MD; SIDDIQUE ABBASI, MD; MARC S. SABATINE, MD, MPH

CIRCULATION

HTTPS://WWW.AHAJOURNALS.ORG/DOI/10.1161/CIRCULATIONAHA.122.061620