Interventions to Improve LDL Receptor Function

New Therapies

Peter H. Jones, MD, FNLA
Objectives

• Close look at PCSK9 action and inhibition: the MOA, efficacy, patient populations evaluated, safety and early outcomes

• Closer examination of efficacy in specific patient groups (FH, statin-intolerant)

• Safety concerns, such as low LDL-C, neurocognitive affects

• Expert recommendations for the use of this class of drugs

• Special look at treatments for HoFH – PCSK9 inhibition, lomitapide and mipomersen
Hepatic LDL Receptors Play a Central Role in Cholesterol Homeostasis

- The LDL/LDLR complex is internalized into the hepatocyte via clathrin-coated vesicles, thereby removing LDL from the blood\textsuperscript{1-3}
- Affinity of hepatic LDLR for apoB on LDL enables LDLRs to clear plasma LDL effectively\textsuperscript{4}

Recycling of LDL-Receptors Enables Efficient Clearance of LDL Particles

• The ability of hepatic LDLRs to be recycled is a key determinant of hepatic efficacy in lowering plasma LDL levels

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Is a Regulator of LDL-R Recycling

- PCSK9 mediates degradation of the LDL-R by interacting with the extracellular domain and targeting the receptor for degradation
- PCSK9 is highly expressed in the liver, small intestine, and kidney

Genetic Variants of PCSK9 Demonstrate Its Importance in Regulating LDL Levels


PCSK9 Gain of Function (GOF) = Less LDL-Rs$^{1,3,5}$

PCSK9 Loss of Function (LOF) = More LDL-Rs$^{2,4,5}$

1-3% of population$^{6,7}$
PCSK9 Loss-of-Function Mutations Resulted in Lower LDL-C Levels and Reduced CHD Rates

- Wild-type PCSK9 degrades LDL receptors.\textsuperscript{1,2}

- Loss-of-function (LOF) mutations increase hepatic LDL receptor expression, reducing LDL-C levels by 15%-40\%.\textsuperscript{2,3}

- CHD incidence was reduced 47% to 88% in PCSK9 loss-of-function mutation carriers compared with normal individuals.\textsuperscript{3}

Clinical Outcomes Associated With PCSK9 Gain-of-function (GOF) Mutations

ADH caused by rare PCSK9 GOF mutations have a clinical phenotype resembling FH caused by LDL-R or apoB gene mutations\(^1,2\)

ADH-associated physical abnormalities\(^1\)

Premature CHD\(^1,2\)

Stroke\(^1\)

ADH = autosomal dominant hypercholesterolemia

Impact of PCSK9 mAb on LDL Receptor Expression
PCSK9: Rapid Progress From Discovery to Clinic

- Adenoviral up expression in mice
- PCSK9 KO mouse down LDL-C
- PCSK9 (NARC-1) discovered
- PCSK9 GOF mutations associated with ADH
- PCSK9 LOF mutations found with 28% down LDL-C and 88% down CHD risk
- Humans null for PCSK9 have LDL-C ~15 mg/dL
- First subject treated with PCSK9 mAb
- LDL-C in mice and non-human primates treated with anti-PCSK9 mAb
- First patients with FH & nonFH treated with PCSK9 mAb
- First publication POC in patients

## PCSK9 Inhibitors: Approved and in Development

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Company</th>
<th>Stage of development</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monoclonal antibodies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evolocumab</td>
<td>Amgen</td>
<td>Approved (EU, US)</td>
</tr>
<tr>
<td>Alirocumab</td>
<td>Sanofi/Regeneron</td>
<td>Approved (US)</td>
</tr>
<tr>
<td>Bococizumab</td>
<td>Pfizer</td>
<td>Discontinued</td>
</tr>
<tr>
<td><strong>Other biologics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclisarin (siRNA)$^1$</td>
<td>Alynlam/Medicines Company</td>
<td>Stage 1/2</td>
</tr>
<tr>
<td>Vaccine</td>
<td>Affris</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>

1. NEJM 2017; 376: 1430
Dynamic Relationship Between mAb Levels, PCSK9 and LDL-C
Dynamic Relationship Between mAb Levels, PCSK9 and LDL-C
Dynamic Relationship Between mAb Levels, PCSK9 and LDL-C
Approved Indications

FDA (alirocumab and evolocumab)

- In combination with maximum tolerated statin in adults with heterozygous familial hypercholesterolemia and
- In combination with maximum tolerated statin therapy in patients with ASCVD, who require additional lowering of LDL-C
- In patients with homozygous familial hypercholesterolemia (evolocumab only)

European Commission (evolocumab)

- In combination with maximum tolerated statin therapy in patients unable to reach LDL-C goal
- Alone or in combination with other LLT in patients who are statin-intolerant or for whom a statin is contraindicated
- In patients with homozygous familial hypercholesterolemia
Administration of Q2W and Q4W mAb

Evolocumab 420 mg SC
3 x 1ml 140 mg SC autoinjections

OR
1 x 3.5 ml (120 mg/ml) autoinjection

Alirocumab 75 mg and 150 mg SC
Evolocumab 140 mg SC

27 g needle
Patient Populations Evaluated for PCSK9 mAb Therapy in Phase III Development

• Patients with familial hypercholesterolemia
• Patients with high CVD risk and not at desirable LDL-C with max dose statin
• Patients intolerant to statin therapy
• Patients receiving monotherapy
Mean LDL-C % Reductions in the Phase III Programs of Evolocumab (12 wks) and Alirocumab (24 wks)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Baseline LDL-C</th>
<th>LDL-C Change</th>
<th>LDL-C Goal Attainment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HeFH Patients (max tolerated statin +/- other LLT)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evolocumab 420 mg SC Q4W</td>
<td>155 mg/dL</td>
<td>-61%</td>
<td>63%</td>
</tr>
<tr>
<td>Alirocumab 75 mg SC Q2W (↑prn)</td>
<td>148 mg/dL</td>
<td>-58%</td>
<td>70%</td>
</tr>
<tr>
<td><strong>High Risk, ASCVD Patients, Not at Desirable LDL-C (stable statin therapy)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evolocumab 420 mg SC Q4W</td>
<td>110 mg/dL</td>
<td>-65%</td>
<td>93%</td>
</tr>
<tr>
<td>Alirocumab 75 mg SC Q2W (↑prn)</td>
<td>109 mg/dL</td>
<td>-51%</td>
<td>77%</td>
</tr>
<tr>
<td><strong>Statin Intolerant Patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evolocumab 420 mg SC Q4W</td>
<td>192 mg/dL</td>
<td>-55%</td>
<td>82%</td>
</tr>
<tr>
<td>Alirocumab 75 mg SC Q2W (↑prn)</td>
<td>191 mg/dL</td>
<td>-45%</td>
<td>41%</td>
</tr>
<tr>
<td><strong>Monotherapy Patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evolocumab 420 mg SC Q4W</td>
<td>144 mg/dL</td>
<td>-56%</td>
<td>69%</td>
</tr>
<tr>
<td>Alirocumab 150 mg SC Q2W</td>
<td>123 mg/dL</td>
<td>-66%</td>
<td>93%</td>
</tr>
</tbody>
</table>

2. Kastelein et al Presented to ESC, 2014
5. Stroes et al. JACC 2014; 63: 2541-8
6. Moriarty et al. JCL in press
8. Roth et al Int J Cardiol 2014; 176: 55
Efficacy in Long-Term Studies

**Osler¹**: Open label study of 4465 pts randomized to evolocumab 140 mg SC Q2W or 420 mg SC QM + standard of care (SOC) vs SOC for 48 weeks

**Odyssey Long Term²**: Blinded study of 2341 high risk pts on max-tolerated statin with LDL-C > 70 randomized to alirocumab 150 mg or placebo SC Q2W for 78 wks

<table>
<thead>
<tr>
<th>Patients</th>
<th>% LDL-C Δ</th>
<th>% LDL-C Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evolocumab 140 mg SC Q2W or 420 mg SC QM¹</strong> (baseline LDL-C = 120 mg/dL)</td>
<td>-61% (P&lt;0.001)*</td>
<td>-61% (P&lt;0.001)</td>
</tr>
<tr>
<td><strong>Alirocumab 150 mg SC Q2W²</strong> (baseline LDL-C = 123 mg/dL)</td>
<td>-62% (P&lt;0.001)**</td>
<td>-56% (P&lt;0.001)</td>
</tr>
</tbody>
</table>

*Proportion of patients with LDL-C < 70 mg/dL = 74%
† Proportion of patients with LDL-C < 70 mg/dL = 79%

Efficacy in Long-Term Studies

**Osler**\(^1\): Open label study of 4465 pts randomized to evolocumab 140 mg SC W2W or 420 mg SC QM + standard of care (SOC) vs SOC for 12 wks

**Odyssey Long Term**\(^2\): Blinded study of 2341 high risk pts on max-tolerated statin with LDL-C > 70 randomized to alirocumab 150 mg or placebo SC Q2W for 24 wks

<table>
<thead>
<tr>
<th>Treatments</th>
<th>LDL-C</th>
<th>nonHDL-C</th>
<th>Apo B</th>
<th>Lp(a)</th>
<th>TG</th>
<th>HDL-C</th>
<th>Apo A1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evolocumab</strong>(^1)</td>
<td>-61%</td>
<td>-52%</td>
<td>-47%</td>
<td>-26%</td>
<td>-13%</td>
<td>7.0%</td>
<td>4.2%</td>
</tr>
<tr>
<td><strong>Alirocumab</strong>(^2)</td>
<td>-62%</td>
<td>-52%</td>
<td>-54%</td>
<td>-26%</td>
<td>-17%</td>
<td>4.6%</td>
<td>2.9%</td>
</tr>
</tbody>
</table>

# Safety

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Osler(^1) (n=4465 pts, 48 weeks)</th>
<th>Odyssey Long Term(^2) (n=2341 pts, 78 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Evolocumab</td>
<td>SOC</td>
</tr>
<tr>
<td>Any adverse events</td>
<td>69.2%</td>
<td>64.8%</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>7.5%</td>
<td>7.5%</td>
</tr>
<tr>
<td>AE leading to DC of Rx</td>
<td>2.4%</td>
<td>NA</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>4.3%</td>
<td>NA</td>
</tr>
<tr>
<td>Transaminase &gt; 3x ULN</td>
<td>1.0%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Muscle-related/myalgia</td>
<td>6.4%</td>
<td>6.0%</td>
</tr>
<tr>
<td>CK &gt; 5x/&gt; 3x ULN</td>
<td>0.6%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Neurocognitive events/disorders</td>
<td>0.9%</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

## “Low LDL-C”

Alirocumab-treated patients in the Global Safety Pool

<table>
<thead>
<tr>
<th>Category</th>
<th>Alirocumab n=3340</th>
<th>≥ 2 LDL-C &lt; 25 mg/dL n=796 (24%)</th>
<th>≥ 2 LDL-C &lt; 15 mg/dL n=288 (7%)</th>
<th>LDL-C ≥ 25 mg/dL n=2544 (76%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal and connective tissue</td>
<td>24.2%</td>
<td>21.1%</td>
<td>20.1%</td>
<td>23.8%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>4.9%</td>
<td>3.1%</td>
<td>3.8%</td>
<td>4.9%</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>1.9%</td>
<td>1.0%</td>
<td>1.0%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>17.0%</td>
<td>12.7%</td>
<td>10.1%</td>
<td>16.7%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4.3%</td>
<td>3.0%</td>
<td>1.4%</td>
<td>4.0%</td>
</tr>
<tr>
<td>Nervous System</td>
<td>14.9%</td>
<td>10.3%</td>
<td>9.0%</td>
<td>15.1%</td>
</tr>
<tr>
<td>Headache</td>
<td>4.6%</td>
<td>1.8%</td>
<td>1.4%</td>
<td>4.8%</td>
</tr>
<tr>
<td>Metabolism and nutrition</td>
<td>6.9%</td>
<td>7.0%</td>
<td>7.3%</td>
<td>6.4%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.2%</td>
<td>1.5%</td>
<td>2.4%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>4.6%</td>
<td>5.3%</td>
<td>6.9%</td>
<td>4.0%</td>
</tr>
<tr>
<td>Cataract</td>
<td>0.8%</td>
<td>1.5%</td>
<td>2.4%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>2.5%</td>
<td>2.8%</td>
<td>2.4%</td>
<td>2.3%</td>
</tr>
</tbody>
</table>
### New Onset DM or IFG in Patients Receiving Alirocumab in the Global Safety Pool

<table>
<thead>
<tr>
<th>Global Safety Pool</th>
<th>Placebo-Controlled Studies</th>
<th>Ezetimibe-Controlled Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alirocumab</td>
<td>Placebo</td>
</tr>
<tr>
<td><strong>New Onset Diabetes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline normoglycemia (FBG &lt; 100 mg/dL)</td>
<td>0.1% n=718</td>
<td>0.3% n=365</td>
</tr>
<tr>
<td>Baseline impaired fasting glucose (FBG 100-126 mg/dL)</td>
<td>5.7% n=865</td>
<td>3.8% n=420</td>
</tr>
<tr>
<td><strong>New Onset Impaired Fasting Glucose</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline normoglycemia (FBG &lt; 100 mg/dL)</td>
<td>31.2% n=718</td>
<td>26.6% n=365</td>
</tr>
<tr>
<td>Baseline impaired fasting glucose (FBG 100-126 mg/dL)</td>
<td>20.6% n=865</td>
<td>18.1% n=420</td>
</tr>
<tr>
<td><strong>Reverted to Normoglycemia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline impaired fasting glucose (FBG 100-126 mg/dL)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Neurologic Events

Logic: Cholesterol is major component of cellular membranes and myelin. Indicators of Neurologic AE include central (unlikely b/c mAb unlikely to cross BBB) and peripheral neuropathies.

<table>
<thead>
<tr>
<th>Global Safety Pool</th>
<th>Placebo-Controlled Studies</th>
<th>Ezetimibe-Controlled Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alirocumab n=2476</td>
<td>Alirocumab n=864</td>
</tr>
<tr>
<td>Patients with a Neurologic TEAE</td>
<td>3.5%</td>
<td>2.4%</td>
</tr>
<tr>
<td></td>
<td>Placebo n=1276</td>
<td>Ezetimibe n=618</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>0.98 (0.68-1.41)</td>
<td>1.43 (0.76-2.69)</td>
</tr>
<tr>
<td>Demyelination</td>
<td>0.2%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Guillain-Barre</td>
<td>3.2%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>2.8%</td>
<td>2.3%</td>
</tr>
<tr>
<td>DC due to neurologic AE</td>
<td>0.2%</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

# Neurocognition

<table>
<thead>
<tr>
<th>Median exposure (mo)</th>
<th>Global Safety Pool</th>
<th>Osler</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any control n=2080</td>
<td>Evolocumab n=3946</td>
</tr>
<tr>
<td>Neurocognition TEAE</td>
<td>0.3%</td>
<td>0.1%</td>
</tr>
<tr>
<td>DC due to TEAE</td>
<td>&lt;0.1%</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>Memory impairment</td>
<td>&lt;0.1%</td>
<td>&lt;0.1%</td>
</tr>
<tr>
<td>Amnesia</td>
<td>-</td>
<td>0.1%</td>
</tr>
<tr>
<td>Dementia</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mental impairment</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Disorientation</td>
<td>0.1%</td>
<td>&lt;0.1%</td>
</tr>
</tbody>
</table>

Summary of AEs/Safety of PCSK9 Drugs

1. No difference in muscle or liver AEs between active drug and comparator
2. “Very low” LDL-C AEs not different from LDL-C > 25 mg/dL
3. New-onset DM not different from comparator
4. Neurologic AEs not different from comparator, however neurocognitive needs firmer delineation
Patients are censored at the end of TEAE period (last injection of study treatment + 70 days).

†Primary endpoint for the ODYSSEY OUTCOMES trial: CHD death, Non-fatal MI, Fatal and non-fatal ischemic stroke, Unstable angina requiring hospitalisation. “Unstable angina requiring hospitalisation” is limited to the UA events with definite evidence of progression of the ischemic condition (strict criteria).

<table>
<thead>
<tr>
<th>% (n) of patients</th>
<th>Alirocumab (n=1550)</th>
<th>Placebo (n=788)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients on background of max tolerated statin ± other lipid-lowering therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV events confirmed by adjudication</td>
<td>1.7% (27)</td>
<td>3.3% (26)</td>
</tr>
<tr>
<td>CHD death</td>
<td>0.3% (4)</td>
<td>0.9% (7)</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>0.9% (14)</td>
<td>2.3% (18)</td>
</tr>
<tr>
<td>Fatal + non-fatal ischaemic stroke</td>
<td>0.6% (9)</td>
<td>0.3% (2)</td>
</tr>
<tr>
<td>Unstable angina requiring hospitalisation</td>
<td>0</td>
<td>0.1% (1)</td>
</tr>
</tbody>
</table>
Impact Of Alirocumab vs Placebo on MACE in 2341 Patients in the Odyssey Long Term Study

Odyssey Long Term: Blinded study of 2341 high risk pts on max-tolerated statin with LDL-C > 70 randomized receiving alirocumab 150 mg or placebo SC Q2W for 78 wks

MACE
- CHD death
- Nonfatal MI
- Fatal/nonfatal ischemic CVA
- UA requiring hospitalization

MACE
Placebo = 3.3%
Alirocumab = 1.7%

Impact Of Evolocumab vs Placebo on MACE in 4465 Patients in the Osler Study

Osler: Open label study of 4465 pts randomized to evolocumab 140 mg SC Q2W or 420 mg SC QM + standard of care (SOC) or SOC for 48 wks

CV Events
- Death
- MI
- UA requiring hospitalization
- CVA
- TIA
- Hosp w CHF

Sabatine et al NEJM 2015; 372:1500-9
Immunogenicity

Antidrug antibodies (binding antibodies)

- 146 or 3033 (4.8%) in alirocumab-treated subjects
- 13 of 4915 (0.3%) in evolocumab-treated subjects.
  - Most are transient
  - Low concentration
  - Have no effect on efficacy or PK

Neutralizing antibodies

- 36 of 3033 (1.2%) in alirocumab-treated patients
- 0 in evolocumab-treated patients
  - Most are transient
  - Low concentration
  - Most had no effect on efficacy or PK but some did

Safety of evolocumab – PROFICIO Circulation 2017; 135: 1819
OSLER 4 year OLE JAMA Cardiol 2017; online March
Effect of Antidrug Antibodies on the Durability of LDL-C Lowering and on Plasma Bococizumab and PCSK9 Levels.
Effects of PCSK9 Antibodies in Adults with Hypercholesterolemia

• Systematic review and meta-analysis. Evaluated 24 trials with 10,159 patients. Mean follow up 44.6 months

• LDL-C reduced 47.5% with therapy and Lp(a) reduced 25%

• All-cause mortality reduced (OR 0.45) and non-fatal MI reduced (OR 0.49)

• There were no serious AEs, and no mention of neurocognitive differences
Impact of PCSK9 Inhibitors on Lipids and Outcomes: A Network Meta-analysis

• Evaluated 17 trials with 13,083 patients

• Baseline mean LDL-C was 122 mg/dL, and reduced 57% to 51 mg/dL

• Therapy reduced all-cause mortality (OR 0.43) however the incidence of neurocognitive AEs was higher (OR 2.34)
No Standard Definition of Statin Intolerance

• Inability to tolerate a dose of statin required to reduce a person’s risk sufficiently from their baseline risk¹

• Statin intolerance is a clinical syndrome characterized by the inability to tolerate at least 2 statins:
  o 1 statin at the lowest starting daily dose AND
  o Another statin at any daily dose
  o Due to:
    ▪ Either objectionable symptoms (real or perceived)
    ▪ Abnormal lab determinations, which are temporally related to statin treatment and reversible upon statin discontinuation, but reproducible by re-challenge with other known determinants being excluded²

ODYSSEY ALTERNATIVE: PCSK9 in Statin-Intolerant Patients

Study Design

Double-blind Treatment Period (24 weeks)

N = 100
Alirocumab 75/150 mg SC Q2W + placebo PO QD

N = 100
Ezetimibe 10 mg PO QD + placebo SC Q2W

N = 50
Atorvastatin, 20 mg PO QD + placebo SC Q2W

Open-label treatment period/8-week follow-up

Moderate-to very high-risk statin-intolerant patients*

Placebo PO QD + Placebo SC Q2W

Assessments

Week 0  Week 4  Week 8  Week 12  Week 16  Week 24

Patients discontinued if muscle-related AEs reported with placebos during run-in

Per-protocol dose increase if Week 8 LDL-C ≥70 or ≥100 mg/dL (depending on CV risk)

Primary end point (LDL-C % change from baseline)
Safety analysis

*Unable to tolerate at least 2 different statins, including one at the lowest dose, due to muscle-related symptoms.
# ODYSSEY ALTERNATIVE: Baseline Lipids

<table>
<thead>
<tr>
<th></th>
<th>Alirocumab (N=126)</th>
<th>Ezetimibe (N=125)</th>
<th>Atorvastatin (N=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C (calculated), mg/dL, mean (SD)</td>
<td><strong>191.1</strong> (72.7)</td>
<td><strong>193.5</strong> (70.9)</td>
<td><strong>187.3</strong> (59.5)</td>
</tr>
<tr>
<td>Non-HDL-C, mg/dL, mean (SD)</td>
<td><strong>230.0</strong> (80.4)</td>
<td><strong>229.8</strong> (82.7)</td>
<td><strong>223.8</strong> (64.8)</td>
</tr>
<tr>
<td>Apo B, mg/dL, mean (SD)</td>
<td><strong>141.7</strong> (39.5)</td>
<td><strong>138.2</strong> (37.4)</td>
<td><strong>139.1</strong> (34.7)</td>
</tr>
<tr>
<td>Lp(a), mg/dL, median (IQR)</td>
<td><strong>18</strong> (8:47)</td>
<td><strong>14</strong> (7:43)</td>
<td><strong>12</strong> (6:50)</td>
</tr>
<tr>
<td>Triglycerides, mg/dL, median (IQR)</td>
<td><strong>164</strong> (114:233)</td>
<td><strong>140</strong> (95:218)</td>
<td><strong>158</strong> (119:246)</td>
</tr>
<tr>
<td>HDL-C, mg/dL, mean (SD)</td>
<td><strong>48.9</strong> (15.3)</td>
<td><strong>50.7</strong> (14.1)</td>
<td><strong>51.1</strong> (12.5)</td>
</tr>
<tr>
<td>Apo A1, mg/dL, mean (SD)</td>
<td><strong>149.4</strong> (25.0)</td>
<td><strong>150.0</strong> (24.2)</td>
<td><strong>154.2</strong> (24.8)</td>
</tr>
</tbody>
</table>
ODYSSEY Alternative

Achieved calculated LDL-C over time – on-treatment analysis (modified ITT – observed data only)

- **Alirocumab**
- **Ezetimibe**

<table>
<thead>
<tr>
<th>Week</th>
<th>LDL-C, mean (SE), mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>156 mg/dL</td>
</tr>
<tr>
<td>4</td>
<td>97 mg/dL</td>
</tr>
<tr>
<td>12</td>
<td>97 mg/dL</td>
</tr>
<tr>
<td>16</td>
<td>92 mg/dL</td>
</tr>
<tr>
<td>24</td>
<td>92 mg/dL</td>
</tr>
</tbody>
</table>

Δ 59 mg/dL

49.5% received 150 mg Q2W at W12

Δ 65 mg/dL

JCL 2015; 9: 758-769
ODYSSEY Alternative: Reductions in Secondary Lipid Measures

![Graph showing reductions in lipid measures with Alirocumab and Ezetimibe]
The GAUSS-3 Trial

Goal Achievement after Utilizing an anti-PCSK9 antibody in Statin Intolerant Subjects-3

Steven E. Nissen MD MACC*
Erik Stroes MD PhD

JAMA 2016; 315:1580
Study Design: Two Double-Blind Phases

Phase A
- 511 patients enrolled at 53 centers with a history of intolerance to multiple statins due to muscle-related adverse effects.
- 10 weeks:
  - Atorvastatin 20 mg
  - Placebo
- 10 weeks:
  - Atorvastatin 20 mg
  - Placebo

Phase B
- Patients proceeded to Phase B only if they had *intolerable* muscle symptoms on atorvastatin, but not placebo, or CK ≥ 10 x ULN during prior statin treatment.
- 24 weeks:
  - Monthly SC evolocumab 420 mg
  - Daily oral ezetimibe 10 mg
# Phase A: Study Drug Discontinuation Events

<table>
<thead>
<tr>
<th>Intolerable Muscle Symptoms</th>
<th>N = 491</th>
</tr>
</thead>
<tbody>
<tr>
<td>On atorvastatin, but not placebo</td>
<td>209 (42.6%)*</td>
</tr>
<tr>
<td>On placebo, but not atorvastatin</td>
<td>130 (26.5%)</td>
</tr>
<tr>
<td>On both placebo and atorvastatin</td>
<td>48 (9.8%)</td>
</tr>
<tr>
<td>No symptoms on either treatment</td>
<td>85 (17.3%)</td>
</tr>
<tr>
<td>Did not complete Phase A</td>
<td>20/511</td>
</tr>
<tr>
<td>Bypassed Phase A due to CK elevation ≥ 10 x ULN</td>
<td>19 (3.9%)*</td>
</tr>
</tbody>
</table>

*218 of these 228 eligible patients proceeded to Phase B*
Mean baseline LDL-C: 212 mg/dL

Mean reduction 16.7% (LDL-C = 181 mg/dL)

Mean reduction 53.0% (LDL-C = 104 mg/dL)
Important Efficacy in FH Patients

- FH 1 and FH 2 were 78 week studies in 735 FH subjects on maximally tolerated statin +/- LLT randomized to alirocumab 75 mg q2week (or 150 mg)
  
  LDL-C baseline 145 mg/dL reduced to 71 mg/dL (-58%) in FH 1, and from 135 mg/dL to 68 mg/dL (-51%) in FH 2. (Eur Heart J 2015;36:2996)

- ODYSSEY ESCAPE trial evaluated 62 HeFH patients on maximal lipid therapy and LDL apheresis randomized to alirocumab or PBO. The frequency of LDL apheresis reduced in 75%, and stopped in 63% with alirocumab c/w PBO. (JCL 2016; 10: 627-634)
Reduction in Lp(a) with Evolocumab: Pooled Analysis of > 1,300 Patients in 4 Phase II Trials

Error bars represent standard error.

* P < 0.001
Alirocumab: Lp(a) Reductions in ODYSSEY Combo II, Long Term, FH I and FH II Studies

Percent change from baseline to Week 24:

- **Combo**: LS mean (SE) % change = -29.3
- **Long Term**: LS mean (SE) % change = -27.8
- **FH I**: LS mean (SE) % change = -25.2
- **FH II**: LS mean (SE) % change = -30.3

All comparisons vs. placebo are \( P < 0.0001 \)

Adjusted mean (SE) shown for Lp(a). LLT = lipid-lowering therapy.

Robinson, Farnier. Presented at the ESC; Barcelona, August 31, 2014.
# Outcome Studies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alirocumab</strong></td>
<td></td>
</tr>
<tr>
<td><strong>ODYSSEY OUTCOMES</strong>&lt;br&gt;(NCT01663402)</td>
<td>Enrolling post-acute MI or hospitalized UA w/in 12 mon; Rx w/ atorvastatin 40/80 mg/d, rosvuastatin 20/40 mg/d or max tolerated; LDL &gt; 70, nonHDL &gt; 100, or apo B &gt; 80; Endpoint – time to ASCVD event; n=18,000; est completion January 2018</td>
</tr>
<tr>
<td><strong>Evolocumab</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Fourier</strong>&lt;br&gt;(NCT01764633)</td>
<td>Enrolling MI, CVA, or PAD + RF; Rx with atorvastatin ≥ 20 mg or equivalent; LDL &gt; 70 or nonHDL &gt; 100; Endpoint – time to 1st ASCVD event; Rx w/ evolocumab 140 Q2W or 420 mg QM vs placebo; n=22,500; est completion October 2017</td>
</tr>
<tr>
<td><strong>Glagov</strong>&lt;br&gt;(NCT01813422)</td>
<td>IVUS study enrolling pts with evidence for coronary stenosis; LDL &gt; 80 or 60-80 w/ RF; Rx w/ statin, niacin or ezetimibe; Rx evolocumab 420 mg SC QM for 72 mon; n=950</td>
</tr>
<tr>
<td><strong>Bococizumab</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Spire-1</strong>&lt;br&gt;(NCT01975376)</td>
<td>Enrolling high risk CVD event; LDL 70-100 or nonHDL 100-130; on LLRx; Randomized to Bococizumab 150 mg SC Q2W vs placebo; n=12,000; est completion April 2018</td>
</tr>
<tr>
<td><strong>Spire-2</strong>&lt;br&gt;(NCT01975389)</td>
<td>Same as above except LDL &gt; 100 or nonHDL &gt; 130; n=6300; est completion January 2018</td>
</tr>
</tbody>
</table>
Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients
The GLAGOV Randomized Clinical Trial

Stephen J. Nicholls, MBBS, PhD; Rishi Puri, MBBS, PhD; Todd Anderson, MD; Christie M. Ballantyne, MD; Leslie Cho, MD; John J. P. Kastelein, MD, PhD; Wolfgang Koenig, MD; Ransi Somaratne, MD; Helina Kassahun, MD; Jingyuan Yang, PhD; Scott M. Wasserman, MD; Robert Scott, MD; Imre Ungi, MD, PhD; Jakub Podolec, MD, PhD; Antonius Oude Ophuis, MD, PhD; Jan H. Cornel, MD, PhD; Marilyn Borgman, RN, BSN; Danielle M. Brennan, MS; Steven E. Nissen, MD

**INTERVENTIONS** Participants with angiographic coronary disease were randomized to receive monthly evolocumab (420 mg) (n = 484) or placebo (n = 484) via subcutaneous injection for 76 weeks, in addition to statins.
GLAGOV – Percent Change in LDL-C During Treatment

Mean LDL-C 36.6 mg/dL
Change from baseline 3.9%

Mean LDL-C 93.0 mg/dL
Change from baseline -59.8% 29 mg/dL

Study Week

LDL-C Percentage Change from Baseline (%)
GLAGOV Primary Endpoint: Percent Atheroma Volume

Change in Percent Atheroma Volume (%)

-1.2
-1
-0.8
-0.6
-0.4
-0.2
0
0.2

Statin monotherapy

Statin-evolocumab

0.05

P = NS

P < 0.0001

P < 0.001

P = NS
GLAGOV: Mean On-Treatment LDL-C vs. Change in PAV

Locally Weighted Polynomial Regression (LOESS) Plot with 95% confidence limits
FOURIER
Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk

MS Sabatine, RP Giugliano, AC Keech, N Honarpour, SM Wasserman, PS Sever, and TR Pedersen, for the FOURIER Steering Committee & Investigators

American College of Cardiology – 66th Annual Scientific Session
Late-Breaking Clinical Trial

NEJM 2017; doi:10.1056/NEJMmoa1615664 (online 3/17)
Trial Design

27,564 high-risk, stable patients with established CV disease (prior MI, prior stroke, or symptomatic PAD)

Screening, Lipid Stabilization, and Placebo Run-in
High or moderate intensity statin therapy (± ezetimibe)

LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL

RANDOMIZED DOUBLE BLIND

Evolocumab SC 140 mg Q2W or 420 mg QM

Placebo SC Q2W or QM

Follow-up Q 12 weeks

### Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years, mean (SD)</strong></td>
<td>63 (9)</td>
</tr>
<tr>
<td><strong>Male sex (%)</strong></td>
<td>75</td>
</tr>
<tr>
<td><strong>Type of cardiovascular disease (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>81</td>
</tr>
<tr>
<td>Stroke (non-hemorrhagic)</td>
<td>19</td>
</tr>
<tr>
<td>Symptomatic PAD</td>
<td>13</td>
</tr>
<tr>
<td><strong>Cardiovascular risk factor (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>80</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>37</td>
</tr>
<tr>
<td>Current cigarette use</td>
<td>28</td>
</tr>
</tbody>
</table>

Median time from most recent event ~3 yrs

Pooled data; no differences between treatment arms
An Academic Research Organization of Brigham and Women’s Hospital and Harvard Medical School

**LDL Cholesterol**

**Placebo**

59% mean reduction (95% CI 58-60), P<0.00001

Absolute reduction: 56 mg/dl (95% CI 55-57)

**Evolocumab**

(median 30 mg/dl, IQR 19-46 mg/dl)
Primary Endpoint

CV Death, MI, Stroke, Hosp for UA, or Cor Revasc

Hazard ratio 0.85 (95% CI, 0.79-0.92) P<0.0001
## Types of CV Outcomes

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Evolocumab (N=13,784)</th>
<th>Placebo (N=13,780)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD, MI, stroke, UA, or revasc</td>
<td>12.6</td>
<td>14.6</td>
<td>0.85 (0.79-0.92)</td>
</tr>
<tr>
<td>CV death, MI, or stroke</td>
<td>7.9</td>
<td>9.9</td>
<td>0.80 (0.73-0.88)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>2.5</td>
<td>2.4</td>
<td>1.05 (0.88-1.25)</td>
</tr>
<tr>
<td>MI</td>
<td>4.4</td>
<td>6.3</td>
<td>0.73 (0.65-0.82)</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.2</td>
<td>2.6</td>
<td>0.79 (0.66-0.95)</td>
</tr>
<tr>
<td>Hosp for unstable angina</td>
<td>2.2</td>
<td>2.3</td>
<td>0.99 (0.82-1.18)</td>
</tr>
<tr>
<td>Coronary revasc</td>
<td>7.0</td>
<td>9.2</td>
<td>0.78 (0.71-0.86)</td>
</tr>
<tr>
<td>Urgent</td>
<td>3.7</td>
<td>5.4</td>
<td>0.73 (0.64-0.83)</td>
</tr>
<tr>
<td>Elective</td>
<td>3.9</td>
<td>4.6</td>
<td>0.83 (0.73-0.95)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>4.8</td>
<td>4.3</td>
<td>1.04 (0.91-1.19)</td>
</tr>
</tbody>
</table>
### Key Subgroups

**Subgroup** | **Patients** | **PEP HR (95% CI)** | **Key SEP HR (95% CI)**
---|---|---|---
**Overall** | 27564 | | |
**Type of disease** | | | |
  MI alone | 19113 | | |
  Stroke alone | 3366 | | |
  PAD alone | 1505 | | |
  Polyvascular disease | 3563 | | |
**Baseline LDL-C** | | | |
  Q1 (<80 mg/dl) | 6961 | | |
  Q2 (80-<92 mg/dl) | 6886 | | |
  Q3 (92-109 mg/dl) | 6887 | | |
  Q4 (>109 mg/dl) | 6829 | | |
**Baseline statin intensity** | | | |
  High | 19103 | | |
  Not high | 8461 | | |
**Ezetimibe** | | | |
  Yes | 1440 | | |
  No | 26124 | | |
**Initial Dosing Regimen** | | | |
  Every 2 weeks | 24774 | | |
  Monthly | 2790 | | |

---

*All P values for interactions NS*
Landmark Analysis

**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
Comparison to Cholesterol Treatment Trialists Collaboration

Hazard Ratio (95% CI) per 1 mmol/L reduction in LDL-C

- Major Coronary Events
  - Lipid-lowering therapy better: 0.78 (0.70-0.86)
  - Lipid-lowering therapy worse: 0.80 (0.71-0.90)

- Stroke
  - Lipid-lowering therapy better: 0.77 (0.66-0.91)
  - Lipid-lowering therapy worse: 0.77 (0.63-0.94)

- Coronary revascularization
  - Urgent: 0.75 (0.67-0.84)
  - Elective: 0.73 (0.62-0.86)

- Major Vascular Events
  - Lipid-lowering therapy better: 0.77 (0.73-0.82)
  - Lipid-lowering therapy worse: 0.83 (0.76-0.90)

CTTC data from *Lancet* 2010;376:1670-81
## Safety

<table>
<thead>
<tr>
<th>Adverse events (%)</th>
<th>Evolocumab (N=13,769)</th>
<th>Placebo (N=13,756)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>77.4</td>
<td>77.4</td>
</tr>
<tr>
<td>Serious</td>
<td>24.8</td>
<td>24.7</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>3.1</td>
<td>2.9</td>
</tr>
<tr>
<td>Injection-site reaction</td>
<td>2.1</td>
<td>1.6</td>
</tr>
<tr>
<td>Treatment-related and led to d/c of study drug</td>
<td>1.6</td>
<td>1.5</td>
</tr>
<tr>
<td>Muscle-related</td>
<td>5.0</td>
<td>4.8</td>
</tr>
<tr>
<td>Cataract</td>
<td>1.7</td>
<td>1.8</td>
</tr>
<tr>
<td>Diabetes (new-onset)</td>
<td>8.1</td>
<td>7.7</td>
</tr>
<tr>
<td>Neurocognitive</td>
<td>1.6</td>
<td>1.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory results (%)</th>
<th>Evolocumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binding Ab</td>
<td>0.3</td>
<td>n/a</td>
</tr>
<tr>
<td>Neutralizing Ab</td>
<td>none</td>
<td>n/a</td>
</tr>
</tbody>
</table>

New-onset diabetes assessed in patients without diabetes at baseline; adjudicated by CEC
EBBINGHAUS:

- A Cognitive Study of Patients Enrolled in the FOURIER Trial

RP Giugliano, F Mach, K Zavitz, AC Keech, TR Pedersen, MS Sabatine, P Sever, C Kurtz, N Honarpour, BR Ott, on behalf of the EBBINGHAUS Investigators

American College of Cardiology – 66th Annual Scientific Session
Late-Breaking Clinical Trial
March 18, 2017
Primary Endpoint
Spatial Working Memory Strategy Index

Mean Number of boxes

Basecase: 17.8, 17.8
Post baseline: 17.6, 17.5
Change: -0.29, -0.21

Non-inferiority boundary: 0.19

\( P_{non-inferiority} < 0.001 \)

Treatment Difference in Z score
(Placebo minus Evolocumab)
Favors Evolocumab
Favors Placebo

\( P_{NI} \) is from fixed estimate
Conclusions

In patients with known cardiovascular disease on background statin followed for 20 months

1. No differences btw evolocumab vs placebo
   A. A battery of cognitive tests
   B. Patient-reported everyday cognition
   C. Adverse cognitive events reported by MD

2. No evidence of differences in cognitive tests by achieved nadir LDL-C, even <25 mg/dL
2016 ACC Expert Consensus Decision Pathway on the Role of Non-statin Therapies in the Management of ASCVD Risk
ACC Expert Consensus

- The Panel was convened by the ACC to answer the following questions regarding use of non-statin therapies:

  1) In what patient populations should non-statin therapies be considered?

  2) In what situations should non-statin therapies be considered, such as, when the amount of LDL-C lowering (percent LDL-C reduction or LDL-C range achieved on therapy) is less than anticipated, less than desired, or inadequate, and which treatment options should be considered in patients who are truly statin intolerant?

  3) If non-statin therapies are to be added, which agents or therapies should be considered and in what order?
FIGURE 2A  Patients with Stable Clinical ASCVD without Comorbidities, on Statin for Secondary Prevention

Patients with stable clinical ASCVD without comorbidities,* on statin for secondary prevention

Patient has ≥50% LDL-C reduction (may consider LDL-C <100 mg/dL) on maximally tolerated statin†

YES

NO

1. Address statin adherence.
2. Intensify lifestyle (may consider phytosterols).
3. Increase to high-intensity statin if not already taking.
4. Evaluate for statin intolerance if unable to tolerate moderate-intensity statin.† Consider referral to lipid specialist if statin intolerant
5. Control other risk factors.

Patient has ≥50% LDL-C reduction (may consider LDL-C <100 mg/dL) on maximally tolerated statin†

YES

NO

CLINICIAN-PATIENT DISCUSSION FACTORS TO CONSIDER
1. Potential for additional ASCVD risk reduction from addition of non-statin therapy to lower LDL-C (see Table 4)
2. Potential for adverse events or drug-drug interactions from addition of non-statin therapy (see Table 3)
3. Patient preferences (see Table 4)

Optional non-statin medications to consider

1. Consider ezetimibe first.§

Patient has >50% LDL-C reduction (may consider LDL-C <100 mg/dL) on maximally tolerated statin/other medications†

NO

YES

Consider adding or replacing with PCSK9 inhibitor second.$

Decision for no additional medication

Continue to monitor adherence to medications and lifestyle, and LDL-C response to therapy.
FIGURE 2B | Patients with Clinical ASCVD with Comorbidities, on Statin for Secondary Prevention

Patients with clinical ASCVD with comorbidities,* on statin for secondary prevention

Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL or may consider non-HDL-C <100 mg/dL in patients with diabetes) on maximally tolerated statin†

NO

YES

1. Address statin adherence.
2. Intensify lifestyle (may consider phytoestrogens).
3. Increase to high-intensity statin if not already taking.
4. Evaluate for statin intolerance if unable to tolerate moderate-intensity statin.† Consider referral to lipid specialist if statin intolerant.
5. Control other risk factors.

Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL or may consider non-HDL-C <100 mg/dL in patients with diabetes) on maximally tolerated statin†

NO

YES

CLINICIAN-PATIENT DISCUSSION FACTORS TO CONSIDER
1. Potential for additional ASCVD risk reduction from addition of non-statin therapy to lower LDL-C (see Table 4)
2. Potential for adverse events or drug-drug interactions from addition of non-statin therapy (see Table 3)
3. Patient preferences (see Table 4)

Decision for no additional medication

Optional non-statin medications to consider

Consider ezetimibe first.§

Consider adding or replacing with PCSK9 inhibitor second.¶

Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL or may consider non-HDL-C <100 mg/dL in patients with diabetes) on maximally tolerated statin†

YES

NO

Continue to monitor adherence to medications and lifestyle, and LDL-C response to therapy.
FIGURE 2C | Patients with Clinical ASCVD and Baseline LDL-C ≥190 mg/dL Not Due to Secondary Causes, on Statin for Secondary Prevention

Patients with clinical ASCVD and baseline LDL-C ≥190 mg/dL not due to secondary causes, on statin for secondary prevention

Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL) on maximally tolerated statin

1. Address statin adherence.
2. Intensify lifestyle (may consider phytosterols).
3. Increase to high-intensity statin if not already taking.
4. Evaluate for statin intolerance if unable to tolerate moderate-intensity statin.†
   Referral to lipid specialist recommended if statin intolerant.
5. Control other risk factors.
6. Consider referral to lipid specialist and RDN for all patients, especially for homozygous FH.§

Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL) on maximally tolerated statin

CLINICIAN-PATIENT DISCUSSION FACTORS TO CONSIDER
1. Potential for additional ASCVD risk reduction from addition of non-statin therapy to lower LDL-C (see Table 4)
2. Potential for adverse events or drug-drug interactions from addition of non-statin therapy (see Table 3)
3. Patient preferences (see Table 4)

Optional non-statin medications to consider

Consider ezetimibe (or BAS second line).]
Consider PCSK9 inhibitor.

Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL) on maximally tolerated statin/other medications

1. Repeat clinician-patient discussion.
2. Add other non-statin medication(s) above.
3. Consider referral to lipid specialist and RDN.

Patient has ≥50% LDL-C reduction (may consider LDL-C <70 mg/dL) on maximally tolerated statin/other medications

Refer to lipid specialist and RDN recommended

Decision for no additional medication

Continue to monitor adherence to medications and lifestyle, and LDL-C response to therapy.
NLA Recommended Candidates for PCSK9 Inhibitors

<table>
<thead>
<tr>
<th>Segment</th>
<th>Specific population</th>
<th>LDL-C (mg/dL) on maximally-tolerated statin (±ezetimibe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FH</td>
<td>Heterozygous FH patients without ASCVD</td>
<td>≥ 130</td>
</tr>
<tr>
<td>ASCVD</td>
<td>ASCVD</td>
<td>≥ 100</td>
</tr>
<tr>
<td></td>
<td>Selected ASCVD patients such as those with recurrent CV events</td>
<td>≥ 70</td>
</tr>
<tr>
<td>Statin Intolerance</td>
<td>High or very high risk patients who meet the NLA definition of statin intolerance</td>
<td>As above</td>
</tr>
</tbody>
</table>
Summary

Monoclonal Antibodies for PCSK9

- Both evolocumab and alirocumab consistently lower LDL-C ≥ 50% with and without background statin therapy in patients with:
  - HeFH
  - High risk on max dose statin and not at a desirable LDL-C level
  - Statin intolerant
  - Statin naïve

- The mAbs for PCSK9 are well tolerated with no signal of significant adverse events thus far, including patients with on-treatment LDL-C < 25 mg/dL

- FOURIER trial confirms the CV benefit of substantial LDL-C reduction on SOC, and confirms the safety and durability of evolocumab treatment. We await confirmation from the ongoing ODYSSEY Outcomes trial.

- EBBINGHAUS provides confidence that short term low LDL-C levels have no adverse affect on cognition