Drug Class Review

PCSK9 Inhibitors
24:06.24 - Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) Inhibitors

Praluent®, alirocumab
(Sanofi/Regeneron)
FDA Approved July 2015

Repatha®, evolocumab
(Amgen)
FDA Approved August 2015

Final Report
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Abbreviations:

AEs    adverse events
ALI    alirocumab
ApoB   apolipoprotein B
ASCVD  atherosclerotic cardiovascular disease
ATO    atorvastatin
CK     creatine kinase
EAS    European Atherosclerosis Society
ESC    European Society of Cardiology
EVO    evolocumab
EZE    ezetimibe
FRS    Framingham risk score
GOF    gain of function
HeFH   heterozygous familial hypercholesterolemia
HoFH   homozygous familial hypercholesterolemia
HDL-C  high-density lipoprotein cholesterol
ITT    Intent to treat
LDL-C  low-density lipoprotein cholesterol
Lp(a)   lipoprotein a
LOF    loss of function
Mab    monoclonal antibody
NLA    National Lipid Association
NonHDL-C Non-high-density lipoprotein cholesterol
PBO    placebo
PCSK9  proprotein convertase subtilisin/kexin type 9 serine protease
Q2W    every 2 weeks
Q4W    every 4 weeks
ROS    rosuvastatin
RR     relative risk
RXN    reaction
SAEs   serious adverse events
SIM    simvastatin
SOC    standard of care
TEAEs  treatment emergent adverse events
TG     triglycerides
ULN    upper limit of normal
URTI   upper respiratory tract infection
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Executive Summary

Introduction:
Cardiovascular disease affects one-third of US adults and is the number one cause of death in the United States. Elevated LDL-C concentrations are linked to cardiovascular disease and death. A goal in pharmacologic therapy is reducing LDL-C concentrations. A number of agents are available to reduce LDL-C with statin agents offering large reductions in LDL-C and a documented ability to reduce cardiovascular events. Some patients are unable to tolerate statin therapy. The most common adverse events limiting therapy are myalgias and arthralgias. Statins are associated with 50% patient adherence and persistence, therefore a significant number of patients do not gain the benefits statin therapy. Additionally, patients with familial hypercholesterolemia often do not achieve adequate LDL-C lowering when treated with statins in addition to other agents. Apheresis remains an option for these patients, however there are only 40 centers in the US offering this therapy, it is expensive and often must be performed as frequently as every 2 weeks. Finally, statins are known to directly increase the expression of PCSK9 resulting in a loss of hepatocyte cell surface LDL-receptors.

The most recent dyslipidemia guidelines have stepped away from setting a target LDL-C. The PCSK9 inhibitors bind to PCSK9 preventing the destruction of LDL-receptors and leading to increased removal of LDL-C from the circulation. Two humanized monoclonal antibodies targeted to inhibit PCSK9 have recently been FDA approved for use in dyslipidemias, evolocumab (Repatha®) and alirocumab (Praluent®).

Clinical Efficacy:
In trials of at least one year, for both agents, long-term adherence was documented. DESCARTES 88%, OSLER 93%, ODYSSEY LONG-TERM 72%.

Alirocumab:
The FDA reviewed data from 10 studies involving 5296 patients supporting the use of alirocumab in three populations, 1) heterozygous familial hypercholesterolemia, 2) non-familial hypercholesterolemia patients at high to very high cardiovascular event risk including those with diabetes and mixed dyslipidemias and 3) statin-intolerant patients due to muscle-related adverse events. Patients who were not randomized to alirocumab continued their current lipid-lowering regimens. Five studies compared alirocumab to placebo and five-compared alirocumab to ezetimibe Studies were at least 52-weeks duration with the efficacy endpoint measured at week 24. Three studies were conducted exclusively in patients with HeFH. In studies with doses ranging from 75-150 mg every 2 weeks, 57-83% of patients did not require a dosage change. In the longest trial to date, ODYSSEY LONG-TERM, 2341 patients were randomized to receive either alirocumab 150 mg or placebo every 2 weeks. At 24 weeks, alirocumab lowered LDL-C 61% from baseline compared to 0.8% in the placebo group (p=0.001).

Evolocumab:
The FDA reviewed data from 5 studies involving 3152 patients supporting the use of evolocumab in the treatment of primary hyperlipidemia or mixed dyslipidemia. Treatment with evolocumab was compared to placebo, ezetimibe or standard lipid-lowering therapy and included statin-intolerant patients. Evolocumab was administered subcutaneously as 140 mg every 2 weeks or 420 mg every 4 weeks. Four of the trials
evaluated LDL-C lowering from baseline at week 12 and found LDL-C reductions with evolocumab 37-47% larger than with ezetimibe and 55-76% larger than placebo. The effects persisted across evolocumab dosing frequencies and studies. Similar findings persisted over the duration of a 52-week study.'

Data was also submitted to support use of evolocumab in the treatment of homozygous familial hypercholesterolemia (HoFH). An open-label pilot study of 8 patients was followed with a randomized, controlled trial adding evolocumab to therapy with a statin, and in 92% of subjects, ezetimibe. In the pilot, LDL-C lowering was not observed in 2 LDL-receptor negative patients. In the remaining 6 LDL-receptor defective patients LDL-C lowering of 19.3% to 26.3% was documented.

**Safety:**
The PCSK9 inhibitors appear to be well tolerated. Studies are limited to less than two years and the long-term effects of these drugs remains unknown. Ongoing 5-year outcome trials are expected to yield results in 2-3 years. Side effects reported with monoclonal antibody therapy include injection site reactions, allergic reactions, elevated liver enzymes, myalgia and low LDL-C concentrations. In clinical trials, discontinuation of therapy was most commonly the result of injection site reactions, allergic reactions and elevations of liver function tests. Non-significant, but more common neurocognitive and ophthalmic events in the PCSK9 inhibitor groups led to speculation that very low LDL-C concentrations might impair cholesterol homeostasis and functioning in these cholesterol rich organs. Systematic reviews by Navarese and Zhang report adverse events do not increase with when the use of these agents results in very low LDL-C concentrations.

**Summary:**
The PCSK9 inhibitors offer a novel mechanism of action resulting in significant reductions of LDL-C. The agents are more effective than placebo, statins, ezetimibe, combinations of lipid-lowering therapies and are effective when added to existing therapy. Efficacy has been demonstrated in the setting of hyper- and dyslipidemias, HeFH, HoFH (for evolocumab) and in statin-intolerant patients. The agents are generally well tolerated. The most common adverse events relate to injection site reactions, allergic reactions, nasopharyngitis, very low LDL-C levels, elevated liver enzymes and myalgias. The most common reasons for discontinuation were allergic reactions, elevated liver function tests and myalgias. Adherence for over a year is demonstrated in clinical trials with most patients administering their own subcutaneous doses. Long-term studies will address efficacy and specific safety concerns (e.g. low LDL-C, neurocognitive effects, ophthalmic effects, cardiovascular outcomes, immunogenicity, diabetes) with results anticipated in 2017-18. The PCSK9 inhibitors are administered via subcutaneous injection and require specific storage requirements. Evolocumab may be given every 2 weeks or at a higher dosage every 4 weeks administered in 3 SQ injections with similar LDL-C reductions. The dose of alirocumab may be doubled in patients that do not achieve target LDL-C lowering with a 75 mg dosage. Studies suggest 16-20% of alirocumab patients require a dosage increase resulting in ~10-20% additional LDL-C lowering. The selection of appropriate candidates for therapy is guided by the Medicaid Prior Authorization process.
**Background:**

Cardiovascular disease affects one-third of US adults representing more than 73 million people resulting in 25% of deaths in the US representing > 600,000 people yearly. Risk factors for cardiovascular disease include family history, lifestyle choices relating to exercise, smoking or diet as well as underlying comorbidities such as diabetes, kidney disease, thyroid disease, Cushing’s, cholestasis disorders, hypertension and a number of medications which increase cholesterol levels (e.g. atypical antipsychotics, azole antifungals, beta-blockers, corticosteroids, cyclosporine, HIV protease inhibitors, isotretinoin, linagliptin, oral contraceptives, tacrolimus and thiazide diuretics).

Cholesterol is essential for the production of hormones, bile acids, vitamin D, cell membranes and linings while elevated LDL-C concentrations are clearly linked to cardiovascular disease. Treatment of lipid-associated cardiovascular disease is geared to reduce LDL-C and improve outcomes. The target for LDL-C lowering remains controversial. Guidelines are divided on whether to treat to a target LDL-C concentration or just treat aggressively. It is unknown whether very low LDL-C concentrations are problematic, however, people with very low levels of LDL-C due to non-sense mutations appear to function normally suggesting we do not know how low we may reduce levels before harms arise. Many believe “the lower the better”.

Familial hypercholesterolemia is the most common serious genetic disorder and encompasses a group of genetic defects that impair the removal of LDL-cholesterol. A homozygous defect (affecting 1 in 1 million persons) results in a lack of LDL-C receptors with LDL-C levels exceeding 600 mg/dL, while a heterozygous defects (affecting 1 in 300-500 persons) results in LDL-C levels of 200-400 mg/dL. Approximately 620,000 persons in the US are affected. These patients have significantly higher risk for CVD and present with sequelae at a young age, ~ 20 years for HoFH and ~40-50 for HeFH. Intensive lifestyle modification and high-intensity statin therapy remain the mainstay of therapy with a goal reduction of LDL-C by 50%.

Hydroxymethylglutaryl coenzyme A (HMGCoA) reductase inhibitors, or statins, are potent inhibitors of cholesterol synthesis with the ability to dramatically lower LDL-C. These agents comprise the first-line option for treatment of elevated LDL-C levels and guidelines recommend the use of maximally tolerated statin doses. A number of patients are unable to tolerate the recommended doses of statin therapy due to myalgias or arthralgias. Adherence and persistence with statin therapy is below 50% resulting in significant increases in CVD (RR 1.22 to 5.26) and mortality (RR 1.25 to 5.00). Patients with HoFH and others with very high baseline LDL-C levels do not achieve adequate reductions with statin therapy. Mechanistically, by inhibiting the HMGCoA enzyme, statin medications both inhibit cholesterol synthesis and increase the expression of PCSK9. Finally, statin medications appear to be linked to the development of diabetes particularly in predisposed patients (e.g. impaired glucose tolerance).

Proprotein convertase subtilisin/kexin type 9 (PCSK9) was identified in 2003. Genetic mutations of PCSK9 with gain of function and loss of function abnormalities have been documented in humans. Loss-of-function abnormalities result in PCSK9, which is unable to down regulate LDL receptors. This genetic variant is found in approximately 2-3% of the population. These people have 15-28% lower LDL-C levels and 40-60% reductions in CVD.
The ARIC study found those with LOF mutations had 28% lower LDL-C levels and an 88% reduction in CVD risk after 15 years when compared with those without the mutation. A gain of function genetic abnormality results in a reduction in LDL-receptors on the hepatocyte, higher levels of LDL-C and higher rates of premature CAD. The role of PCSK9 in LDL receptor recycling led to the development of antibodies to PCSK9 as a target for reducing LDL-C levels.

The purpose of the review is to review the available clinical efficacy and safety data for the PCSK9 inhibitors.

**Pharmacology**

The liver facilitates plasma removal of VLDL particles and chylomicron remnants. It synthesizes cholesterol, and synthesizes and secretes HDL particles, cholesterol and bile salts. It is also involved in reverse cholesterol transport where cholesterol is brought to the liver from the plasma and excreted through the bile to the feces. Hepatic cholesterol levels are controlled by the rate of hepatic synthesis of cholesterol and the activity of LDL-receptors, which remove cholesterol (in the form of LDL) from the blood. As intracellular cholesterol levels decline steroid receptor element binding protein-2 (SREBP-2) increases stimulating the expression of more LDL receptors on the hepatocyte resulting in increasing cholesterol concentrations within the cell. SREBP-2 additionally causes an increase in PCSK9 expression, which leads to a reduction in the expression of LDL receptors. Thus SREBP-2 stimulation leads to an increase in intracellular cholesterol with a built in control (via PCSK9) mechanism to maintain cholesterol levels.

**Mechanism of Action**

PSCK9 is a serine protease which functions to regulate the number of LDL-receptors expressed on the surface of the hepatocyte. A PCSK9 precursor is produced by the hepatocyte, is self-cleaved and secreted into the plasma as PCSK9. Circulating PCSK9 binds to the LDL-receptors on the surface of the hepatocyte. LDL binds to the LDL-receptor/PCSK9 complex and the receptor is internalized via the clathrin-coated pits into an endosome. The LDL particle is released from the receptor in the acidic endosome but the LDL-receptor/PSCK9 complex does not disassociate. PCSK9 targets the entire contents of the endosome, the LDL-particle as well as the PCSK9/LDL-receptor complex to the lysosome for degradation. LDL receptors are prevented from recirculating to the surface of the hepatocyte resulting in fewer LDL-receptors on the surface of the cell and higher circulating levels of LDL particles.

The PCSK9 inhibitors, evolocumab, alirocumab, and bococizumab (in clinical trials) are monoclonal antibodies targeted to bind to PCSK9 and prevent the PCSK9 particle from binding to the LDL-receptor and marking it for destruction. Inhibition of PCSK9 results in increased recycling of LDL receptors to the cell surface and reductions in circulating LDL particles and blood cholesterol concentration.

In the past, non-human monoclonal antibodies resulted in the development of antibodies-to-the-antibody resulting in more rapid clearance, hypersensitivity reactions and poor penetration to target sites. The use of humanized antibodies has reduced the incidence of cytokine release
A number of agents are used to treat hyperlipidemia, targeting a variety of mechanisms and with differing effects on cholesterol and lipoproteins. See Table 1 for a comparison of the available non-PCSK9 inhibitor agents. Table 2 presents a comparison of the PCSK9 inhibitors, evolocumab and alirocumab. These agents must be refrigerated and protected from light and are injected subcutaneously with prefilled syringes or pens at rotated healthy skin sites via aseptic technique. Both agents are approved for use as an adjunct to maximally tolerated statin therapy in adult patients requiring further lowering of LDL-C with HeFH or clinical atherosclerotic cardiovascular disease. Evolocumab is additionally indicated in adults and adolescents with HoFH who are on maximally tolerated statin +/- other therapies and require further LDL-C lowering. Alirocumab is administered at 75 mg every 2 weeks which may be increased to 150 mg every 2 weeks if the response is inadequate, while evolocumab is administered as 140 mg every 2 weeks or 420 mg every 4 weeks. Injection of a 420 mg dose of evolocumab involves 3 separate subcutaneous injections administered within 30 minutes.
<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism of Action</th>
<th>Range Across Agents</th>
<th>Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atorvastatin - Lipitor</strong></td>
<td>Inhibition of HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis</td>
<td>-21 to -63</td>
<td>Documented reduction of cardiovascular events. Some with CYP3A4 inhibition - Lescol, Livalo preferred with CYP3A4 inhibitors Adverse events ≥ 10% diarrhea, arthralgia, nasopharyngitis, elevated creatine kinase Risk of myopathy, rhabdomyelosis, new-onset type-2 diabetes in at-risk patients</td>
</tr>
<tr>
<td><strong>Fluvastatin – Lescol</strong></td>
<td>Inhibition of HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis</td>
<td>+3 to +16</td>
<td></td>
</tr>
<tr>
<td><strong>Lovastatin – Mevacor, Altoprev</strong></td>
<td>Inhibition of HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis</td>
<td>-10 to -37</td>
<td></td>
</tr>
<tr>
<td><strong>Pitavastatin - Livalo</strong></td>
<td>Inhibition of HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis</td>
<td>+3 to +16</td>
<td></td>
</tr>
<tr>
<td><strong>Pravastatin - Pravachol</strong></td>
<td>Inhibition of HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis</td>
<td>+3 to +16</td>
<td></td>
</tr>
<tr>
<td><strong>Rosuvastatin - Crestor</strong></td>
<td>Inhibition of HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis</td>
<td>+3 to +16</td>
<td></td>
</tr>
<tr>
<td><strong>Simvastatin – Zocor</strong></td>
<td>Inhibition of HMG-CoA reductase, the rate-limiting enzyme in cholesterol synthesis</td>
<td>+3 to +16</td>
<td></td>
</tr>
<tr>
<td><strong>Cholestyramine - Questran, Questra Light, Prevalite Colesevelam - Welchol Colestipol - Colesid</strong></td>
<td>Interrupt enterohepatic cholesterol circulation by binding to bile acids, preventing cholesterol reabsorption.</td>
<td>-15 to -30</td>
<td>Bile acid sequestrants + low-intensity statin provide benefit to statin-intolerant patients, no specific guideline recommendations, adverse events are dose-limiting (eg constipation, ↓ absorption of FA, CA, FE, fat soluble vitamins</td>
</tr>
<tr>
<td><strong>Fenofibrate – Antara, Fibrocor, Fenoglide, Lipofen, Lofibra, Tricor, Triglide, Trilipix</strong></td>
<td>PPAR-α agonist. Increases VLDL catabolism, fatty acid oxidation, and elimination of triglyceride-rich particles.</td>
<td>-20 to -31</td>
<td>Effective in combination with statin, inhibits CYP2A6, CYP2C8, and CYP2C9, may cause cholelithiasis, Lipofer and Lofibra must be taken with food, adverse events include headache 12-13%, increased serum transaminases 2-3%</td>
</tr>
<tr>
<td><strong>Gemfibrozil – Lopid</strong></td>
<td>Mechanism of action is not clearly defined</td>
<td>-5 to -10</td>
<td>May increase statin levels and incidence of myopathy, may promote weight loss, take on an empty stomach; may cause cholelithiasis, GI AEs, myopathy, inhibits CYP1A2, CYP2C19, CYP2C9, CYP2C9, SCL1B1, and UGT1A1</td>
</tr>
<tr>
<td><strong>Mipomersen – Kynamro</strong></td>
<td>Antisense oligonucleotide inhibitor of apoB-100</td>
<td>-21%</td>
<td>Orphan drug for HoFH which requires risk evaluation and mitigation strategy (REMS) due to liver toxicity, steatosis; effective in combination with statins; administered by SQ injection weekly, injection site reactions common, flu-like symptoms, maximal effects may take 6 months</td>
</tr>
<tr>
<td><strong>Niacin – Niacin-OTC, Niacin ER, Niapen, Niacor, Slo-Niacin, Flush-Free Niacin</strong></td>
<td>Not fully elucidated. Inhibits release of FFAs from adipose tissue prevents esterification of TG and increases lipase activity.</td>
<td>-5 to -25</td>
<td>Can raise HDL-C levels at low doses, higher doses not well tolerated (Flushing, headache), the addition of niacin to statin did not reduce CV risk, may increase statin-associated myopathy, increase blood glucose levels</td>
</tr>
<tr>
<td><strong>Ezetimibe - Zetia</strong></td>
<td>Inhibits cholesterol absorption at the small intestine brush border inhibits (NPC1L1) protein transporter.</td>
<td>-15 to -20</td>
<td>Reduces LDL-C, non-HDL-C, total cholesterol, triglycerides, bile acid sequestrants may decrease absorption, moderate increases in transaminases Some reports of myalgia</td>
</tr>
<tr>
<td><strong>Omega-3-Acid Ethyl Esters - Lovaza, Omtryg, Vascepa</strong></td>
<td>Mechanism of action not clearly defined</td>
<td>+44.5</td>
<td>May reduce cardiovascular risk, high pill burden for one drug, may enhance antiplatelet and anticoagulation effects, diarrhea common (7-15%)</td>
</tr>
<tr>
<td><strong>Lomitapide - Luxtapi3</strong></td>
<td>Inhibitor of microsomal triglyceride transfer protein (MTP). Reduces chylomicron and VLDL synthesis</td>
<td>-40</td>
<td>Orphan drug for HoFH, weight loss possible, black box warning for hepatotoxicity with REMS, inhibits CYP3A4, common adverse events relate to cardiac and gastrointestinal systems</td>
</tr>
<tr>
<td><strong>Ezetimibe + Simvastatin - Vytorin</strong></td>
<td>See: ezetimibe, simvastatin</td>
<td>- 45 to -60</td>
<td>Decrease pill burden</td>
</tr>
<tr>
<td><strong>Niacin + Lovastatin - Advicor</strong></td>
<td>See: niacin, lovastatin, simvastatin</td>
<td>- 45 to -60</td>
<td>Decrease pill burden, increased risk of myopathy</td>
</tr>
<tr>
<td><strong>Niacin + Simvastatin - Simcor</strong></td>
<td>See: niacin, lovastatin, simvastatin</td>
<td>- 45 to -60</td>
<td>Decrease pill burden, increased risk of myopathy</td>
</tr>
</tbody>
</table>
### Table 2: Comparison of PCSK9 Inhibitors\(^1,33-39\)

<table>
<thead>
<tr>
<th>Praluent (alirocumab)</th>
<th>Subcutaneous</th>
<th>Prefilled syringe, 1mL (single-use)</th>
<th>Hyperlipidemia: As an adjunct to diet and maximally tolerated statin therapy in patients requiring further LDL-cholesterol lowering:</th>
</tr>
</thead>
</table>
|                       |              | • 75 mg/1ml                        | • Adults with heterozygous familial hypercholesterolemia (HeFH)  
|                       |              | • 150 mg/1ml                      | • Clinical arteriosclerotic cardiovascular disease  
|                       |              | Pen Injector, 1mL (single-use)    | Limitation of use: The effect on cardiovascular morbidity and mortality has not been determined.  
|                       |              | • 75 mg/1ml                        | |
|                       |              | • 150 mg/1ml                      | |
|                       |              | Rotate sites (thigh, abdomen, upper arm) |  
|                       |              | Do not administer to injured skin |  
|                       |              | Do not administer other injectable drugs at the same site | |
|                       |              | Subcutaneous |  
| Repatha (evolocumab) | Auto-injector, 1mL (single-use) | Sureclik™ 140 mg/mL | Hyperlipidemia: As an adjunct to diet and maximally tolerated statin therapy in adults requiring further LDL-cholesterol lowering: |
|                       | Pre-filled syringe, 1mL (single-use) | 140 mg/mL | • Adults with heterozygous familial hypercholesterolemia (HeFH)  
|                       | | | • Clinical artherosclerotic cardiovascular disease  
|                       | | | Homozygous Familial Hyperlipidemia: Adults and Adolescents (13-17 years):  
|                       | | | Adjunct to diet and LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients who require additional lowering of LDL-cholesterol.  
|                       | | | Limitation of use: The effect on cardiovascular morbidity and mortality has not been determined.  
|                       | | | |
|                       | | | Administer SQ: 75 mg every 2 weeks  
|                       | | | Inadequate response: If the response at 4 to 8 weeks is inadequate the dose may be increased to 150 mg (maximum dose) administered every 2 weeks beginning on the day the next dose is scheduled.  
|                       | | | |
|                       | | | Administer SQ: 140mg every 2 weeks*  
|                       | | | or  
|                       | | | Administer SQ: 420 mg monthly*‡  
|                       | | |  
|                       | | | Administer SQ: 420 mg monthly ‡  
|                       | | |  
|                       | | | *Changes to the regimen should be made on the day the next dose is scheduled.  
|                       | | | ‡ Doses of 420 mg are administered as three separate injections of 140 mg within a 30 minute period  
|                       | | |  

No
Pharmacokinetics:

**Evolocumab:** Due to non-linear pharmacokinetics at doses up to 140 mg and linear pharmacokinetics at doses between 140 mg and 420 mg a larger dose is required to produce the same effect when dosed every other week (140 mg) vs. every 4 weeks (420 mg). Following subcutaneous dosing, a 140 mg dose yields a Cmax of 18.6-20.3 mg/L with an AUC of 188-226 mg·day/L and following a 420 mg dose, a Cmax of 59.0-63.8 mg/L with an AUC of 903-924 mg·day/L. Evolocumab is 72% bioavailable, has a volume of distribution of 3.3 L and reaches Cmax in 3-4 days with steady state concentrations achieved at 12 weeks regardless of dose. At low concentrations, evolocumab is eliminated via complete protein binding to PCSK-9. At high concentrations, evolocumab is eliminated via a proteolytic pathway following degradation to small peptides and amino acids. The elimination half-life ranges from 11 to 17 days. 33,34,38

- Free PCSK9 levels reached a nadir within 4 hours post-dosing.33,34

**Alirocumab:** The site of injection affects Cmax, AUC, and Tmax. Following a 75 mg subcutaneous dose, Cmax levels of 8.18 mg/L (abdomen), 6.77 mg/L (upper arm), and 7.13 mg/L (thigh) have been obtained with AUC levels of 129 mg·day/L (abdomen), 130 mg·day/L (upper arm), and 115 mg·day/L (thigh). Tmax is observed at 2.96 days (abdomen), 6.95 days (upper arm), and 3.06 days (thigh). A dose of 150 mg results in a 2.1- to 2.7-fold increase in Cmax and AUC with an extended duration of activity. Alirocumab is estimated to be 85% bioavailable with a volume of distribution of 0.04-0.05 L/kg. Steady state concentrations are achieved following 2 to 3 doses. Low concentrations of alirocumab are eliminated via binding at PSCK-9, with higher concentrations eliminated via a proteolytic pathway. The elimination half-life ranges from 17 to 20 days.33,34,38,40

- Free PCSC9 levels reached a nadir within 4 to 8 hours post.33,34,38,40

**Table 3: Pharmacokinetic Properties of PCSK9 Inhibitors**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Bioavailability</th>
<th>Distribution</th>
<th>Time to Peak</th>
<th>Elimination Half-life</th>
<th>Metabolism</th>
<th>Excretion</th>
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<td></td>
</tr>
<tr>
<td>Evolocumab</td>
<td>72%</td>
<td>3.3 L</td>
<td></td>
<td>11-17 days</td>
<td>Non-saturable proteolysis</td>
<td>Feces: 21% ~15% as parent drug Urine: 75% &lt; 2% as parent drug</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3-4 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alirocumab</td>
<td>85%</td>
<td>0.04-0.05 L/kg</td>
<td></td>
<td>17-20 days</td>
<td>Proteolysis and degradation to small peptides and amino acids</td>
<td>Feces: 41.5% as unchanged drug, 7% as hydroxylated metabolite, 3.2% as O-glucuronide metabolite Urine: ~33%; 30.5% as O-glucuronide metabolites, &lt;1% as unchanged drug</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Peak effect on PCSK9 suppression</td>
<td>12 days when combined with a statin</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>3 – 7 days</td>
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<td></td>
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<td></td>
<td>4 – 8 hours</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 – 7 days</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

33,34,37,41
Guidelines
All guidelines recommend aggressive lowering of LDL-C. Most guidelines were published prior to the availability to the PCSK9 inhibitors and do not address their use. Part II of the NLA recommendations has incorporated indications for PCSK9 inhibitor use. The current guidelines for treatment of dyslipidemias are found in Table 4.

Table 4: PSCK9 Inhibitors and Current Guidelines Addressing Dyslipidemias

<table>
<thead>
<tr>
<th>Guideline</th>
<th>PCSK9 Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemias: Part I[42]</td>
<td>Awaiting further data before recommendation (see below, Part II)</td>
</tr>
<tr>
<td>National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemias: Part II[43]</td>
<td>Recommend a conservative approach limiting use to:</td>
</tr>
<tr>
<td></td>
<td>• Patients with ASCVD with LDL-C ≥100 mg/dL (non-HDL-C ≥130 mg/dL) on maximally-tolerated statin (±ezetimibe)</td>
</tr>
<tr>
<td></td>
<td>• Heterozygous FH patients without ASCVD who have LDL-C ≥130 mg/dL (non-HDL-C ≥160 mg/dL) on maximally-tolerated statin (±ezetimibe) therapy.</td>
</tr>
<tr>
<td></td>
<td>May be considered for</td>
</tr>
<tr>
<td></td>
<td>• Selected high-risk patients with ASCVD (e.g., recurrent ASCVD events) with atherogenic cholesterol levels below the specified values listed, but above their treatment goals (i.e., LDL-C ≥70 mg/dL [non-HDL-C ≥100 mg/dL]).</td>
</tr>
<tr>
<td></td>
<td>• Selected high or very high risk statin-intolerant patients who requiring additional atherogenic cholesterol lowering.</td>
</tr>
<tr>
<td>National Institute for Health and Clinical Excellence[14]</td>
<td>No PCSK9 Recommendation</td>
</tr>
<tr>
<td>2012 Update of the Canadian Cardiovascular Society Guidelines for the Diagnosis and Treatment of dyslipidemia for the Prevention of Cardiovascular Disease in the Adult [46]</td>
<td>No PCSK9 Recommendation</td>
</tr>
<tr>
<td>2011 ESC/EAS Guidelines for the management of dyslipidaemias (The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS)) [48]</td>
<td>No PCSK9 Recommendation</td>
</tr>
</tbody>
</table>

ASCVD – atherosclerotic cardiovascular disease; NLA – national lipid association; ACC/AHA – American College of Cardiology/American Heart Association
Safety Information

The PCSK9 inhibitors appear to be well tolerated. Studies are limited to less than two years and the long-term effects of these drugs remains unknown. Ongoing ~5-year outcome trials are expected to yield results in 2-3 year.\(^{50,51}\) (ODYSSEY OUTCOMES: NCT01663402, FOURIER: NCT10764633). The most common adverse events reported in clinical trials of evolocumab and alirocumab are presented in Table 5.

Immunogenicity

Although rare, severe hypersensitivity reactions with alirocumab have required hospitalization.\(^{33}\) As humanized monoclonal antibodies, these agents carry the same risk as other potentially immunogenic compounds. To date, no clinical trial has documented the development of significant evolocumab- or alirocumab-binding-antibodies or titers (ALI 0.6%, EVO 4.8%).\(^{37,38}\) In subjects who did produce antibodies, they were often transient or absent upon repeat testing. The presence of evolocumab- or alirocumab-binding-antibodies did not affect LDL-C lowering or raise other safety concerns.

Local Injection Site Reactions

In most cases, injection site reactions (~3.2% with evolocumab and ~7% with alirocumab) comprising erythema, pain, bruising, itching, swelling, tenderness were transient, mild and did not require study drug discontinuation.

Allergic Reactions

Allergic reactions were reported more commonly in PCSK9-treated patients (evolocumab 5.1% vs. 4.7% and alirocumab 8.6% vs. 7.8%) than those who did not receive a PCSK9 inhibitor. These reactions (e.g. rash, eczema, erythema, urticaria and hypersensitivity vasculitis) resulted in more discontinuations of therapy in the evolocumab- or alirocumab-treated patients.

Neurocognitive Impairment

Neurocognitive impairment, including amnesia, memory impairment and confusional states, have been reported in patients taking PCSK9 inhibitors.\(^{52-55}\) Because the brain is cholesterol rich and cholesterol is needed for structure and function of the neurons and neural pathways, the effects of lowering LDL-C on cognitive function have been of interest.\(^{1,35,39,56}\) Importantly, persons with loss of function mutations having very low LDL-C have not presented with neurocognitive impairment.\(^{20-22}\)

In long-term trials Osler 1 and Osler 2 (evolocumab) and ODYSSEY LONG TERM (alirocumab) more neurocognitive AEs were reported in the treatment group than the comparator arm (evolocumab 0.9% vs. 0.3% and alirocumab 1.2% vs. 0.5%).\(^{53,54}\) A network meta-analysis looking at hypercholesterolemic patients treated with PCSK9 inhibitors and receiving either ezetimibe or placebo identified 17 RCTs of 13,083 patients of which 8,250 received a PCK9 inhibitor. More neurocognitive adverse events [OR 2.34 (95% CI 1.11-4.93), I\(^2\) = 4%, P = 0.02] were observed with PCSK9 inhibitors when compared with placebo\(^{57}.\) It is known that cardiovascular disease itself is associated with the development of impaired cognition.\(^{58}\) The FDA requested Amgen and Sanofi-Aventis to assess the incidence and severity of specific AEs (new-onset diabetes, neurologic events, hypersensitivity, injection site reactions and
immunogenicity) in long-term trials.\textsuperscript{1,39} These trials are ongoing.

**Low LDL-C Levels**
LDL-C levels below 25 mg/dL occurred in 1988 evolocumab treated and 796 alirocumab treated patients. Treatment was not modified or interrupted in these subjects. No adverse events were identified with low LDL-C levels and no effect on LDL-C lowering was observed.

**Diabetes**
Pancreatic islet cells express PCSK9. The effects of PCSK9 inhibition of glucose homeostasis remains undefined and the potential for an increased risk of the development of diabetes is of concern. To date, no data from short or long-term studies suggests that PCSK9 inhibitors are associated with impairment of glucose homeostasis or the development of type-2 diabetes.\textsuperscript{1,39,56}

**Ophthalmologic Effects**
In long-term trials using evolocumab (OSLER-1 and OSLER-2 and DESCARTES) and alirocumab (ODYSSEY LONG-TERM) a difference in the incidence of ophthalmologic events was noted. Alirocumab was associated with an increased incidence of ophthalmic AEs compared with placebo (2.9% vs. 1.9%), which were not noted in the evolocumab trials.\textsuperscript{53,54,59} These AEs were defined as “eye disorders” and were not further defined.

**Creatine Kinase/Musculoskeletal Effects**
Creatine kinase elevations $>5x$ ULN occurred more commonly in evolocumab patients (n=7, 1.2% vs. n=1, 0.3%). Levels $>10x$ ULN occurred in 3-evolocumab and 1-placebo treated patient. Myalgias were more common in the evolocumab- vs. placebo-treated patients (4% vs. 3%). In alirocumab studies myalgias occurred more commonly (5.4% vs. 2.9%) in those receiving alirocumab. Many patients were receiving statin therapy and the significance of these findings will be determined through additional patient exposures.\textsuperscript{1,39}
Table 5: Adverse Event Reports from Pooled Clinical Trials *

<table>
<thead>
<tr>
<th></th>
<th>Repatha† Evolocumab</th>
<th>Placebo</th>
<th>Praluent¥ Alirocumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>3.9%</td>
<td>4.0%</td>
<td>11.3%</td>
<td>11.1%</td>
</tr>
<tr>
<td>Back Pain</td>
<td>3.2%</td>
<td>2.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>URTI</td>
<td>2.0%</td>
<td>2.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1.6%</td>
<td>1.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>1.2%</td>
<td>1.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>1.0%</td>
<td>1.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle Spasms</td>
<td>1.2%</td>
<td>1.3%</td>
<td>3.1%</td>
<td>2.4%</td>
</tr>
<tr>
<td>UTI</td>
<td>1.2%</td>
<td>1.3%</td>
<td>4.8%</td>
<td>4.6%</td>
</tr>
<tr>
<td>Cough</td>
<td>0.7%</td>
<td>1.2%</td>
<td>2.5%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Influenza</td>
<td>1.1%</td>
<td>1.2%</td>
<td>5.7%</td>
<td>4.6%</td>
</tr>
<tr>
<td>Contusion</td>
<td>0.5%</td>
<td>1.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection Site Reactions</td>
<td>3.2%</td>
<td>3.0%</td>
<td>7.2%</td>
<td>5.1%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
<td>4.7%</td>
<td>4.4%</td>
</tr>
<tr>
<td>Bronchitis</td>
<td></td>
<td></td>
<td>4.3%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>2.0%</td>
<td>1.8%</td>
<td>4.2%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td></td>
<td></td>
<td>3.0%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Contusion</td>
<td></td>
<td></td>
<td>2.1%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Musculoskeletal Pain</td>
<td></td>
<td></td>
<td>2.1%</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

† AEs occurring in greater than or equal to 2% of subjects and more frequently than with placebo.
‡ AEs occurring in greater than 1% of subjects and more frequently than with placebo.

Special Populations
Data concerning the use of the PCSK9 inhibitors in special populations is presented in Table 6. There are a number of groups the National Lipid Association has identified to be at higher than normal risk for cardiovascular events. It is possible in the future we will have recommendations for the treatment of dyslipidemias and the use of PCSK9 inhibitors in these patient groups (e.g. women, pregnancy, menopause, polycystic ovary syndrome, Hispanic/Latinos, African Americans, South Asians, American Indians and Alaska Natives, HIV-infected individuals and rheumatoid arthritis).43
Table 6: Information concerning use of PCSK9 Inhibitors in Special Populations

<table>
<thead>
<tr>
<th>Step</th>
<th>Evolocumab (Repatha)</th>
<th>Alirocumab (Praluent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children and Adolescents</td>
<td>Approved for ages 13-17 in treatment of HoFH No Data &lt; 13 years No Data for HeFH or hyperlipidemia</td>
<td>Safety and efficacy are not established</td>
</tr>
<tr>
<td>Pregnancy Lactation</td>
<td>No Data No Data</td>
<td>No Data No Data</td>
</tr>
<tr>
<td>Renal Impairment</td>
<td>No data available in severe renal impairment. No dosage adjust required in mild-to-moderate impairment</td>
<td>No data available in severe renal impairment. No dosage adjust required in mild-to-moderate impairment</td>
</tr>
<tr>
<td>Hepatic Impairment</td>
<td>No data available in severe hepatic impairment. No dosage adjustment required in mild-to-moderate (Child-Pugh A or B) impairment</td>
<td>No data available in severe hepatic impairment. No dosage adjustment required in mild-to-moderate (Child-Pugh A or B) impairment</td>
</tr>
<tr>
<td>Geriatric Use</td>
<td>In 1420 patients ≥ 65 years and 171 patients ≥ 75 years No differences in or efficacy</td>
<td>In 1158 patients ≥ 65 years and 241 patients ≥ 75 years No differences in safety or efficacy</td>
</tr>
</tbody>
</table>

**Methods**

A literature search was conducted to identify clinical trials and systematic reviews evaluating the safety and efficacy of evolocumab and alirocumab in the treatment of dyslipidemias. The search included The MEDLINE database (1950 - 2015), Embase, the Cochrane Library, National Institute for Health and Care Excellence (NICE), CDC, NIH Clinical Trials database and reference lists of review articles.

**Systematic Reviews/Meta-Analysis**

A systematic review and meta-analysis by Navarese et al, identified 24 phase 2 or 3 RCTs of 10,159 patients. Their assessment was that these agents seem safe and effective for adults with hyperlipidemia. The use of PCSK9 monoclonal antibodies in comparison to no mAB is effective in “reducing LDL-C levels (mean difference, -47.49% [95% CI, -60.64% to -25.35%]; p<0.001 and other atherogenic lipid fractions, and it reduced all-cause mortality (odds ratio [OR], 0.45 [CI, 0.23 to 0.86]; p=0.015; heterogeneity P = 0.63; I2 = 0% and cardiovascular mortality (OR, 0.50 [CI 0.23 to 1.10]; P = 0.084; heterogeneity P = 0.78; I2 – 0%. The rate of myocardial infarction was significantly reduced with use of PCSK9 antibodies (OR, 0.49 [CI, 0.26 to 0.93] p=0.030; heterogeneity P = 0.45; I2 = 0% and increases in the serum creatine kinase level were reduced (OR, 0.72 [CI, 0.52 to 0.96]; P = 0.026; heterogeneity P = 0.65; I2 = 0%).” Outcome data were rare and the analysis was performed on study-level rather than patient-level data.28

The Institute for Clinical and Economic Review (ICER) report identified 41 reports (8-phase 2 trials, 16-phase 3 trials, 1-long-term follow up study) and a “high-quality meta-analysis.” With respect to clinical effectiveness no head to head studies were identified. Evolocumab and alirocumab performed similarly in lowering LDL-C levels. With respect to harms, the PCSK9 inhibitors caused more injection site reactions and drug discontinuations (which may be due to the injection site reaction), slightly more neurocognitive events and interestingly more myalgias
but fewer subjects with creatine kinase elevations. Current limitations to the data are the lack of safety information for long-term use and the lack of safety data surrounding sustained very low LDL-C levels. Long-term outcome data has not yet validated the intermediate endpoint data.³

Zhang et al, performed a meta-analysis of 25 randomized, controlled trials involving 12,200 patients to evaluate the safety and efficacy of evolocumab or alirocumab in lowering LDL-C levels. They found, “largely no significant difference between anti-PCSK9 antibodies and placebo (or ezetimibe), except that alirocumab was associated with reduced rates of death (relative risk (RR): 0.43, 95 % confidence interval (CI): 0.19 to 0.96, \( P = 0.04 \)) and an increased rate of injection-site reactions (RR: 1.48, 95 % CI: 1.05 to 2.09, \( P = 0.02 \)) while evolocumab reduced the rate of abnormal liver function tests (RR: 0.43, 95 % CI: 0.20 to 0.93, \( P = 0.03 \)), both compared with placebo. For evolocumab, no significant difference in safety outcomes were detected between 420 mg monthly or 140 mg biweekly treatments. Monthly 420 mg evolocumab treatment significantly reduced LDL-C by \( \sim 54.6 \% \) (95 % CI: \( \sim 58.7 \) to \( \sim 50.5 \% \)) and by absolute \( \sim 78.9 \) mg/dl (95 % CI: \( \sim 88.9 \) to \( \sim 68.9 \) mg/dl) versus placebo, and by \( \sim 36.3 \% \) (95 % CI: \( \sim 38.8 \) to \( \sim 33.9 \% \)) versus ezetimibe, and increased high-density lipoprotein cholesterol (HDL-C) by 7.6 % (95 % CI: 5.7 to 9.5 %) versus placebo and 6.4 % (95 % CI: 4.3 to 8.4 %) versus ezetimibe. An equal or even greater change was observed following biweekly 140 mg administration. Significant and favorable changes were also detected in other lipids following evolocumab treatment. Biweekly 50 to 150 mg alirocumab lowered LDL-C by \( \sim 52.6 \% \) (95 % CI: \( \sim 58.2 \) to \( \sim 47.0 \% \)) versus placebo, by \( \sim 29.9 \% \) (95 % CI: \( \sim 32.9 \) to \( \sim 26.9 \% \)) versus ezetimibe, and increased HDL-C by 8.0 % (95 % CI: 4.2 to 11.7 %) versus placebo.” No significant AEs were noted, with no difference in AEs between the 2 doses of evolocumab. The lowest LDL-C levels documented fell below 50 mg/dL. The authors note that the safety of long-term low LDL-C levels remains unknown. Limitation to the review include the use of study-level and not patient level data, high heterogeneity in some trials, the lack of long-term efficacy and safety trials, confidence intervals surrounding some safety data were wide and finally most of the trials were of short duration.⁶⁰

The Cochrane library has an in-process review, “PCSK9 monoclonal antibodies for the primary and secondary prevention of cardiovascular disease.” The abstract defines the project will review short, medium and long-term effects of these agents on lipid parameters and CVD risk. Secondarily, they will review safety issues (type 2 diabetes, neurocognitive function and cancer) and attempt to identify any patient subgroups with differing responses. The anticipated publication date is unavailable. ⁶¹

Effects of PCSK9 Inhibitors on Lipid Parameters
The following tables (Tables 7 & 8, below) provides concise information regarding the effects of the PCSK9 inhibitors on lipid parameters from studies presented in further detail below. These potent agents reduce LDL-C levels in patients receiving no therapy and in patients receiving maximally tolerated statin therapy +/- ezetimibe. Reductions of LDL-C by 40-60% are common. Changes in the concentrations of other lipid parameters were also very favorable.
Table 7: Alirocumab Effects on Lipid Endpoints, Percent Change versus Baseline

<table>
<thead>
<tr>
<th>Trial</th>
<th>LDL-C</th>
<th>ApoB</th>
<th>HDL-C</th>
<th>Lp(a)</th>
<th>Non-HDL-C</th>
<th>Total cholesterol</th>
<th>TG</th>
<th>Comparator</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ODYSSEY COMBO I</td>
<td>-48.2</td>
<td>-36.7</td>
<td>+3.5</td>
<td>-20.5</td>
<td>-39.1</td>
<td>-27.9</td>
<td>-6.0</td>
<td>PBO (baseline regimen)</td>
<td>p&lt;0.0001 except TG</td>
</tr>
<tr>
<td>ODYSSEY COMBO II</td>
<td>-51.2</td>
<td>-40.7</td>
<td>+8.6</td>
<td>-27.8</td>
<td>-42.1</td>
<td>-29.3</td>
<td>-1.0</td>
<td>EZE/statin</td>
<td>&lt;0.0001 except TG</td>
</tr>
<tr>
<td>ODYSSEY OPTIONS I ATOR 20/ALI 75/150</td>
<td>-48.4</td>
<td>-33.7</td>
<td>+4.8</td>
<td>-23.6</td>
<td>-36.7</td>
<td>NR</td>
<td>-12.0</td>
<td>EXE10/ATOR20</td>
<td>Significant for LDL and Apo B</td>
</tr>
<tr>
<td>ATOR40/ALI 75/150</td>
<td>-50.5</td>
<td>-41.9</td>
<td>+7.7</td>
<td>-30.8</td>
<td>-47.6</td>
<td>NR</td>
<td>-19.1</td>
<td>EZE20/ATOR40</td>
<td>Significant for LDL-C and Apo B</td>
</tr>
<tr>
<td>ODYSSEY OPTIONS II (ROSU 10)/ALI 75</td>
<td>-49.6</td>
<td>-36.5</td>
<td>+9.1</td>
<td>-27.9</td>
<td>-42.7</td>
<td>NR</td>
<td>-11.2</td>
<td>EZE/ROSU10 ROSU20</td>
<td>p&lt;0.0001 except TG and HDL</td>
</tr>
<tr>
<td>ROSU 20/ALI 75</td>
<td>-32.3</td>
<td>-28.3</td>
<td>+7.2</td>
<td>-22.7</td>
<td>-31.4</td>
<td>NR</td>
<td>-8.7</td>
<td>NR</td>
<td>PBO (baseline regimen) p&lt;0.001 all values</td>
</tr>
<tr>
<td>ODYSSEY ALTERNATIVE ALI 75 Q2W</td>
<td>-45.0</td>
<td>-36.3</td>
<td>+7.7</td>
<td>-25.9</td>
<td>-40.2</td>
<td>-31.8</td>
<td>-9.3</td>
<td>NR</td>
<td>p&lt;0.0001 except TG and HDL</td>
</tr>
<tr>
<td>ODYSSEY LONG-TERM</td>
<td>-61</td>
<td>-52.8</td>
<td>+4.0</td>
<td>-29.3</td>
<td>-51.6</td>
<td>-37.8</td>
<td>-15.6</td>
<td>PBO (baseline regimen)</td>
<td>p&lt;0.001 all values</td>
</tr>
<tr>
<td>ODYSSEY MONO</td>
<td>-47.2</td>
<td>-36.7</td>
<td>+6.0</td>
<td>-16.7</td>
<td>-40.6</td>
<td>-29.6</td>
<td>-14.7</td>
<td>EZE</td>
<td>p&lt;0.0001 except HDL, TG and Lp(a)</td>
</tr>
<tr>
<td>ODYSSEY FH (via clinicaltrials.gov, unpublished)</td>
<td>-39.1</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>PBO (baseline regimen)</td>
<td>p&lt;0.05</td>
<td>NR</td>
<td>not reported; NS – not statistically significant</td>
</tr>
<tr>
<td>NR – not reported</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 8: Evolocumab Effects on Lipid Endpoints, Percent Change versus Baseline

<table>
<thead>
<tr>
<th>Trial</th>
<th>LDL-C</th>
<th>ApoB</th>
<th>HDL-C</th>
<th>Lp(a)</th>
<th>Non-HDL-C</th>
<th>Total cholesterol</th>
<th>TG</th>
<th>Comparator</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAUSS 2</td>
<td>-56.1</td>
<td>-45.8</td>
<td>+5.5</td>
<td>-26.2</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>EZE1-0</td>
<td>EZE10 p&lt;0.001 for all values</td>
</tr>
<tr>
<td>EVO140Q2 EVO 420 Q4Wonth</td>
<td>-52.6</td>
<td>-43.1</td>
<td>+7.2</td>
<td>-23.7</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>EZE10</td>
<td>p&lt;0.001 for all values</td>
</tr>
<tr>
<td>RUTHERFORD-2</td>
<td>-61.3</td>
<td>-49.8</td>
<td>+8.1</td>
<td>-22.9</td>
<td>-56.2</td>
<td>NR</td>
<td>-16.1</td>
<td>PBO</td>
<td>EVOQ2 and EVOQ4W statistically superior to PBO in all measures</td>
</tr>
<tr>
<td>EVO140Q2W EVO420Q4W</td>
<td>-55.7</td>
<td>-44.8</td>
<td>+5.4</td>
<td>-21.6</td>
<td>-49.7</td>
<td>NR</td>
<td>-5.1</td>
<td>SOC</td>
<td>p&lt;0.001 all values</td>
</tr>
<tr>
<td>OSLER1 + OSLER2 Long-term</td>
<td>-61.0</td>
<td>-47.3</td>
<td>+7.0</td>
<td>-25.5</td>
<td>50.2</td>
<td>-36.1</td>
<td>-12.6</td>
<td>EZE or PBO</td>
<td>LDLC, ApoB p&lt;0.001 vs both HDL + TG p&lt;0.001 vs PBO</td>
</tr>
<tr>
<td>DESCARTES</td>
<td>-57.0</td>
<td>-41.3</td>
<td>+5.8</td>
<td>-27.7</td>
<td>-41.8</td>
<td>-30.7</td>
<td>-2.6</td>
<td>all groups</td>
<td>Statistically significant all values</td>
</tr>
<tr>
<td>MENDEL-2</td>
<td>-57.0</td>
<td>-47.2</td>
<td>+4.8</td>
<td>-20.4</td>
<td>-50.1</td>
<td>NR</td>
<td>-8.1</td>
<td>EZE or PBO</td>
<td>LDLC, ApoB p&lt;0.001 vs both HDL + TG p&lt;0.001 vs PBO</td>
</tr>
<tr>
<td>EVO140 Q2W EVO420Q4W</td>
<td>-56.1</td>
<td>-49.4</td>
<td>+4.1</td>
<td>-17.8</td>
<td>-49.7</td>
<td>NR</td>
<td>-15.6</td>
<td>None</td>
<td>p=0.781, p=0.1484 vs baseline</td>
</tr>
<tr>
<td>Stein et al, 2013</td>
<td>-13.3</td>
<td>-13.1</td>
<td>+3.9</td>
<td>-24.6</td>
<td>NR</td>
<td>NR</td>
<td>-6.8</td>
<td>None</td>
<td>Excluding 2 receptor-negative non responders: -19.3%,-26.3%, p=0.0313 for each regimen</td>
</tr>
<tr>
<td>EVO420 Q4W dosing</td>
<td>-16.9</td>
<td>-16.0</td>
<td>-0.2</td>
<td>-18.6</td>
<td>NR</td>
<td>NR</td>
<td>-20.7</td>
<td>None</td>
<td>p=NS for HDL and TG</td>
</tr>
<tr>
<td>TESLA</td>
<td>-23.1</td>
<td>-19.2</td>
<td>+4.0</td>
<td>-9.4</td>
<td>NR</td>
<td>NR</td>
<td>-1.4</td>
<td>PBO (continued baseline lipid lowering therapy)</td>
<td>p=NS for HDL and TG</td>
</tr>
</tbody>
</table>

NR – not reported; NS – not statistically significant
Clinical Efficacy
In trials of at least one year, long-term adherence was documented (DESCARTES 88%, OSLER 93%, ODYSSEY LONG-TERM 72%).

Overview of Alirocumab Clinical Efficacy:
The FDA reviewed data from 10 studies involving 5296 patients supporting the use of alirocumab in three populations, 1) heterozygous familial hypercholesterolemia, 2) non-familial hypercholesterolemia with high to very high cardiovascular event risk including patients with diabetes and mixed dyslipidemias and 3) statin-intolerant due to muscle-related adverse event patients.

Patients not randomized to alirocumab continued their current lipid-lowering regimen. Five studies compared alirocumab to placebo and five compared alirocumab to ezetimibe. Studies were at least 52-weeks with the efficacy endpoint measured at week 24. Three studies were conducted exclusively in patients with HeFH. In studies that initiated therapy at 75 mg every 2 weeks followed by up-titration to 150 mg based upon response at week 12, 57-83% did not require a dosage change. In the longest trial to date, ODYSSEY LONG-TERM, 2341 patients with LDL-C ≥ 70 mg/dL on statin +/- other lipid-lowering therapy were randomized to receive either alirocumab 150 mg every 2 weeks or placebo. At 24 weeks of therapy, alirocumab lowered LDL-C 61% from baseline compared to 0.8% in the placebo group (p=0.001).

Overview of Evolocumab Clinical Efficacy:
The FDA reviewed data from 5 studies involving 3152 patients supporting the use of evolocumab in the treatment of primary hyperlipidemia or mixed dyslipidemia. Treatment with evolocumab was compared to placebo, ezetimibe or standard lipid-lowering therapy and included statin-intolerant patients. Four of the trials evaluated LDL-C lowering from baseline at week 12. LDL-C reductions were 37-47% greater than with ezetimibe and 55-76% greater than placebo. The effects persisted across evolocumab dosing frequencies and studies. Similar findings persisted over the duration of a 52-week study.

Data was also submitted to support use in the treatment of homozygous familial hypercholesterolemia (HoFH). An open-label pilot study in 8 patients was followed with a randomized, controlled trial adding evolocumab 420 mg to statin therapy and in 92% of subjects additionally to ezetimibe. No reduction in LDL-C was observed in 2 LDL-receptor negative patients. In the remaining 6 LDL-receptor defective patients additional LDL-C lowering of 19.3% and 26.3% was documented with every 4- and every 2-week dosing.

Clinical Trial Results:
Evolocumab Trials

GAUSS-2 This trial enrolled 307 statin-intolerant, patients with hyperlipidemia to evaluate the efficacy of evolocumab 140 mg every 2 weeks or evolocumab 420 mg every 4 weeks or ezetimibe 10 mg (with SQ placebo given every 2 or 4 weeks) in lowering LDL-C. Low-dose statin therapy was used by 18%, a total of 33% were taking lipid-lowering therapy and 56% of the patients met the criteria for high cardiovascular risk. At 12-weeks, the reductions in LDL-C for the evolocumab 140 mg every 2 week group were -56.1%, for the evolocumab 420 mg every
4 week group -52.6%, for the ezetimibe+placebo every 2 weeks -18.1% and for the ezetimibe+placebo every 4 weeks -15.1%. Differences were significant for all evolocumab vs. ezetimibe, p<0.001. The LDL-C target was achieved with evolocumab every 2 and every 4 weeks (48% and 37.5%, respectively) much more commonly than with the ezetimibe every 2 or every 4 weeks. (1% vs. 0%). The incidence of adverse muscular events was 12% with evolocumab and 23% with ezetimibe. Patients receiving ezetimibe and a statin had a higher incidence of muscle-related adverse events (23% vs. 12%) than other treatments.30

RUTHERFORD-2 This trial compared the efficacy of evolocumab140 mg every 2 weeks or 420 mg monthly vs. placebo given every 2 or 4 weeks in 331 HeFH patients on stable lipid-lowering therapy with a fasting LDL-C ≥ 100 mg/dL. At 12 weeks, the percent LDL-C reduction with evolocumab every 2 weeks (-59.2%) and evolocumab every 4 weeks (-61.3%) was superior to placebo (p<0.0001 at both dosing intervals). Nasopharyngitis was the most commonly reported AE (evolocumab 9% vs. placebo 5%). Muscle-related adverse events were noted more commonly with evolocumab (5%) than placebo (1.0%).63

DESCARTES This trial randomized 901 patients to a 4 to 12 week run-in period of 4 baseline regimens; diet alone, atorvastatin 10 mg (ATOR10), atorvastatin 80 mg (ATOR80) or atorvastatin 80 mg and ezetimibe 10 mg (ATOR/EZE). If the LDL-C did not fall below 75 mg/dL on therapy, evolocumab 420 mg every 4 weeks (EVO) was added to the baseline regimen for 52 weeks. The completion rate was 88.4%. Compared to baseline LDL-C, the addition of EVO resulted in a statistically significant mean percent reduction in LDL-C of -57% for all patients. The changes in specific groups documented similar findings; for EVO + diet -57%, for EVO/ATOR10 -61.6%, for EVO/ATOR80 -56.8%, for EVO + ATOR/EZE -48.5% (p value for all results <0.001). The percentage of patients achieving a target LDL-C below <70 mg/dL was 83.6% (EVO + diet), 90.1% (EVO + ATOR10), 80.8% (EVO + ATOR80) and 67% (EVO + ATOR/EZE). Common AEs included, nasopharyngitis, URTI, influenza and back pain. The incidence of AEs with EVO was 74.8% and with PBO (diet) 74.2% and for SAEs 5.5% vs. 4.3%, EVO vs. PBO. Discontinuations due to an AE ranged from 2.2% on EVO to 1.0% on PBO. The rate of injection site reactions was similar across groups. Elevations in transaminases (>3x ULN) or creatine kinase (>5x ULN) were uncommon. No changes in fasting blood glucose were noted. Anti-evolocumab antibodies were measured over the course of the study. Statin patients had higher baseline PCSK9 levels and 4 weeks after receiving evolocumab (trough level) the PCSK9 levels increased more rapidly in these patients than non-statin patients supporting the fact that statin therapy increases PCSK9 levels.59

MENDEL-2 This trial randomized lipid-therapy naïve patients to one of six groups using combinations of ezetimibe 10 mg daily, evolocumab 140 mg every 2 weeks or evolocumab 420 mg every 4 weeks. Groups consisted of (subcutaneous/oral) PBO (every 2 or 4 weeks)/PBO, PBO (every 2 or 4 weeks)/EZE, or EVO/PBO with the SQ injection given 140 mg every 2 weeks or 420 mg every 4 weeks. Changes in LDL-C were significantly greater with any evolocumab regimen than either PBO or EZE (-57 to -56.1% vs. placebo and -38 to -40% compared to ezetimibe; p<0.001). Evolocumab was generally well tolerated compared with ezetimibe or placebo therapy. Four SAEs occurred in the evolocumab group with 2 of 4 considered study related. One patient developed pancreatitis and a second patient developed elevations in transaminase and creatine kinase >8x the upper limit of normal. Discontinuation rates were
higher with evolocumab vs. ezetimibe or placebo (3.9% vs. 3.2% vs. 2.3%, respectively). Injection site reactions occurred similarly across groups.64

LAPLACE-2 This trial evaluated the efficacy and tolerability of evolocumab in combination with moderate to high-intensity statin therapy in 1896 adults with hypercholesterolemia or mixed dyslipidemia. Subjects were randomized to 1 of 24 treatment groups in 2 steps. The initial, step-1 randomization was to moderate- (ATO 10 mg, SIM 40 mg or ROS 5 mg) or high intensity (ATO 80 mg or ROS 40 mg) statin for a period of 4 weeks at which time they were further randomized to receive evolocumab (140 mg every 2 weeks or 420 mg monthly) or placebo (every 2 weeks or monthly) or ezetimibe or placebo (ATO patients only). The primary outcome measure was the percent LDL-C change from baseline at weeks 10-12 and week 12. At weeks 10-12 and week 12, in both the moderate- and high-intensity statin groups, evolocumab was superior to ezetimibe and placebo, p<0.001. Mean LDL-C reductions with evolocumab vs. placebo were -63 to -75% and with ezetimibe vs. placebo -17% to -24%. Evolocumab 140 mg every 2 weeks or 420 mg every 4 weeks demonstrated clinical equivalence in LDL-C lowering. LDL-C reductions to < 70 mg/dL was achieved in 86-94% of moderate-intensity statin patients and in 93-95% of high-intensity statin patients treated with evolocumab. The most commonly reported adverse events were headache, back pain, muscle spasms, arthralgia and pain in the extremities, all at an incidence of < 2%.65

OSLER This trial enrolled 1104 patients from four phase-2 trials (using 6 different evolocumab regimens) and randomized them to open-label evolocumab 420 mg every 4 weeks plus standard of care or standard of care for 52 weeks. Approximately 90% completed the study in each group. For subjects that received evolocumab in the prior trial and were randomized to standard of care, the LDL-C returned to pre-treatment levels from -53.1% lowering at study entry (on evolocumab in prior trial) to -17.9% at 4 weeks and -5.8% at 12 weeks. The percent LDL-C reduction for those on standard of care in prior trials and now randomized to evolocumab was -54.7 mg/dL at 52 weeks. Those previously receiving any evolocumab regimen and continuing on evolocumab demonstrated no significant change in LDL-C over the 52 weeks. The most common adverse events were nasopharyngitis, URTI, influenza, arthralgia and back pain occurring at 81.4% in EVO+SOC (5.6% possibly EVO-related) vs. 73.1% in SOC. SAEs occurred similarly in both groups. Injection site reactions were noted in 5.2% of evolocumab patients resulting in 1 treatment discontinuation. A similar incidence of increases in AST >3 times the upper limit of normal occurred with increases >5x the upper limit of normal for AST or ALT in 1 SOC patient and 4 EVO+SOC patients. Neurocognitive AEs occurred more commonly in the evolocumab group. Three reported amnesia and 5 reported memory or mental impairment (both <1%) with no reports in the SOC group. Interpretation of these AEs is difficult as the study was open-label and the patients in the evolocumab group were seen twice as often as those in the SOC group thus increasing the opportunity for reporting an AE. Adjudicated cardiovascular AEs occurred 2.2% with SOC and 1.2% with EVO resulting in 3 deaths. Two deaths were reported in the SOC group (1-unknown cause, 1-pulmonary embolism) and 1 death in the EVO group (longstanding significant CAD and ventricular aneurysm, found deceased). Neutralizing antibodies were not detected. 66

OSLER-1 and OSLER-2 This report combined long-term results (included 12 phase 2 or 3 studies, n=4465) were assessed for adverse events and secondarily for changes in LDL-C.
Patients received evolocumab 420 mg every month or 140 mg every 2 weeks by subcutaneous injection. Baseline lipid lowering therapies were continued. Pooled baseline LDL-C levels of 120 mg/dL were reduced with evolocumab therapy by ~61% (95% CI, 59 to 63; p<0.001) in both studies. At 12 weeks, the percentage of patients achieving LDL-C < 100 mg/dL was 90.2% with evolocumab and 26.0% with standard of care. The percentage achieving the lower goal of an LDL-C <70 mg/dL was 73.6% with evolocumab vs. 3.8% standard of care. AE’s occurred in 7.5% of patients in each group; 69.2% of the evolocumab group (n=2060) and 64.8% of standard care group (1489). Events reported more commonly in the evolocumab group were arthralgia (4.6% vs. 3.2%), headache (3.6% vs. 2.1%), limb pain (3.3% vs. 2.1%) and fatigue (2.8% vs. 1.0%). ALT, AST and CK elevations rose similarly in groups, 1% evolocumab group and 1.2% in standard of care group. Neurocognitive AEs were low (EVO 0.9% vs. SOC 0.3%), heterogeneous in nature and unrelated to strata of LDL-C (<25 mg/dL, 25-50 mg/dL or >25 mg/dL). Injection site reactions occurred in 4.3% of the evolocumab group leading to 0.2% discontinuations. The composite of all cardiovascular events was significantly reduced in the evolocumab group at 1 year (HR 0.47; 95% CI, 0.28 to 0.78; p=0.003).54

Stein et al. This trial evaluated the effects of evolocumab in 8 patients (age 12-65) with LDL receptor negative- or defective HoFH and a mean baseline LDL-C of 440.8 mg/dL. Treatment was evolocumab 420 mg every 4 weeks for at least 12 weeks followed by a change in the dosing interval to every 2 weeks. Current lipid lowering therapy was continued in all patients. Overall, the reduction in LDL-C was -16.5% with every 4 week dosing and 13.9% with every 2 week dosing. A significant change from baseline was observed only with the every 4 week dosing regimen, however, when two receptor-negative patient data was removed from the analysis the LDL-C lowering was significant with both regimens; every 4 week dosing reducing LDL-C -19.3% (p=0.0313) and every 2 week dosing reducing LDL-C -26.3% (p=0.0313). No antibodies develop to evolocumab. No significant increases in CK, AST or ALT were noted and AEs were considered unrelated to study drug.62

TESLA Part B This trial was a follow-up study to Stein et al. This international phase 3 study involved 49 subjects with HoFH receiving a stable regimen of lipid-lowering therapy (without apheresis) for at least 4 weeks. Subjects were randomized to evolocumab 420 mg every 4 weeks or placebo. Baseline LDL-C was 355 mg/dL in the evolocumab arm and 336 in the placebo (standard of care) arm. In comparison to placebo, evolocumab resulted in LDL-C reductions of -30.9% (95% CI – 43.9 to -18; p<0.0001). The most common AEs were URTI, influenza, gastroenteritis, nasopharyngitis and musculoskeletal pain. No anti-evolocumab antibody development was observed.67

Alirocumab Trials:
ODYSSEY MONO This trial evaluated the safety and efficacy of alirocumab 75 mg every 2 weeks vs ezetimibe 10 mg daily for 24 weeks in 103 hypercholesterolemic patients (LDL-C 100-190 mg/dL) with moderate cardiovascular risk (Risk score ≥1 to <5%). At 12-weeks, if the LDL-C remained ≥ 70 mg/dL the dose of alirocumab was increased to 150 mg every 2 weeks. Completion rates were 85% and 86% for alirocumab and ezetimibe, respectively. More than 90% of patients self-administered all subcutaneous doses. Alirocumab dose-escalation occurred in 28% of patients. Those requiring the higher dosage had higher baseline LDL-C (153.2 vs. 134.7 mg/dl). The primary efficacy response, LS mean (SE) percent change in LDL-C at week 24
compared to baseline for alirocumab was -47.2 (3.0) and for ezetimibe -15.6 (3.1), \( p<0.0001 \).

TEAEs occurred with alirocumab (69%) and ezetimibe 78%. Two SAEs were noted, one in each group and unrelated to study drug. Discontinuation rates were 10% in the alirocumab group and 8% in the ezetimibe group. Muscle related TEAEs occurred at 4% in each group. Mild injection site reactions were more common in the ezetimibe group (4% vs. 2%). Six patients receiving alirocumab with baseline abnormal fasting blood glucose had glucose measurements \( \geq 126 \) mg/dL during therapy. No anti-drug antibodies to alirocumab were noted.68

**ODYSEY COMBO I** This trial evaluated the benefit of alirocumab 75 mg every 2 weeks vs. continuation of baseline therapy in 316 patients at high cardiovascular risk, taking maximally tolerated doses of statin, with or without other therapies and having LDL-C levels above target. The dose of alirocumab was increased to 150 mg every 2 weeks if target LDL-C goal had not been achieved at 8 weeks (16.8% required dosage increase). At 24 weeks, the difference in LDL-C reduction between alirocumab and placebo was -45.9 mg/dL (\( p<0.0001 \)). LDL-C lowering to \( \leq 70 \) mg/dL was found in 75% of alirocumab vs. 9% placebo patients (\( p<0.0001 \)). Patients with dose increases to 150 mg every 2 weeks demonstrated additional LDL-C lowering of 22.8%. ADEs were reported in 75% of both groups. TEAEs and SAEs were similar between groups. Injection site reactions were more common with alirocumab (5.3% vs. 2.8%) as were potential general allergic reactions (8.7% vs. 6.5%). LDL-C < 25 mg/dL on \( \geq 2 \) occasions occurred in 39/209 (19%) patients and <15 mg/dL in 9 patients receiving alirocumab. Non-persistent anti-drug antibodies developed in 6.6% of patients.69

**ODYSEY COMBO II** This trial enrolled 720 patients at high cardiovascular risk taking a maximally tolerated statin dose with LDL-C remaining above target values. Statin therapy was continued with the addition of alirocumab 75 mg SQ every 2 weeks or ezetimibe 10mg every day. An increase to alirocumab 150mg every 2 weeks was implemented in 18.4% of participants who did not achieve target LDL-C at 4 weeks. The study is ongoing (104-week), however, a pre-specified 52-week evaluation was performed evaluating outcomes at 24 weeks. Alirocumab resulted in additional LDL-C reductions of 29.8% (95% CI 34.4-25.3; \( p<0.0001 \)) compared to ezetimibe. The percentage of patients who reached their target LDL-C goal was 77% with alirocumab and 45.6% with ezetimibe (\( p<0.0001 \)). AEs were reported in 71.2% of alirocumab and 67.2% of ezetimibe patients. The most common AEs at >5% were URTI, accidental over dosage, dizziness and myalgia. Treatment emergent adverse events (TEAEs) were similar between groups as were serious adverse events (SAEs). Adjudicated cardiovascular ADEs occurred in 4.8% of alirocumab vs. 3.7% of ezetimibe patients. Injection site reactions were more common in the alirocumab group (2.5% vs. 0.8%). Alirocumab was associated with more increases in alanine ALT and ezetimibe with more impaired glucose control. LDL-C < 25 mg/dL on at least 2 occasions occurred in 22.8% of alirocumab and 0% of ezetimibe patients.70

**ODYSEY OPTIONS I** This trial compared alirocumab 75 or 150 mg every 2 weeks in 355 patients at high or very high cardiovascular risk taking atorvastatin 20 or 40 mg among a number of treatments; alirocumab was added to atorvastatin 20 mg, 40 mg or ezetimibe 10 mg or ezetimibe 10 mg was added to atorvastatin 20 or 40 mg or patients receiving atorvastatin 40 mg were switched to rosuvastatin 40 mg. At 8 weeks, 14% of patients required to dosage increase to alirocumab 150 mg, having not achieved target LDL goal. The addition of alirocumab to atorvastatin 20 mg 40 mg resulted in a reduction of LDL-C of -44.1% and -54.0% (\( p<0.001 \) vs
other treatments). Ezetimibe 10 mg added to atorvastatin 20 and 40 mg reduced LDL-C by -20.5 and -22.6%, doubling the atorvastatin dose (to 40 mg or 80 mg) reduced LDL-C by -5% and -4.8%; finally switching atorvastatin 40 mg to rosuvastatin 40 mg yielded addition LDL-C reduction of -21.4%. The goal LDL-C was achieved with ATO20/ALI in 87.2% and for ATO40/ALI 84.6% of patients. TEAEs were common (65.4% alirocumab, 64.4% ezetimibe and 63.8% double atorvastatin dose, 63.8% rosuvastatin) and similar among groups. 71

ODYSSEY OPTIONS II This trial compared the effects of adding alirocumab 75 mg every 2 weeks, or ezetimibe 10 or doubling the dose of baseline rosuvastatin in 305 patients at very high or high cardiovascular risk with of LDL-C levels above target. After 8 weeks, those receiving alirocumab 75 mg and not achieving LDL-C goal had their dose increased to 150 mg (20% of patients). At 24 weeks, in the baseline rosuvastatin 10 mg group reductions in LDL-C were alirocumab -50.6%, ezetimibe -14.4% and rosuvastatin 20 mg -16.3% statistically favoring alirocumab vs. both comparators (p<0.0001). In the baseline rosuvastatin 20 mg group reductions in LDL-C were -36.3%, -11% and -15.9%, respectively and did not achieve the pre-specified significance level of p<0.0125. The LDL-C goal was reached in 84.9% of ALI/ROS10 patients and 66.7% of ALI/ROS20 patients. In pooling treatment groups to detect safety issues, TEAEs were noted in the alirocumab group 56.3%, ezetimibe group 53.5% and the double-dose rosuvastatin group 67.3% with no marked differences among groups. Mild local injection site reactions were noted more commonly with alirocumab 3.9%, than ezetimibe 0%, or double-dose rosuvastatin 2.0%.72

ODYSSEY ALTERNATIVE This trial evaluated the benefit of alirocumab in hyperlipidemic patients with moderate to high cardiovascular risk who were intolerant to statin therapy. Patients (n=361) were allocated to alirocumab 75 mg every 2 weeks or ezetimibe 10 mg or atorvastatin 20 mg (if tolerated during a 4-week run-in, blinded re-challenge period; assessed for safety only). After 8 weeks, those receiving alirocumab 75 mg and not achieving LDL-C goal had their dose increased to 150 mg (49.5% of patients). Mean baseline LDL-C was 193.3 mg/dL. The percent reduction in LDL-C over baseline for alirocumab was -45.0 and for ezetimibe -14.6 (p<0.0001; 95% CI 0.38 to 0.99). The percentage of patients achieving the LDL-C goal was 41.9% for alirocumab and 4.4% for ezetimibe (p<0.0001). Adverse events were reported evenly in alirocumab (82.5%), ezetimibe (80.6%) and in atorvastatin (85.7%) groups. Treatment emergent adverse events and serious adverse events also occurred evenly between groups. AEs requiring discontinuation of therapy were less common in the alirocumab group. The most common AEs for all groups were skeletal muscle in nature. The rate of skeletal muscle AEs was lower with alirocumab than atorvastatin (p=0.042). AEs occurring at >5% in alirocumab group included, myalgia 24.6%, Nasopharyngitis 6.3%, URTI 5.6%, and arthralgias 5.6% One patient in the alirocumab group had a non-fatal MI. The rate of injection site reactions was equivalent with alirocumab and ezetimibe and higher than for the atorvastatin group.73

ODYSSEY LONG-TERM This trial evaluated the efficacy of alirocumab 150 mg every 2 weeks vs. baseline maximally tolerated statin +/- other therapies in 2341 patients at high risk of cardiovascular events, over 78 weeks with results presented for week 24 of therapy. Baseline LDL-C was ~ 122 in both groups. The percent change in LDL-C from baseline was statistically significant (-62%, ALI vs. SOC; p<0.001). The percentage of patients that reached goal LDL-C (<70 mg/dL or <100 mg/dL) was 80.7% for alirocumab and 8.5% for standard of care; p<0.001).
The percentage of patients that achieved an LDL-C less than 70 mg/dL was 79.3% for alirocumab and 8% for standard of care (p<0.001). Major cardiovascular adverse events occurred less frequently in the alirocumab group (1.7% vs. 3.3%, HR 0.52) and over time. AEs were not significantly different between groups, most commonly, injection site reactions (5.9 vs. 4.2%), myalgias (5.4 vs. 2.9%) and ophthalmologic events (2.9 vs. 1.9%). Neurocognitive adverse events were more common in the alirocumab group (1.2 vs. 0.5%, p=0.17) as five patients reported amnesia and 4 each reported memory impairment or confusional state (each <1%). Within the standard of care group there were 4 reports of neurocognitive AEs (0.5%) with 1 report each of memory impairment or confusional state.53

ODYSSEY FH This completed but unpublished study (results posted at clinicaltrials.gov.) evaluated the benefit of alirocumab in the treatment of HeFH, when maximally-tolerated statins, with or without other lipid-lowering therapy did not reduce LDL-C < 160 mg/dL. Participants (n=322) received alirocumab or placebo every 2 weeks for 78 weeks while continuing their current lipid-lowering regimen. In FH-1 and FH-2, alirocumab was dosed at 75 mg and increased to 150 mg after 8 weeks if LDL-C remained ≥ 70 mg/dL. The third trial, HIGH-FH utilized alirocumab 150 mg as the treatment dose throughout. Baseline LDL-C was 201 mg/dL for the FH-1 and FH-2 studies and 196.3 mg/dL in the HIGH-FH study. Results were presented as a combined primary efficacy endpoint describing the percent reduction in LDL-C over 24 weeks. Compared to placebo the addition of alirocumab to baseline lipid-therapy was associated with a change in LDL-C of -39.1% (95% CI -51.1. to -27.2; p<0.05).74

Conclusion:

The PCSK9 inhibitors offer a novel mechanism of action resulting in significant reductions of LDL-C. The agents are more effective than placebo, statins, ezetimibe, combinations of lipid-lowering therapies and are effective when added to existing therapy. Efficacy has been demonstrated in the setting of hyper- and dyslipidemias, HeFH, HoFH (for evolocumab) and in statin-intolerant patients. The agents are generally well tolerated. The most common adverse events relate to injection site reactions, allergic reactions, nasopharyngitis, very low LDL-C levels, elevated liver enzymes and myalgias. The most common reasons for discontinuation were allergic reactions, elevated liver function tests and myalgias. Adherence for over a year is demonstrated in clinical trials with most patients administering their own subcutaneous doses. Long-term studies will address efficacy and specific safety concerns (e.g. low LDL-C, neurocognitive effects, ophthalmic effects, cardiovascular outcomes, immunogenicity, diabetes) with results anticipated in 2017-18. The PCSK9 inhibitors are administered via subcutaneous injection and require specific storage requirements. Evolocumab may be given every 2 weeks or at a higher dosage every 4 weeks administered in 3 SQ injections with similar LDL-C reductions. The dose of alirocumab may be doubled in patients that do not achieve target LDL-C lowering with a 75 mg dosage. Studies suggest 16-20% of alirocumab patients require a dosage increase resulting in ~10-20% additional LDL-C lowering. The Medicaid Prior Authorization process guides the selection of appropriate candidates for therapy.
### Appendix 1: Clinical Trials Evaluating Evolocumab

<table>
<thead>
<tr>
<th>Reference /Trial</th>
<th>Population</th>
<th>Baseline Therapy</th>
<th>Treatment</th>
<th>Baseline LDL-C (mg/dL)</th>
<th>Results: Percent change in LDL-C, % achieving target goal</th>
<th>CV</th>
<th>AE</th>
</tr>
</thead>
</table>
| **GAUSS-2**  
Randomized, double-blind, PBO and EZE controlled | Statin intolerant hyperlipidemic patients (56% high risk) | Low-dose statin (18%), Other lipid lower agent (33%) | EVO 140 Q2  
EVO 420 Q4W  
EZE10  
EZE10  
Continue baseline therapy | 192  
192  
195  
195 | -56.1%  
-52.6%  
-18.1%  
-15.1%  
p<0.001 EVO vs EZE | Not Reported | Muscle related AEs EVO 8% EZE 18% (esp. EZE/statin pts.) |
| **RUTHERFORD-2**  
Randomized, double-blind, placebo-controlled | HeFH on stable LLT with LDL-C >100 mg/dL | Stable LLT | EVO140Q2  
PBOQ2  
EVO420Q4W  
PBOQ4W | 162.4  
154.7  
150.8  
150.8 | -59.2%  
p<0.001 vs. PBO  
-61.3%  
p<0.0001 vs. PBO | Not Reported | Muscle-related AEs EVO 5% vs. PBO 1% Nasopharyngitis EVO 9%, vs. PBO 5% |
| **DESCARTES**  
Randomized, double-blind, parallel-assignment (52-week) | After 4-12 weeks of diet or ATO10, or ATO80, or ATO80/EZE with LDL-C remaining ≥75 mg/dL | Diet  
ATO10  
ATO80  
ATO80/EZE | EVO 420 mg Q4W  
Baseline therapy + PBO (PBO) | 112.3  
98.4  
96.2  
119.8 | %LDL-C ↓  
%LDL-C<70  
-55.7  
83.6%  
-61.6  
90.1%  
-56.8  
80.8%  
-48.5  
67%  
p<0.001 all regimens | Not-reported | EVO 74.8%, PBO 74.2% Nasopharyngitis, URTI, influenza, back pain SAE 5.5%A vs 4.3% D/C doe to AE 2.2% vs 1% Injection site rxn EVO=PBO Transaminase↑ >3xULN 5 (0.8%) vs 3 (1.0%) CK>5x ULN 7 (1.2%) vs 1 (0.3%) Myalgias 24 (4%) vs 9 (3%) |
| **MENDEL-2**  
Randomized, double-blind, parallel-assignment (12 weeks) | LDL-C > 100 to < 190 mg/dL, FRS 10% | No current therapy | SQ/PO Q2W  
PBO/PBO  
PBO/EZE  
EVO140/PBO  
SQ/PO Q4W  
PBO/PBO  
PBO/EZE  
EVO420/PBO | 140  
143  
142  
144  
144  
144 | +0.1  
-17.8  
-57.0  
p<0.001 all regimens  
-1.3  
-18.6  
-56.1  
p<0.001 all regimens | EVO vs PBO vs EZE  
D/C rate 3.9% vs 3.2% vs 2.3%  
TEAEs:  44% vs 44% vs 46%  
SAE: 2/4 EVO study drug related: Pancreatitis (1), CK + transaminase > 8xULN (1)  
No death/CV events | EVO vs PBO vs EZE  
D/C rate 3.9% vs 3.2% vs 2.3%  
TEAEs:  44% vs 44% vs 46%  
SAE: 2/4 EVO study drug related: Pancreatitis (1), CK + transaminase > 8xULN (1)  
No death/CV events |
| **LAPLACE-2**  
Randomized, double-blind, placebo- and ezetimibe controlled (12-week) | Adults with hypercholesterolemia or mixed dyslipidemia TG<400 mg/dL  
LDL-C ≥ 150 mg/dL without statin  
LDL-C ≥ 100 mg/dL | Discontinued prior to study | Statin/PBO  
ATO/EZE  
Statin/EVO | 108  
109  
110 | Versus PBO  
EVO -63 to -75%  
EZE -19 to -32%  
P<0.001  
Versus ATO  
EVO -61 to -62%  
EZE -17 to -24%  
P<0.001 | Statin/PBO n=2; 0.4%  
ATO/EZE n=2 (0.9%)  
Statin/EVO n=5 (0.4%) | No differences in safety or tolerability |
<table>
<thead>
<tr>
<th>Reference /Trial</th>
<th>Population</th>
<th>Baseline Therapy</th>
<th>Treatment</th>
<th>Baseline LDL-C (mg/dL)</th>
<th>Results: Percent change in LDL-C, % achieving target goal</th>
<th>CV</th>
<th>AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>OSLER-1 and OSLER-2 Combined Long-Term study (48-56 weeks)</td>
<td>Enrolled from 2 studies OSLER-1 and OSLER-2</td>
<td>EVO or SOC</td>
<td>EVO 420 Q4W or EVO 140 Q2</td>
<td>Not reported</td>
<td>LDL-C &lt; 70 mg/dL EVO + Moderate Intensity Statin 86-94% EVO + High Intensity Statin 93-95% EZE + mod int. ATO 17-20% EZE + high int. ATO 51-62% EVO + ATO 86-94% EVO Q2W = EVO Q4W</td>
<td></td>
<td>AEs EVO 69.2% vs SOC 64.8% SAEs EVO = SOC AST or CK ↑ similar Neurocognitive AE &lt;1%, more common with EVO + unrelated to LDL-C level Injection site rxn EVO 4.3% AE, SAE equivalent @ low LDL-C (&lt;40 or &lt;25 mg/dL) CV AEs EVO&lt;SOC; HR 0.47 (95% CI, 0.28 to 0.78, p&lt;0.003)</td>
</tr>
<tr>
<td>OSLER-Open-label, long-term study (52 week)</td>
<td>Enrolled from 4-phase 2 studies (MENDEL, LAPLACE-TIMI, GAUSS, RUTHERFORD)</td>
<td>See particular study EVO 70- or 105- or 140 mg every 2 weeks or 280- or 350- or 420 mg every 4 weeks.</td>
<td>SOC 57.9% statin 24.5% intensive EVO 420 mg Q4W + SOC</td>
<td>143</td>
<td>Change from baseline 4-week LDL-C -17.9% 12 week LDL-C -5.8% Prior EVO regimen -1.7 (p&lt;0.31) Prior other regimen -54.7 (p&lt;0.0001)</td>
<td></td>
<td>AEs SOC 73.1% EVO + SOC 81.4% EVO related 5.6% 5.2% Inj. site rxn (1 D/C) Common AEs for both: Nasopharyngitis, URTI, influenza, arthralgia, back pain SAE SOC 6.3% EVO related 0%</td>
</tr>
<tr>
<td>Reference / Trial</td>
<td>Population</td>
<td>Baseline Therapy</td>
<td>Treatment</td>
<td>Baseline LDL-C (mg/dL)</td>
<td>Results: Percent change in LDL-C, % achieving target goal</td>
<td>CV</td>
<td>AE</td>
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<tr>
<td>Stein EA et al, 2013</td>
<td>HoFH</td>
<td>12-65 y.o. &gt; 40kg LDL-C ≥ 130 mg/dL</td>
<td>Stable drug therapy</td>
<td>EVO420 Q4W x 12weeks, then EVO420 Q2W x12 weeks</td>
<td>440.8</td>
<td>All patients Q4W -16.5%, p=0.0781 Q2W -13.9%, p =0.1484 Excluding 2 receptor (-) Q4W -19.3, p=0.0313 Q2W -26.3, p=0.0313</td>
<td>None</td>
</tr>
<tr>
<td>TESLA Part B Randomized, double-blind, placebo-controlled (12 week)</td>
<td>&gt;12 y.o. Stable drug therapy no apheresis</td>
<td>Stable drug therapy 100% receiving Statins 90% receiving ezetimibe</td>
<td>EVO 420 mg Q4W PBO</td>
<td>Continue baseline therapy</td>
<td>355</td>
<td>336</td>
<td>EVO vs PBO -30.9% LDL-C (95% CI -43.9 to -18; p&lt;0.0001)</td>
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</table>

Appendix 2: Clinical Trials Evaluating Alirocumab71,72,73,74,75,3,76

<table>
<thead>
<tr>
<th>Reference Trial</th>
<th>Population</th>
<th>Baseline Therapy</th>
<th>Treatment</th>
<th>Baseline LDL-C (mg/dL)</th>
<th>Results: Percent change in LDL-C, % achieving target goal</th>
<th>CV</th>
<th>AE ALI vs Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>ODYSSEY-MONO Randomized, double-blind, double-dummy 24-weeks</td>
<td>Adults LDL-C &gt;100&lt; 190 mg/dL 10 year CV risk &gt;1 to ≤ 5% No lipid-lowering therapy</td>
<td>None</td>
<td>ALI 75 Q2 weeks (150 mg at week 12 if not at LDL-C goal) EZE 10 QD</td>
<td>141.1 138.3</td>
<td>-47.2% -15.6% (p&lt;0.0001) 85-86% completion rate 90% self-administered all doses</td>
<td>Unrelated to study drug (1 in each arm)</td>
<td>TEAEs 69% vs 78% D/C therapy 10% vs 8% Muscle AEs 4% each Inj. site rxn 4% vs 2% 6 ALI pts with baseline abnormal FBS had on therapy FBS &gt; 126 mg/dL</td>
</tr>
<tr>
<td>ODYSSEY COMBO I Randomized, double-blind</td>
<td>High CV risk, established CHD or risk and hypercholesterolemia on max tolerated statins +/- Other therapies</td>
<td>Maximally tolerated statin +/- other therapies</td>
<td>ALI 75 Q2 weeks (150 mg at week 8 if not at LDL-C goal) PBO (baseline therapy)</td>
<td>100 106</td>
<td>-45.9% (p&lt;0.0001) LDL&lt;70 mg/dL ALI 75% PBO 9% (p&lt;0.0001) 16.8% with higher baseline LDL-C had dose ↑ → additional -22.8% LDL-C</td>
<td>Comparable</td>
<td>Inj. site rxn 5.3% vs 2.8% General allergic rxn 8.7% vs 6.5% Occurring in ALI ≥5% Nasopharyngitis, UTI, URTI, Dizziness, Sinusitis, Inj. site rxn</td>
</tr>
<tr>
<td>Study</td>
<td>Patients</td>
<td>CV Risk/Event Risk</td>
<td>Comparison</td>
<td>Mean Range across groups</td>
<td>LDL Goal Achieved</td>
<td>AEs</td>
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<tr>
<td>ODYSSEY COMBO II</td>
<td>720</td>
<td>High CV, elevated LDL-C</td>
<td>ALI75/150 EZE10</td>
<td>98.9 to 116.4</td>
<td>84.6% (p&lt;0.0001 vs EZE)</td>
<td>ALI 0.4% EZE 1.7%</td>
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<tr>
<td></td>
<td></td>
<td>and receiving maximally tolerated doses of statins</td>
<td>Continuing background statin therapy</td>
<td>108.3 104.4</td>
<td>-50.6% (p&lt;0.0001 vs EZE)</td>
<td>20.7%</td>
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<td>Achieve target ≤70 mg/dL</td>
<td>AI 77% (p&lt;0.0001 vs EZE)</td>
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<td></td>
<td>EZE 45.6%</td>
<td>18% with higher baseline LDL-C had dose ↑ → additional -10.5% LDL-C</td>
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<tr>
<td>ODYSSEY OPTIONS I</td>
<td>355</td>
<td>High and very high CV risk</td>
<td>ATOR 20 mg or ATOR 40 mg</td>
<td>98.9 to 116.4</td>
<td>-44.1% (p&lt;0.001 vs other treatments)</td>
<td>Not addressed</td>
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<td>ATOR20/ALI 75/150 Q2W ATOR40/ALI/150 75 Q2W ATOR20/EZE10 ATOR40/EZE10 2xATOR20 2xATOR40 ATOR40 to ROSU40</td>
<td>107.3 102.4 105.9</td>
<td>-49.6 (p&lt;0.0001 vs EZE10 +2xROSU)</td>
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<td>-17.4</td>
<td>18% with higher baseline LDL-C had dose ↑ → additional -10.5% LDL-C</td>
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<td>-17.1</td>
<td>ALI dose increase 8-20.9% of pts.</td>
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<td>-32.3 (NSS, large standard error)</td>
<td>For all at &lt;70 mg/dL 77.79%</td>
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<td>-19.3</td>
<td>LDL Goal achieved (predetermined): ATOR20/ALI 87.2% ATOR40/ALI 84.6%</td>
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<td></td>
<td>-22.1</td>
<td>For all at &lt;70 mg/dL 77.79%</td>
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<td>Achieved LDL-C target goal</td>
<td>TEAEs (pooled data)</td>
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<td></td>
<td>ROSU10/ALI 84.9% (SS vs others)</td>
<td>ALI56.3% EZE 53.5% 2xROSU 67.3</td>
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<td></td>
<td>ROSU20/ALI 66.7% (SS vs ROSU40)</td>
<td>CV AES and SAEs were comparable among groups</td>
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<tr>
<td>ODYSSEY OPTIONS II</td>
<td>305</td>
<td>High or moderate cardiovascular event risk</td>
<td>ROSU10 or ROSU20</td>
<td>98.9 to 116.4</td>
<td>-45.0% (p&lt;0.0001 vs EZE)</td>
<td>No significant differences across groups</td>
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<td>ROSU10/ALI75/150 ROSU10/EZE10 2xROSU10</td>
<td>107.3 102.4 105.9</td>
<td>-49.6 (p&lt;0.0001 vs EZE10 +2xROSU)</td>
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<td></td>
<td>ROSU20/ALI75/150 ROSU20/EZE10 2xROSU20</td>
<td>118.3 119.0 112.9</td>
<td>-17.4</td>
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<td>-17.1</td>
<td>LDL-C goal achieved: ALI75/150 41.9% (p&lt;0.0001 vs EZE)</td>
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<td>-32.3 (NSS, large standard error)</td>
<td>EZE 4.4%</td>
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<td>-19.3</td>
<td>LDL-C goal achieved: ALI75/150 41.9% (p&lt;0.0001 vs EZE)</td>
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<td>-22.1</td>
<td>EZE 4.4%</td>
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<td>Achieved LDL-C target goal</td>
<td>TEAEs (pooled data)</td>
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<td>ROSU10/ALI 84.9% (SS vs others)</td>
<td>ALI56.3% EZE 53.5% 2xROSU 67.3</td>
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<td>ROSU20/ALI 66.7% (SS vs ROSU40)</td>
<td>CV AES and SAEs were comparable among groups</td>
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<tr>
<td>ODYSSEY ALTERNATIVE</td>
<td>361</td>
<td>Moderate to high Cardiovascular risk with statin intolerance and LDL-C above target</td>
<td>No therapy or non-statin therapies</td>
<td>98.9 to 116.4</td>
<td>-45.0% (p&lt;0.0001 vs EZE)</td>
<td>No significant differences across groups</td>
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<td>ALI75/150 EZE10 ATOR20</td>
<td>191.1 193.5 187.3</td>
<td>-14.6%</td>
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<td>LDL-C goal achieved: ALI75/150 41.9% (p&lt;0.0001 vs EZE)</td>
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<td>EZE 4.4%</td>
<td>18% with higher baseline LDL-C had dose ↑ → additional -10.5% LDL-C</td>
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<td>TEAEs (pooled data)</td>
<td>ALI TEAEs ≥5% myalgia (24.6%), nasopharyngitis 6.3%, URTI 5.6%, arthralgias (5.6)</td>
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<td></td>
<td>skeletal muscle AEs</td>
<td>ALI&lt;ATOR p&lt;.042</td>
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<tr>
<td>ODYSSEY LONG-TERM</td>
<td>Randomized, double-blind, placebo-controlled, parallel-group</td>
<td>2341</td>
<td>High CV risk On statins +/- other therapies</td>
<td>Maximally tolerated statin +/- other therapy</td>
<td>ALI 150 mg Q2 weeks Placebo Added to baseline therapy</td>
<td>~122 each group</td>
<td>-62% (p&lt;0.001) Reach goal: 80.7% vs. 8.5% (P&lt;0.001) Achieve &lt;70: 79.3% vs 8.0% (p&lt;0.001) 1.7% vs. 3.3% HR 0.52; p=0.02</td>
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</tbody>
</table>
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