

Evolocumab (REPATHA®)

National Drug Monograph

December 2015

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information¹

Description/Mechanism of Action

Evolocumab (REPATHA®) is a humanized monoclonal antibody targeting proprotein convertase subtilisin/kexin type 9 (PCSK9). Proprotein convertase subtilisin/ kexin type 9 binds to LDL receptors on the surface of hepatocytes and promotes degradation of the LDL receptor in the liver. Inhibition of PCSK9 by evolocumab leads to reduced degradation of the LDL receptor resulting in a greater number of LDL receptors available to clear LDL and subsequently, lower circulating LDL.

Indication(s) Under Review in this document (may include off label)

Evolocumab was approved by the FDA as an adjunct to diet and:

- 1) Maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low-density lipoprotein cholesterol (LDL-C).
- 2) Other LDL lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional LDL lowering.

**The effect of evolocumab on cardiovascular morbidity or mortality has not yet been determined.*

Dosage Form(s) Under Review

For patients with HeFH or those with established ASCVD who require additional LDL lowering, the initial dose of evolocumab is 140 mg given subcutaneously (SQ) every 2 weeks OR 420 mg once a month.

For patients with HoFH, the recommended dose is 420 mg given SQ once a month.

(Available as a single-use prefilled syringe or SureClick autoinjector containing 140 mg of evolocumab. Packaged as 1, 2 or 3 autoinjectors or a single syringe containing 140 mg of evolocumab)

REMS

REMS No REMS Post-marketing Requirements

Pregnancy

No data are available in pregnant women. Consider the benefits and risks of evolocumab and the potential risk to the fetus before prescribing evolocumab in pregnant women. *(See Special Populations for additional information)*

Executive Summary

Efficacy

Summary of Efficacy

- For FDA approval, the efficacy and safety of evolocumab in lowering LDL from baseline was examined in four Phase 3 clinical trials of twelve weeks duration

(N=3,146) and a single 52-week Phase III trial (N=901), along with a number of Phase II clinical trials.

- The 12-week trials enrolled varied patient populations including evolocumab as monotherapy in low risk patients (Framingham 10-year risk $\leq 10\%$); patients on background statin therapy; patients who were considered statin intolerant and patients with HeFH.
- In the long-term 52-week trial, patients at mild, moderate or high cardiovascular (CV) risk were included. In this trial, background lipid lowering therapy included diet alone, statins or statins in combination with ezetimibe. Assignment to each group (e.g., diet alone, diet+statin, etc.) was based upon screening LDL, prior statin use and CV risk. Randomization to evolocumab or placebo was stratified based upon background lipid lowering therapy.
- The efficacy and safety of evolocumab was also evaluated in patients with homozygous familial hypercholesterolemia (HoFH) in three trials; one was a single arm, unblinded proof of concept study (n=8), another was a double-blind, placebo-controlled trial (n=49) and the third is an ongoing open-label extension trial (N=96). *Trials in patients with HoFH excluded patients receiving mipomersen, lomitapide or were receiving LDL apheresis. However the extension trial will enroll patients on LDL apheresis.*
- All trials were designed to assess the effect of evolocumab on surrogate or intermediate endpoints (e.g., LDL and other atherogenic lipoproteins) and not health outcomes. The primary outcome in most studies was the mean percent reduction in LDL from baseline to 12 weeks. Several trials included a co-primary endpoint of the percent reduction from baseline in LDL-mean of weeks 10 and 12.
 - Mean percent LDL reduction from baseline with evolocumab 140 mg SQ q2w ranged from 58.8-61.8% in non-HoFH patients.
 - Mean percent LDL reduction from baseline with evolocumab 420 mg SQ q4w ranged from 46.7%-59.4% in non-HoFH patients.
 - The mean percent LDL reduction from baseline at weeks 10 and 12 were similar to the response observed at 12 weeks.
 - Mean or median on treatment LDL with evolocumab ranged from 44.7-69 mg/dL.
 - In trials comparing evolocumab to ezetimibe, reductions in LDL ranged from approximately 55-65% for evolocumab vs. approximately 15-22% for ezetimibe.
 - All reductions in LDL from baseline were statistically significant in the evolocumab group vs. control (placebo or ezetimibe) in the non-HoFH populations.
 - The LDL lowering response was less in patients with HoFH (about 23% from baseline) and was absent in patients who were LDL receptor negative as compared to the response observed in patients with HeFH or other patients without familial disease.
 - Since patients with HoFH who were receiving mipomersen, lomitapide or LDL apheresis were excluded from clinical trials examining evolocumab, the safety and efficacy of concomitant use of evolocumab with these other treatments is unknown.
- **At this time, the effect of evolocumab on clinical outcomes is unknown. There is an ongoing trial (FOURIER) designed to examine the effect of evolocumab added to statins on clinical outcomes in 27,500 patients with established CV disease. Study completion is expected in late 2017 or early 2018. *Cardiobrief (12-21-15) Update: Results of FOURIER may be presented at the annual American Heart Association meeting in November 2016.***
 - In a prespecified analysis of positively adjudicated CV events in the

	<p>OSLER 1 and 2 studies, 29 CV events were reported in the Evo (0.95%) vs. 31 events in the placebo group (2.18%), HR 0.47, 95% CI 0.28-0.78, p=0.003, ARR 1.23%, NNT 81.3. The number of individual events occurring by 52 weeks as well as combined events was small.</p> <ul style="list-style-type: none"> ○ In the 52 week DESCARTES trial enrolling patients with varying levels of baseline CV risk, the number of positively adjudicated CV events was also small (Evo: n=6 [1%]; PBO: n=2 [0.7%]) and no clear differences were reported. ○ One meta-analyses/systematic review of PCSK9 inhibitors, focusing on clinical outcomes, reported that PCSK9 inhibitors had a significant impact on clinical outcomes but the authors cite a number of limitations to the analysis, including study design, short study duration, small number of clinical events, etc. None of the studies in the meta-analysis was designed with clinical outcomes as an endpoint.
<p>Safety</p>	<ul style="list-style-type: none"> ● The safety of evolocumab was examined in eight short-term, phase 2/3 trials in patients with primary hyperlipidemia, a phase 2 trial conducted in Japanese patients, a long-term 52-week trial and two open-label extension trials involving 5710 patients exposed to any dose of evolocumab. These trials utilized ezetimibe, placebo or standard lipid lowering therapy as comparators. Duration of exposure to evolocumab was at least three months in 5416 patients; at least a year in 1824 patients; and two or more years in 614 patients. ● In a 52 week trial (N=302 placebo, N=599 evolocumab 420 mg SQ once monthly), the following adverse drug reactions were reported in ≥3% of patients and occurred at a higher frequency with evolocumab vs. placebo: nasopharyngitis, upper respiratory tract infection, influenza, back pain, injection site reactions, cough, urinary tract infection, sinusitis, headache, myalgia, dizziness, musculoskeletal pain, hypertension, nausea, diarrhea and gastroenteritis. In this trial, 2.2% of patients receiving evolocumab discontinued treatment due to adverse drug events vs. 1% with placebo. The most common adverse event leading to withdrawal of treatment and occurring at a higher rate with evolocumab vs. placebo was myalgia (0.3% evolocumab vs. 0% placebo). ● Adverse drug events reported in seven pooled short-term clinical trials of 12 weeks in duration (N=1224 placebo, N=2052 evolocumab) were similar to that observed in the 52-week trial. ● In a trial of 49 patients with HoFH, adverse events reported in at least two patients and reported more often in the treatment vs. placebo group were: upper respiratory infection, influenza, gastroenteritis and nasopharyngitis. ● During the clinical development program, there were 15 deaths reported. Eleven of the deaths were cardiovascular in nature (0.1% in each group). No imbalance in deaths was noted between evolocumab and controls (placebo or ezetimibe). ● Nonfatal serious adverse events (ADEs) occurred in 3% of patients on evolocumab, 2.4% placebo and 2.1% placebo or ezetimibe. The most common serious ADEs included: myocardial infarction (MI): 0.1% evo vs. 0% control; angina: 0.1% evo and control and pneumonia: 0.1% evo vs. 0% control). The FDA reviewer commented that although the numbers of events were small, there was a higher incidence of angina and MI, pancreatitis, appendicitis, pneumonia and back pain that was reported in patients taking evolocumab vs. control. ● Because of the limited number of patients exposed to evolocumab and because the exposure has been of a relatively short duration, the FDA has required the manufacturer to conduct a large, prospective, Phase IV, randomized trial to assess the incidence and severity of new onset diabetes, injection site reactions, hypersensitivity, immunogenicity and its associated consequences and the potential for neurologic adverse events in patients taking evolocumab.
<p>Other Considerations</p>	<ul style="list-style-type: none"> ● Evolocumab is contraindicated in patients with a history of serious hypersensitivity reaction to evolocumab.

	<ul style="list-style-type: none"> • Since evolocumab is administered as a subcutaneous injection, patients must be educated on proper technique for preparation and administration. • In patients receiving the 420 mg dose subcutaneously once a month, the three required separate injections (140 mg each) to achieve that dose must be given consecutively within 30 minutes. • Evolocumab must be stored in the refrigerator and allowed to come to room temperature for 30 minutes prior to use. Evolocumab may also be stored at room temperature but must be used within 30 days if stored outside of the refrigerator. • To assess response to evolocumab, LDL should be measured within 4-8 weeks of treatment initiation. Additionally, LDL should be measured periodically during treatment to ensure patients continue to have a substantive and durable LDL lowering response in the case of 1) development of neutralizing antibodies or 2) non-adherence to treatment.
<p>Projected Place in Therapy</p>	<p>Projected place in therapy</p> <ul style="list-style-type: none"> • Because of the inadequate clinical outcome and long-term safety data with evolocumab, use of evolocumab should be limited to patients with a diagnosis of HeFH (clinical or laboratory diagnosis), who have not achieved at least a 50% reduction in LDL from untreated baseline despite treatment with and confirmed adherence to maximum dose statins in addition to at least one other lipid lowering therapy (ezetimibe +/- bile acid sequestrants). Additionally, use of evolocumab may be considered in those patients with a diagnosis of HoFH who are receiving and are adherent to maximum lipid lowering therapy (e.g., statins, ezetimibe, LDL apheresis, etc.) and who required additional LDL lowering. <i>Note: In clinical trials, the LDL lowering response was lower in patients with HoFH and no response was observed in patients who were LDL receptor negative.</i> <ul style="list-style-type: none"> ○ No clinical outcome data available until late 2017 or early 2018 ○ Statins should remain first-line for primary or secondary prevention. In secondary prevention, moderate dose statins reduce all-cause mortality, nonfatal MI, coronary heart disease (CHD) death, fatal and nonfatal stroke. High dose statins reduce nonfatal events in patients at greatest risk vs. moderate dose statins. Statins should be maximized prior to considering combination therapy. ○ Evidence supports a modest reduction in major cardiovascular events with the addition of ezetimibe to simvastatin 40 mg daily in patients with acute coronary syndrome (IMPROVE-IT study). Although the reduction was limited to nonfatal events over a median of six years of treatment, there are no prospective clinical outcome data for the PCSK9 inhibitors at this time. ○ Existing guidelines for reducing cardiovascular risk no longer recommend treating to specific LDL targets but instead managing higher risk patients with high dose statins (VA/DoD 2014 and American College of Cardiology/American Heart Association [ACC/AHA 2013]. Therefore, in those patients with established ASCVD who are receiving high dose statins, existing evidence is lacking to provide clear, evidence-based guidance on which patients would be the most optimal candidates for PCSK9 inhibitors. ○ Limited exposure to date and lack of long-term safety data.
<p>Potential Impact</p>	<p>Patient Convenience:</p> <ul style="list-style-type: none"> • Unclear if the need to self-administer a subcutaneous injection every two weeks will be a deterrent for some patients or affect adherence over time. Although a once a month injection is a dosing option for evolocumab, three separate injections are required to achieve the 420 mg dose.

Potential Cost Impact:

- Significant impact on reducing LDL but the effect on outcomes is unknown. Therefore, the cost for further lowering LDL will rise significantly. The value of this increased cost to VHA will not be known until the FOURIER Outcomes study is completed in late 2017 or early 2018.

Background

Purpose for review

- FDA approval July 2015
- What is the evidence of need for evolocumab?
- Does evolocumab offer advantages to currently available alternatives?
- What safety issues need to be considered?
- Does evolocumab have specific characteristics best managed by the non-formulary process, prior authorization or criteria for use?

Other therapeutic options

Formulary Alternatives	Other Considerations	CFU, Restrictions or Other Guidance
Bile acid sequestrants:		
Colestipol (tablets and granules)		
Cholestyramine powder		
Non-formulary Alternative (if applicable)	Other Considerations	
Ezetimibe		CFU
Alirocumab	Administered subcutaneously every 2 weeks.	CFU. Limited to patients with a clinical or laboratory diagnosis of HeFH.

*Niacin and fibrates were not included in this table because studies have not demonstrated an incremental benefit of these agents when added to statins; in the populations studied. Statins are not included in this table since it is assumed that PCSK9 inhibitors or alternatives would be added to statins.

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to November 2015) using the search terms evolocumab, Repatha and proprotein convertase subtilisin/kexin type 9 (PCSK9). The search was limited to studies performed in humans and published in the English language. Reference lists of review articles were searched for relevant trials, medical reviews and transcripts of FDA advisory committees available on the FDA website were reviewed for relevant information and the clinicaltrials.gov site was searched for planned, ongoing and completed trials. All randomized controlled trials published in peer-reviewed journals were included.

Review of Efficacy

For FDA approval, the efficacy and safety of evolocumab in lowering LDL from baseline was examined in four Phase 3 clinical trials of twelve weeks duration (N=3,146) and a single 52-week Phase III trial (N=901), along with a number of Phase II clinical trials. The 12-week trials enrolled varied patient populations including evolocumab as monotherapy in low risk patients (Framingham 10-year risk $\leq 10\%$); patients on background statin therapy; patients who were considered statin intolerant and patients with HeFH. In the long-term 52-week trial, patients at mild, moderate or high cardiovascular (CV) risk were included. The efficacy and safety of evolocumab was also evaluated in patients with homozygous familial hypercholesterolemia (HoFH) in three trials; one was a single arm, unblinded proof of concept study (n=8), another was a double-blind, placebo-controlled trial (n=49) and the third is an ongoing open-label extension

trial (N=96). The trials were all designed to assess the effect of evolocumab on surrogate or intermediate endpoints (e.g., LDL and other atherogenic lipoproteins) and not health outcomes. Therefore, the trials are considered to be of lower quality. There is an ongoing trial (FOURIER) designed to examine the effect of evolocumab added to statins on clinical outcomes in 27,500 patients with established CV disease. Study completion is expected in late 2017 or early 2018. Therefore, the effect of evolocumab on CV morbidity or mortality is currently unknown.

In the Phase 3 studies, eligible patients were randomly assigned to evolocumab 140 mg given SQ every two weeks, evolocumab 420 mg SQ every four weeks or control (placebo or ezetimibe) for a duration of twelve to fifty-two weeks. The primary endpoint in most trials was the mean percent reduction from baseline at twelve weeks while a few trials included the mean percent LDL reduction at weeks ten and twelve as a co-primary endpoint. Mean percent reduction in LDL from baseline ranged from the mid 40s to 65% and was similar to that observed at the mean of weeks ten and twelve. At fifty-two weeks, least squares mean percent reduction in LDL from baseline was 50.1% in the evolocumab 420 mg SQ every four weeks vs. +6.8% for placebo.⁵ Reduction in LDL was similar with the 140 mg SQ every two weeks and 420 mg SQ every four weeks doses. Patients included in the Phase 3 trials were largely of moderate risk with some patients in the DESCARTES study⁵ receiving diet alone or low dose statins in two of the risk stratified groups that were then randomized to receive evolocumab or placebo. Patients completing participation in one of the parent evolocumab studies were offered participation in OSLER 1 or 2 and were randomized to open-label evolocumab 140 mg every two weeks or 420 mg every four weeks given subcutaneously (patients were offered the choice of dosing) in addition to standard therapy (n=2976) or standard treatment alone (n=1489) for nearly one year to assess longer term safety, as well as other endpoints. Patient characteristics in OSLER 1 and 2 represent more moderate risk patients, as follows: 1) Approximately 70% of patients were receiving statins at baseline, 2) 20% had known coronary artery disease (CAD), 3) about 45% were at moderate to high CV risk, 4) 26% were receiving high dose/intensity statins, 5) 12-15% were also receiving ezetimibe and 6) mean baseline LDL was 120-121 mg/dL. In a pre-specified analysis of positively adjudicated CV events in OSLER 1 and 2, 0.95% of patients on evolocumab (n=29) had a CV event versus vs. 2.18% on standard treatment (n=31) (HR 0.47, 95% CI 0.28-0.78, p=0.003, ARR 1.23%, NNT 81.3). However, a limitation of this analysis was that “standard therapy” was not controlled or well defined and could vary according to region and/or provider practice and the number of individual CV events and combined events was small. In OSLER 1 and 2, 773 (26%) patients had a LDL <25 mg/dL and 759 (25.5%) had a LDL of 25 to < 40mg/dL. The consequence of prolonged levels of very low LDL in the presence of evolocumab is unknown. In the trial that included patients with HeFH, these patients had higher baseline LDL, more patients had established CV disease and a higher number were receiving high dose statins with or without concomitant ezetimibe.⁴ (For details on individual trials, see table 1 below).

TABLE 1. PATIENTS WITH HETEROZYGOUS OR HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA, ESTABLISHED CARDIOVASCULAR DISEASE OR AT HIGH RISK For CARDIOVASCULAR DISEASE^{4,9}

Clinical Trial	Trial Details
Raal, et al.⁴ R, DB, PC, MC N=331 12 weeks	<u>Methods:</u> <ul style="list-style-type: none"> Adult patients with HeFH (according to Simon-Broome criteria) stable on statins +/- other LLTs (for at least 4 weeks, excluding fibrates), 39 sites. Patients were excluded if they had HoFH or underwent apheresis with the prior 4 months
RUTHERFORD-2 Study Sponsored by Amgen	<ul style="list-style-type: none"> Treatments: Evo SQ 140 q2w (n=111), Evo SQ 420 q4w (n=110), PBO SQ q2w (55) or PBO SQ q4w (n=55) for 12 weeks. Randomization was stratified by baseline LDL value and use of ezetimibe. Primary endpoint: 1) Percent change in LDL from baseline at 12 weeks and 2) at the mean from baseline at weeks 10 and 12. Secondary endpoints included the effect of Evo on other atherogenic lipoproteins, hs-CRP, HDL and safety. <u>Results:</u> <ul style="list-style-type: none"> 415 screened, 331 R, 329 analyzed (2 withdrew prior to receiving any study med) 42% women, 89% white, mean age 51 years, 31% with known CAD, mean baseline LDL 155 mg/dL

- 87% were taking high dose statins, 62% were on ezetimibe

	Evo 140 q2w	Evo 420 q4w	Placebo q2w	Placebo q4w
% Mean ↓ LDL from baseline to 12 wks	61.3% p<0.0001	55.7% p<0.0001	2%	+5.5%
% Mean ↓ LDL 10-12 wks	61.2% p<0.0001	63.3% p<0.0001	1.1%	+2.3%
Mean LDL at 12 wks	65 mg/dL	69 mg/dL	147 mg/dL	158 mg/dL

Differences are vs. placebo at the same dosing frequency as Evo

Adverse events:

- ADEs were reported in 55-57% Evo vs. 43-55% PBO. Serious ADEs were reported in 3-4% Evo and 3-5% PBO, none were felt to be related to study drug and none led to w/d from study drug. No deaths were reported.
- Common ADEs: nasopharyngitis (Evo 7-10% vs. PBO 4-5%); muscle related: (Evo 2-7% [higher in the Evo q2w dosing] vs. PBO 0-2%). Other common ADEs there were similar between groups: headache, contusion, back pain, nausea and injection site reactions.
- Positively adjudicated cardiovascular ADEs: Evo 140 q2w: n=2 (2%), Evo 420 q4w: n=1 (1%). None were reported in the PBO groups.
- No neurocognitive events, changes in LFTs [AST or ALT] or CK or development of anti-drug antibodies or neutralizing antibodies were reported in any group.

Comments:

- Post-hoc analysis: 264/329 pts agreed to undergo genetic testing to confirm HeFH. 20% of pts tested had no detectable LDL receptor mutation whereas 3% (n=7) had mutations in both LDLR alleles suggesting HoFH or compound HeFH. These seven patients had similar reductions in LDL from baseline as the study population. Authors comment that knowing the specific genetic abnormality in HeFH may not help predict response to Evo as response appeared unrelated to genetic mutation.

Blom, et al.⁵
R, DB, PC, MC
N=901
52 weeks

DESCARTES Study

Sponsored by Amgen

Methods:

- Adults at various degrees of risk based upon screening LDL value, prior statin use and calculated CV risk were enrolled into a 4-week run-in treatment period.
- After a 4-week stabilization period (Single 6 ml PBO injection and open-label LLT), if LDL values exceeded a set target dependent upon patients CV risk, patients were randomized to: Evo SQ 420 mg q4w or PBO SQ q4w for 52 weeks.
- Randomization stratified by background treatment:
 - No treatment required=diet only (N=111)
 - Low dose statin required=diet + atorvastatin 10 mg daily (N=383)
 - High dose statin required=diet + atorvastatin 80 mg daily (N=218)
 - Maximum LLT required=diet + atorvastatin 80 mg + ezetimibe 10 mg daily (N=189)
- Primary endpoint: Percent change from baseline in LDL at 52 weeks. Also analyzed by background LLT.
- Secondary endpoints include effect of Evo on other atherogenic lipoproteins at 52 weeks.

Results:

- 2120 screened, 905 R, 901 analyzed (4 w/d prior to receiving study drug)
- Mean age 55-56 years, 46-48% males, 79-82% white, baseline LDL 104 mg/dL, 26% high CV risk, known CAD 14.5-15.9%
- LSM change in LDL from baseline (All patients): Evo 50.1% (range 46.7-54.7%) at 52 weeks and 57.5% at week 12 (12 week is reported as “versus placebo”). Reduction in LDL at 52 weeks vs. placebo is 57%. *All reductions from baseline were statistically significant vs. PBO.*
 - No treatment required=diet only (LDL ↓ 51.5% vs. PBO)
 - Low dose statin required=diet + atorvastatin 10 mg daily (LDL ↓ 54.7% vs. PBO)
 - High dose statin required=diet + atorvastatin 80 mg daily (LDL ↓ 46.7% vs. PBO)
 - Maximum LLT required=diet + atorvastatin 80 mg + ezetimibe 10 mg

daily (LDL↓ 46.8% vs. PBO)

- Mean LDL at 52 weeks: Evo: 50.9 mg/dL vs. PBO: 107.9 mg/dL
- ApoB, non-HDL cholesterol, Lp(a) and TGs significantly reduced in favor of Evo. No change in hs-CRP.

Adverse events:

- Incidence of ADEs: 74.8% Evo vs. 74.2% PBO
- Most common ADEs: nasopharyngitis, URI, influenza and back pain. Myalgia was reported in 24 (4%) of Evo vs. 9 (3%) of PBO recipients.
- CK elevation: ≥ 5xULN: N=7 (1.2%) Evo vs. N=1 (0.3%) PBO. CK elevation ≥ 10xULN: N=3 (0.5%) Evo vs. N=1 (0.3%) PBO
- Serious ADEs: N=33 (5.5%) Evo vs. N=13 (4.3%) PBO. Type of serious ADEs was broad and numbers of each event were small.
- Positively adjudicated CV ADEs: N=6 (1%) Evo vs. N=2 (0.7%) PBO
- Deaths: N=2 (0.3%) vs. N=0 PBO
 - Death resulted from heart failure and MI, both were included in the adjudicated CV events.
- ADEs leading to D/C of therapy: N=13 (2.2%) Evo vs. PBO N=3 (1%)

Comments:

- Number of serious ADEs or those ADEs cited for D/C of therapy were higher with Evo vs. PBO but number of each type of event reported was small preventing characterization of potential new and/or serious ADEs with Evo.

Robinson, et al.⁶

R, DB, PC, MC
N=1899
12 weeks

LAPLACE-2 Study

Sponsored by Amgen

Methods:

- Adult patients with primary hypercholesterolemia or mixed dyslipidemia were randomized to moderate dose statins (3 groups): atorva 10 mg, simva 40 mg, rosuva 5 mg OR high dose statins (2 groups): atorva 80 mg or rosuva 40 mg. After 4-wk lipid stabilization, pts were further randomized for 12 wks of treatment to:
 - Pts on rosuva or simva randomized to (4 groups): 1) Evo 140 SQ q2w or 2) matching PBO SQ q2w or 3) Evo 420 mg SQ q4w or 4) matching PBO SQ q4w.
 - Pts on atorva randomized to (6 groups): 1) Evo 140 SQ q2w and oral PBO, 2) Evo SQ 420 mg and oral PBO, 3) SQ PBO q2w and oral PBO, 4) SQ PBO q4w and oral PBO, 5) matching SQ PBO q2w and Eze 10 mg daily, 6) SQ PBO mg q4w and Eze 10 mg daily
- Patients were eligible based upon their existing lipid therapy and screening LDL.
- Primary endpoints: 1) Mean % reduction in LDL from baseline to 12 weeks. 2) % reduction in LDL from baseline, mean at weeks 10 and 12.
- If calculated LDL was <40 mg/dL or TGs were >400 mg/dL, LDL was measured using preparative ultracentrifugation.

Results:

- 3590 screened, 2067 R to lipid stabilization phase, 882 atorva users R to 1 of 6 groups, 1,017 rosuva or simva users R to 1 of 4 groups. 1826 (96%) completed the study.
- Mean age: 60 years; 46% women; 92.3-95.1% white; mean baseline LDL 109.1 mg/dL (after lipid stabilization phase); HDL 51.8-54.5 mg/dL
- Established CHD: 23%; PVD or cerebrovascular disease: 10%; DM: 16%

Background Tx	LS Mean % LDL↓ 12 wk	LS Mean % ↓ wk 10/12	Mean 10/12 wk LDL mg/dL
A80+Eze (PBO)	14.6% (q2w) 19.8% (q4w)	16.9% (q2w) 21.3% (q4w)	85.6 (q2w) 72.1 (q4w)
A80+Evo q2w	61.8%	61.8%	35.3
A80+Evo q4w	58.7%	65.1%	34.8
A10+Eze (PBO)	22% (q2w) 17.1% (q4w)	23.9% (q2w) 19% (q4w)	95 (q2w) 94.2 (q4w)
A10+Evo q2w	61.6%	61.4%	47.9
A10+Evo q4w	58.2%	62.5%	46.6
R40+Evo q2w	58.9%	59.1%	37.5
R40+Evo q4w	52.4%	62.9%	33
R5+Evo q2w	60.1%	59.3%	48.9
R5+Evo q4w	59.4%	63.8%	43.3

	S40+Evo q2w	65.9%	66.2%	39
	S40+Evo q4w	57%	62.4%	48.4
	<ul style="list-style-type: none"> Percent change in LDL from baseline was similar across type of statin. Reductions in LDL from baseline were statistically significant favoring Evo vs. PBO or Eze. Overall: Ezetimibe reduced LDL 17-24%; Evo q2w: 61-62%; Evo q4w: 62-65% For patients on moderate dose statins, addition of Evo reduced LDL to <25 mg/dL on 2 separate occasions in 24.5% of patients vs. 42.3% of patients on high dose statins. No difference in LDL lowering was observed in pre-specified subgroups including age, race, and baseline LDL, etc. 			
	<u>Adverse Events:</u>			
	<ul style="list-style-type: none"> ADEs were reported by 36% Evo, 40% Eze, 39% PBO Serious ADEs: Evo: 2.1%, Eze: 0.9% and PBO: 2.3% Tx d/c due to ADE: Evo 1.9%, Eze: 1.8%, PBO: 2.2% Positively adjudicated CV ADEs: Evo: 5 (0.4%), Eze: 2 (0.9%), PBO: 2 (0.4%) 1 death in pt receiving rosuvastatin + PBO Neurocognitive events: Evo: 1 (0.1%), Eze: 3 (1.4%), PBO: 0 Elevation in CK or LFTs was uncommon and no trends were noted. 			
	<u>Comments:</u>			
	<ul style="list-style-type: none"> Before randomization, patients were given a PBM SQ injection to see if they could tolerate SQ injections. Patients remained on the background statins that they were initially randomized through 12 wks. <i>Assignment to specific statin group or dose/intensity was purely random and not based upon risk, prior LLT or screening LDL.</i> Limitations of the trial include short study duration; small sample size in each group (approx. 50 in each control group and 100 in Evo groups); and no formal neurocognitive testing was done. 			
Sabatine, et al. ⁷ R, OL, Extension Study N=4,465 Median 11.1 months	<u>Methods:</u>			
OSLER-1 AND OSLER-2 combined results Sponsored by Amgen	<ul style="list-style-type: none"> Pts completing a phase 2 Evo trial were offered enrollment in OSLER-1 and those completing a phase 3 Evo trial could enroll in OSLER-2. Because the parent trials differed in their eligibility requirements, there was significant variation in the characteristics of the populations enrolled in OSLER-1 and 2. The purpose of OSLER-1 and 2 was to collect longer-term safety information, determine durability of LDL lowering with Evo and to conduct an exploratory analysis of positively adjudicated CV events. Pts were randomly assigned to Evo + standard care or standard care. Stratification in OSLER-1 was according to group assignment in parent study while in OSLER-2 was dependent upon the parent trial and dose frequency of the study drug. In OSLER-1, Evo was given as 420 mg SQ q4w. In OSLER-2, pts could chose to receive Evo 140 mg SQ q2w or 420 mg SQ q4w. All study personnel were aware of the treatment assignments and no PBO was used. Standard therapy was that dictated by local guidelines for treating LDL. Change in concomitant LLT was discouraged. After 48-52 weeks, <u>all</u> pts received unblinded Evo to continue to monitor long-term safety. Primary endpoint: Safety-incidence of ADEs Secondary endpoints: % change in LDL and the effect of Evo on other atherogenic lipoproteins. An exploratory analysis of positively adjudicated CV events was preplanned. Post-hoc, all CV endpoints were combined into a composite of major CV events, excluding CHF. 			
	<u>Results:</u>			
	<ul style="list-style-type: none"> N=2,976 Evo/1,489 standard therapy Mean age: 58 years, only 70.1% were receiving statins prior to enrollment in OSLER and 7.2% stopped Tx with Evo (changes in standard Tx not given). Approx 20% of pts had known CAD and 44.8-46.5% were at moderate to high risk. 26.7-27.9% of pts were on high dose/intensity statins and mean baseline LDL in parent study was 120-121 mg/dL. Majority of pts were white and about 50% males. At 12 weeks, LDL was reduced 61% from baseline (p<0.001 vs. standard Tx) and 58.4% at 48 weeks (p<0.001). Minimal to no change was observed in LDL in the 			

standard Tx alone group.

- Combined adjudicated CV events: Evo n=29 (0.95%) vs. standard Tx n=31 (2.18%) (HR 0.47, 95% CI 0.28-0.78, p=0.003, ARR 1.23%, NNT 81.3)
- Post-hoc analysis of composite major CV events (excluding CHF): Evo: n=28 (0.95%) vs. standard Tx n=30 (2.11%)

Adverse Events:

- ADEs were reported in 69.2% (2060/2976) Evo vs. 64.8% (965/1489) standard Tx
- Serious ADEs: Evo 7.5% (222/2976) vs. standard Tx 7.5% (111/1489)
- ADEs led to discontinuation of Evo in 2.4% of pts (n=71)
- LFT elevation (>3xULN) was similar between groups, Evo 1% vs. standard Tx 1.2%
- CK elevation (>5xULN) was also similar, Evo 0.6% (n=17) vs. standard Tx 1.1% (n=17)
- Neurocognitive events: number of events was low (<1%) but more events occurred in the Evo vs. standard Tx groups: 0.9% (n=27) vs. 0.3% (n=4), respectively
- Arthralgia, headache, limb pain and fatigue were reported more often in Evo vs. standard Tx
- Pts with very low LDL (<25 and <40 mg/dL) experienced a similar incidence of ADEs as those with higher LDL values.
- Deaths: Evo n=4 (0.14%) vs. standard Tx n=6 (0.41%)

Comments:

- Limitations include that “standard therapy” was not controlled or well defined and could vary according to region and/or provider practices. Only 70% of pts were receiving statins at enrollment, 20% of pts were receiving high dose statins. 35% moderate dose statins and only 12.6-15.4% on Eze. It is unclear if addition of Evo to moderate or high dose statins +/- Eze will result in reduced CV events.
- *The number of individual CV events and combined events was small.*
- 773 (26%) pts had LDL <25 mg/dL and 759 (25.5%) 25 to < 40mg/dL

Stein, et al.⁸
 Single arm, OL, MC
 N=8
 36 weeks (3x12 weeks)
 Sponsored by Amgen

Methods:

- Patients aged 12-65 years with HoFH (either a clinical: [LDL >500 mg/dL plus xanthoma before 10 years of age or both parents diagnosed with HeFH] OR genetic diagnosis) were enrolled.
- All patients were genotyped and determined to be either LDLR defective (2-25% LDLR activity) or negative (<2% LDLR activity).
- Pts were required to be on a stable low fat diet, stable LLT for at least 4 weeks and a fasting LDL >130 mg/dL and TG <400 mg/dL.
- Pts receiving LDL apheresis within the prior 8 weeks before screening or scheduled during the trial were excluded. Additionally, pts on mipomersen or lomitapide were also excluded.
- Pts received Evo SQ 420 mg q4w for a total of 24 (2x12 wks) weeks then q2w for a final 12 weeks.
- Primary endpoint: % change in LDL from baseline at the end of each of the 12-week Tx periods.

Results:

- All pts were white, mean age 34.3 years, 6 males, 6 with clinical or angiographic CAD and all pts were receiving at least Eze plus a high dose statin as background LLT.
- 6 pts had defective LDLR activity while 2 were LDLR negative.
- Mean LDL at baseline: 441.7 mg/dL (range 218-563 mg/dL)

Treatment	Mean LDL ↓	Range
Evo q4w (at 12 weeks)	17% (NS)	+5 to -44%
Evo q2w (at 12 weeks)	14% (NS)	+39.9 to -43.3%
Evo q4w (exc. LDLR neg. pts) 12 weeks	22.9%	--
Evo q2w (exc. LDLR neg. pts) 12 weeks	23.6%	--

- *Receptor negative patients had no response to Evo.*
- Mean % LDL lowering at weeks 4, 8 and 12:
 - Evo q4w: 19.3% (p=0.03)
 - Evo q2w: 26% (p=0.03)
- Mean LDL at 12 weeks:

- Evo q4w: 371 mg/dL
- Evo q2w: 382 mg/dL

Adverse Events:

- Adverse events were reported in 6/8 pts but were not considered related to Tx with Evo.
- None of the ADEs were considered serious.

Comments:

- Unclear if there are significant differences in efficacy between 420 mg q2w vs. q4w dosing in lowering LDL from baseline. Numbers of pts was very small.
- Unknown if there are advantages to more frequent dosing for lowering LDL or if there are safety differences.

Raal, et al.⁹

R, DB, PC, MC
N=50
12 weeks

TESLA Part B

Sponsored by Amgen

Methods:

- Patients 12 years of age or older with a clinical or genetic diagnosis of HoFH (same criteria as above study but LDL >500 mg/dL).
- Pts with screening LDL >130 mg/dL and receiving stable LLT and low fat diet for at least 4 weeks and TGs <400 mg/dL were enrolled.
- Pts receiving LDL apheresis within the prior 8 weeks before screening or scheduled during the trial were excluded. Additionally, pts on mipomersen or lomitapide within the prior 5 months were also excluded.
- Pts meeting enrollment criteria were randomized to Evo 420 mg SQ q4w for 12 weeks.
- Primary endpoint: Mean % change in ultracentrifugation LDL from baseline at 12 weeks.

Results:

- 50 pts with HoFH enrolled, 49 analyzed (Evo: 33/PBO: 17). One pt on PBO withdrew consent prior to taking study drug, leaving 16 in the PBO group.
- All patients had genotype confirmed HoFH except 1 pt with HeFH.
- 46/49 (94%) of pts were receiving high dose statins and 45/49 (92%) were also on Eze.
- Mean baseline LDL 350 mg/dL despite LLT.
- 43% of pts had known CAD, 25% had prior CABG surgery, 14% AVR, cerebrovascular or PAD in 8%.
- Mean % LDL reduction from baseline: Evo: 23.1% vs. PBO: +7.9% (Diff from PBO: 30.9%, p<0.0001)

Adverse Events:

- ADEs: 10/16 (63%) of PBO vs. 12/33 (36%) of Evo
- No serious ADEs were reported and no withdrawals due to ADEs.
- Most common ADEs were URI and influenza in Evo while nausea was the more common ADE in the PBO group.
- No differences or trends noted in CK or LFT elevation between groups.

Comments:

- Limitations of the trial include short study duration limiting the ability to identify potential ADEs. Pts in this trial were offered enrollment in an OL extension study along with pts that did not meet inclusion criteria for this study, including pts on LDL apheresis. Dosing can be increased to q2w in the OL extension trial.

ALT=Alanine aminotransferase, ARR=absolute risk reduction, AST=aspartate aminotransferase, AVR=aortic valve replacement, CABG=coronary artery bypass graft, CAD=coronary artery disease, CHD=coronary heart disease, CHF=congestive heart failure, CK=creatinine kinase, CV=cardiovascular, DB=double blind, LDL=low density lipoprotein cholesterol, LDLR=low density lipoprotein receptor, LFTs=liver function tests, HeFH=heterozygous familial hypercholesterolemia, HoFH=homozygous familial hypercholesterolemia, HR=hazard ratio, hs-CRP=high sensitivity c-reactive protein, LLT=lipid-lowering therapy, MC=multicenter, OL=open-label, NNT=number needed to treat, PAD=peripheral artery disease, PBO=placebo, PC=placebo-controlled, PVD=peripheral vascular disease, q2w=every 2 weeks, q4w=every 4 weeks, R=randomized, SQ=subcutaneous, Tx=treatment, ULN=upper limit of normal

Simon-Broome criteria for HeFH: <http://www.ncbi.nlm.nih.gov/books/NBK53810/#!po=25.0000>

Summary of Efficacy

- For FDA approval, the efficacy and safety of evolocumab in lowering LDL from baseline was examined in four Phase 3 clinical trials of twelve weeks duration (N=3,146) and a single 52-week Phase III trial (N=901), along with a number of Phase II clinical trials.

- The 12-week trials enrolled varied patient populations including evolocumab as monotherapy in low risk patients (Framingham 10-year risk $\leq 10\%$); patients on background statin therapy; patients who were considered statin intolerant and patients with HeFH.
 - In the long-term 52-week trial, patients at mild, moderate or high cardiovascular (CV) risk were included.
 - The efficacy and safety of evolocumab was also evaluated in patients with homozygous familial hypercholesterolemia (HoFH) in three trials; one was a single arm, unblinded proof of concept study (n=8), another was a double-blind, placebo-controlled trial (n=49) and the third is an ongoing open-label extension trial (N=96). *Trials in patients with HoFH excluded patients receiving mipomersen, lomitapide or LDL apheresis. However the extension trial will enroll patients on LDL apheresis.*
- All trials were all designed to assess the effect of evolocumab on surrogate or intermediate endpoints (e.g., LDL and other atherogenic lipoproteins) and not health outcomes.
 - The primary outcome in most studies was the mean percent reduction in LDL from baseline to 12 weeks. Several trials included a co-primary endpoint of the percent reduction from baseline in LDL-mean of weeks 10 and 12. (*See table below for specific populations and LDL lowering response*)

Clinical Trial	Population	Evo and Comparator	Mean % LDL ↓ baseline	On Treatment LDL (mg/dL)
RUTHERFORD-2 N=331	HeFH	Evo 140 q2w Evo 420 q2w PBO q2 or q4w (inj)	61.3%, p<0.0001 vs. PBO 55.7%, p<0.0001 vs. PBO +2-5.5%	65 69 147-158
DESCARTES N=901	Dyslipidemia: low to high risk	Dose Evo: 420 q4w Diet only Diet+atorva 10 Diet+atorva 80 Diet+atorva 80+Eze All vs. PBO	-- 51.5% 54.7% 46.7% 46.8% All significant vs. PBO	-- 53.5 44.7 49.6 63.9 PBO Overall: 107.9
LAPLACE-2 N=2,067	Primary hypercholesterolemia or mixed dyslipidemia	24 treatment groups: High or moderate dose statins plus: Evo q2w/q4w vs. PBO q2-q4w or Eze	<u>Mod statin + Evo:</u> 60.1-65.9% (q2w) 57-59.4% (q4w) <u>Mod statin + Eze:</u> 17.1-22% <u>Hi statin + Evo:</u> 58.9-61.8% (q2w) 52.4-58.7% (q4w) <u>Hi statin +Eze:</u> 14.6%-19.8%	<u>Mod statin + Evo:</u> 39-48.9 <u>Mod statin + Eze:</u> 94.2-95 <u>Hi statin + Evo</u> 33-37.5 <u>Hi statin +Eze:</u> 72.1-85.6
OSLER 1 & 2 N=4,465	Patients completing a Phase 2/3 Evo trial: mixed group of patients/risk levels	Evo 140 q 2w or 420 q4w + standard LLT vs. standard LLT alone	61% 12 weeks, p<0.001 58.4% 52 weeks, p<0.001 both vs. standard Tx	Median 48
Proof of concept N=8	HoFH	Evo 420 q2-4w	14-17%, respectively (NS) 23.6-22.9%, respectively (excluding LDL receptor negative pts)	371-382 Baseline: 441
TESLA PART B N=50	HoFH	Evo 420 mg q4w vs. PBO	23.1% vs. +7.9% PBO	Baseline: 350

See table 1 for definitions of the abbreviations included above

- The LDL lowering response was less in patients with HoFH (about 23% from baseline) and was absent in patients who were LDL receptor negative as compared to the response observed in patients with HeFH or other patients without familial disease.
- Since patients with HoFH who were receiving mipomersen, lomitapide or LDL apheresis were excluded from clinical trials examining evolocumab, the safety and efficacy of concomitant use of evolocumab with these other treatments is unknown. However, this question may be answered when the ongoing trial of HoFH patients in the open-label extension trial has been completed.
- **At this time, the effect of evolocumab on clinical outcomes is unknown. There is an ongoing trial (FOURIER) designed to examine the effect of evolocumab added to statins on clinical outcomes in 27,500 patients with established CV disease. Study completion is expected in late 2017 or early 2018. *Cardiobrief Update 12-21-15: Results of Fourier may be presented at the annual American Heart Association meeting in November 2016.*²⁰**
 - In a prespecified analysis of positively adjudicated CV events in the OSLER 1 and 2 studies, 29 CV events were reported in the Evo (0.95%) vs. 31 events in the placebo group (2.18%), HR 0.47, 95% CI 0.28-0.78, p=0.003, ARR 1.23%, NNT 81.3. The number of individual events occurring by 52 weeks as well as combined events was small.
 - In the 52 week DESCARTES trial enrolling patients with varying levels of baseline CV risk, the number of positively adjudicated CV events was also small (Evo: n=6 [1%]; PBO: n=2 [0.7%]) and no clear differences were reported.

Potential Off-Label Use

There are two trials that were conducted in populations where FDA approval was not granted (*See table 2 for trial details*).¹⁰⁻¹¹

TABLE 2. POPULATIONS WHERE FDA APPROVAL WAS NOT GRANTED (OFF-LABEL)

Clinical Trial	Trial Details															
<p>Stroes, et al.¹⁰ R, DB, PC N=307</p> <p>GAUSS-2 Trial</p>	<p><u>Methods:</u></p> <ul style="list-style-type: none"> • Patients with self-reported intolerance to 2 or more statins were randomized to Evo 140 mg SQ q2w, Evo 420 mg SQ q4w or ezetimibe for 12 weeks. • Intolerance was defined as the inability to tolerate any dose or the lowest available statin dose because of muscle adverse events related to statins. <u>Self-reported statin intolerant patients.</u> • The trial was placebo-controlled, using matching PBO in each group to maintain blinding. • Co-primary endpoints were the mean % reduction in LDL from baseline and the mean % reduction from baseline at the mean of weeks 10 and 12. <p><u>Results:</u></p> <ul style="list-style-type: none"> • Adult pts not on statins or only low dose statins (Evo: n=205; Eze: n=102), 94% of pts completed the study (96% Evo, 86% Eze) • Mean age 60-63 years, 47-57% males, baseline LDL approx. 195 mg/dL, 33% receiving LLT, 56% considered as high risk and 18% were taking low dose statins. <table border="1"> <thead> <tr> <th>Intervention</th> <th>Mean % LDL ↓12/10-12 weeks</th> <th>On Treatment LDL (12w)</th> </tr> </thead> <tbody> <tr> <td>Eze + Evo q2w PBO</td> <td>18.1%/19.2%</td> <td>156 (approx)</td> </tr> <tr> <td>Eze + Evo q4w PBO</td> <td>15.1%/16.6%</td> <td>165 (approx)</td> </tr> <tr> <td>Evo 140 q2w</td> <td>56.1%/56.1%</td> <td>89 (approx)</td> </tr> <tr> <td>Evo 420 q4w</td> <td>52.6%/55.3%</td> <td>96 (approx)</td> </tr> </tbody> </table> <p>P<0.001 for all comparisons of Evo vs. Eze</p> <p><u>Adverse Events:</u></p> <ul style="list-style-type: none"> • ADEs were reported in 66% of Evo vs. 73% of Eze pts • No deaths were reported and serious ADEs were reported in 3% Evo vs. 4% Eze • Study withdrawal due to ADEs: Evo: n=8%; Eze: n=13% • Myalgia: Evo 8% vs. Eze: 18%. Discontinuation due to skeletal muscle adverse events did not differ between groups. <p><u>Comments:</u></p>	Intervention	Mean % LDL ↓12/10-12 weeks	On Treatment LDL (12w)	Eze + Evo q2w PBO	18.1%/19.2%	156 (approx)	Eze + Evo q4w PBO	15.1%/16.6%	165 (approx)	Evo 140 q2w	56.1%/56.1%	89 (approx)	Evo 420 q4w	52.6%/55.3%	96 (approx)
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Evo 140 q2w	56.1%/56.1%	89 (approx)														
Evo 420 q4w	52.6%/55.3%	96 (approx)														

	<ul style="list-style-type: none"> • Limitations include the pts were not re-challenged with statins to determine true statin intolerance and the duration of the study was short, only 12 weeks. • 18% were receiving at least a small dose of statin. • Myalgia was reported more often in the ezetimibe vs. Evo groups. It is not clear how this information was obtained from patients (personal contact, written form, etc.). However, there were no differences in study withdrawal due to skeletal muscle adverse events between groups. 																									
<p>Koren, et al.¹¹ R, DB, PC, MC N=614</p> <p>MENDEL-2 Trial</p>	<p><u>Methods:</u></p> <ul style="list-style-type: none"> • Adult pts (18-80 yrs) with LDL \geq100 mg/dL and <190 mg/dL, triglycerides \leq400 mg/dL and a 10-yr Framingham risk score of 10% or less (low risk). <u>Lower risk, not on statins.</u> • Patients randomized to Evo 140 mg q2w, Evo 420 mg q4w or ezetimibe. All groups used matching PBO to maintain blinding. • Randomization was stratified by LDL (<130 mg/dL or \geq 130 mg/dL) • Co-primary endpoints were the mean % reduction in LDL from baseline and the mean % reduction from baseline at the mean of weeks 10 and 12. • Pts receiving lipid-lowering therapy within 3 months are excluded. <p><u>Results:</u></p> <ul style="list-style-type: none"> • 615 pts were randomized to: Evo n=306, Eze n=154, PBO n=155. • Baseline LDL 142 mg/dL, mean age 53 years, 31-40% males. • 97% of pts completed the study <table border="1" data-bbox="602 793 1382 1003"> <thead> <tr> <th>Intervention</th> <th>Mean % LDL weeks</th> <th>\downarrow12/10-12</th> <th>On Treatment (12w)</th> <th>LDL</th> </tr> </thead> <tbody> <tr> <td>Eze + Evo q2w PBO</td> <td>17.8%/17.5%</td> <td></td> <td>--</td> <td></td> </tr> <tr> <td>Eze + Evo q4w PBO</td> <td>18.6%/19.1%</td> <td></td> <td>--</td> <td></td> </tr> <tr> <td>Evo 140 q2w</td> <td>57%/56.9%</td> <td></td> <td>59</td> <td></td> </tr> <tr> <td>Evo 420 q4w</td> <td>56.1%/58.8%</td> <td></td> <td>63</td> <td></td> </tr> </tbody> </table> <p><i>No change for PBO</i> <i>All differences are statistically significant favoring Evo vs. Eze or PBO</i></p> <p><u>Adverse Events:</u></p> <ul style="list-style-type: none"> • ADEs were reported in 44% Evo vs. 46% Eze • No deaths or CV events were reported (low risk population, 12 week study) • 4 serious ADEs reported in Evo (1.3%) vs. 1 in PBO (0.6%) and 1 in Eze (0.6%). Investigators concluded that 2 events were related to study drug (Evo): 1-pancreatitis and 1-LFT and CK elevation. • Withdrawal due to ADEs was reported in: Evo n=7 (2.3%), Eze n=5 (3.2%), PBO n=6 (3.9%) <p><u>Comments:</u></p> <ul style="list-style-type: none"> • Limitations include use of evolocumab in a study population that is low risk. Investigators may have considered comparing this drug to statins to see how statins compare in reducing LDL from baseline in this low risk group; as this group was not specifically intolerant to statins and since there is evidence to support use of statins in primary prevention populations. 	Intervention	Mean % LDL weeks	\downarrow 12/10-12	On Treatment (12w)	LDL	Eze + Evo q2w PBO	17.8%/17.5%		--		Eze + Evo q4w PBO	18.6%/19.1%		--		Evo 140 q2w	57%/56.9%		59		Evo 420 q4w	56.1%/58.8%		63	
Intervention	Mean % LDL weeks	\downarrow 12/10-12	On Treatment (12w)	LDL																						
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Evo 420 q4w	56.1%/58.8%		63																							

Summary of Efficacy

- In two trials randomizing adult patients with self-reported intolerance to statins¹⁰ or adults at low risk for CV disease not receiving statins¹¹, treatment with evolocumab 140 mg SQ q2w and 420 mg SQ q4w for twelve weeks resulted in a mean reduction in LDL from baseline of more than 50% while ezetimibe reduced LDL 15.1% to almost 19%. All differences between evolocumab and ezetimibe or placebo were statistically significant.
- Treatment with evolocumab resulted in a mean on treatment LDL of <100 mg/dL in both trials.

Safety¹⁻²

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	• None
Contraindications	• Evolocumab is contraindicated in patients with a history of a serious

	hypersensitivity reaction to evolocumab.
Warnings/Precautions	<ul style="list-style-type: none"> Hypersensitivity reactions have been reported in patients taking evolocumab and some patients have discontinued their therapy as a result. If signs or symptoms of a serious allergic reaction occur, evolocumab should be discontinued and the reaction treated following standard practices/interventions and the patient should be monitored until the symptoms resolve completely.

Safety Considerations¹⁻²

The safety of evolocumab was examined in eight short-term, phase 2/3 trials in patients with primary hyperlipidemia, a phase 2 trial conducted in Japanese patients, a long-term 52-week trial and two open-label extension trials involving 5710 patients exposed to any dose of evolocumab. These trials utilized ezetimibe or placebo as their comparator. Duration of exposure to evolocumab was at least three months in 5416 patients; at least a year in 1824 patients; and 614 patients had been receiving evolocumab for two or more years. The mean age of study participants was 58 years, more than 80% were white and nearly 30% had a diagnosis of coronary artery disease, cerebrovascular or peripheral vascular disease. Nearly 70% of patients were receiving high dose (30%) or moderate dose (38%) statins.

- Local injection site reactions (ISRs):** Injection site reactions were reported in 3.2% of evolocumab vs. 3% of placebo recipients. Injection site reactions commonly consisted of redness, pain and bruising and led to discontinuation of therapy in 0.1% patients on evolocumab vs. 0% on placebo.
- Allergic reactions:** Allergic reactions were reported in 5.1% of evolocumab vs. 4.6% placebo recipients. The following reactions were reported with evolocumab vs. placebo: rash 1% vs. 0.5%; eczema 0.4% vs. 0.2%, erythema 0.4% vs. 0.2% and urticaria 0.4% vs. 0.1%, respectively.
- Neurocognitive events:** Neurocognitive events were reported \leq 0.2% of patients receiving evolocumab or placebo.
- Low LDL levels:** In clinical trials, 1609 patients had at least one LDL value $<$ 25 mg/dL during treatment with evolocumab. No changes were made in background lipid lowering therapy and treatment with evolocumab was continued without interruption and no associated adverse events were noted. However, the long-term consequence of persistently low LDL values caused by evolocumab is unknown. *The FDA reviewer and Advisory Committee did not feel there was evidence to support providing guidance on a threshold for very low LDL levels or how to manage very low LDL levels in patients on evolocumab. The Committee agreed that reducing statin doses in these patients was NOT an appropriate action since evidence supports statins in reducing adverse CV events.*
- Cardiovascular:** Cardiac events were reported in 2.4% evolocumab vs. 1.4% control with the more common events including: palpitations (0.6% vs. 0.3%, respectively), angina (0.3% vs. 0.2%, respectively) and ventricular extrasystoles (0.3% vs. 0.1%, respectively). Cardiovascular events classified as serious were reported more often in the evolocumab (0.7%) vs. control group (0.2%) and included, respectively: MI (0.1% vs. 0%), angina (0.1% in each group) and acute MI (0.1% vs. 0%).
- Musculoskeletal events:** Musculoskeletal events were reported more often in the evolocumab vs. placebo group (14.3% vs. 12.8%, respectively) with back pain (3.2% vs. 2.9%), arthralgia (2.3% vs. 2.2%) and myalgia (2% vs. 1.8%) being the most common muscle related adverse events that were reported more frequently with evolocumab vs. placebo.
- Pancreatitis:** In the trials reviewed by the FDA for approval, there were a higher number of cases of pancreatitis occurring in the evolocumab vs. standard of care group. Although there were other factors that may have increased the risk for pancreatitis, including alcohol use, diabetes and concomitant medications, a connection between evolocumab and pancreatitis cannot be completely ruled out.
- Renal disease/Proteinuria:** Serious renal events and proteinuria were reported more frequently in statin intolerant and diabetic patients receiving evolocumab vs. control but it is not clear whether evolocumab contributed to these events or whether other factors may be responsible.
- Immunogenicity:** Anti-drug antibodies (ADA) were reported in 0.1% of patients receiving at least one dose of evolocumab. The presence of ADA did not appear to alter the response to evolocumab or impact its safety. Patients testing positive for ADA underwent testing for neutralizing antibodies (Nab). None of the patients testing positive for ADA were positive for Nab. The long-term effect of continuing evolocumab in a patient with ADA has not been established.
- Individual Clinical Trials:** In clinical trials of evolocumab versus ezetimibe or placebo, the percentage of patients reporting “any” adverse event did not differ between groups and withdrawal due to adverse

events was generally not greater in the evolocumab group vs. the comparators. The numbers of positively adjudicated CV events and serious adverse events were rare and the types of events varied, thereby preventing conclusions from being drawn.

Adverse Reactions¹⁻²

Common adverse reactions	<p>In a 52 week trial (N=302 placebo, N=599 evolocumab 420 mg once monthly), the following adverse drug reactions were reported in $\geq 3\%$ of patients and occurred at a higher frequency with evolocumab vs. placebo: nasopharyngitis, upper respiratory tract infection, influenza, back pain, injection site reactions, cough, urinary tract infection, sinusitis, headache, myalgia, dizziness, musculoskeletal pain, hypertension, nausea, diarrhea and gastroenteritis. Adverse drug events reported in seven pooled short-term clinical trials of 12 weeks in duration (N=1224 placebo, N=2052 evolocumab) were similar to that observed in the 52-week trial.</p>
Death/Serious adverse reactions	<p>In a trial of 49 patients with HoFH, adverse events reported in at least two patients and reported more often in the treatment vs. placebo group were: upper respiratory infection, influenza, gastroenteritis and nasopharyngitis.</p> <p>During the clinical development program, there were 15 deaths reported. Eleven of the deaths were cardiovascular in nature (0.1% in each group). No imbalance in deaths was noted between evolocumab and controls (placebo or ezetimibe).</p> <p>Nonfatal serious adverse events (ADEs) occurred 3% evolocumab, 2.4% placebo and 2.1% placebo or ezetimibe. The most common serious ADEs included: myocardial infarction (MI): 0.1% evo vs. 0% control; angina: 0.1% evo and control and pneumonia: 0.1% evo vs. 0% control). The FDA reviewer commented that although the numbers of events were small, there was a higher incidence of angina and MI, pancreatitis, appendicitis, pneumonia and back pain that was reported in patients taking evolocumab vs. control.</p>
Discontinuations due to adverse reactions	<p>In a 52-week trial of evolocumab vs. placebo, 2.2% of patients receiving evolocumab discontinued treatment due to adverse drug events vs. 1% with placebo. The most common adverse event leading to withdrawal of treatment and occurring at a higher rate with evolocumab vs. placebo was myalgia (0.3% evolocumab vs. 0% placebo).</p>

Drug Interactions¹

Drug-Drug Interactions

- In the presence of high dose statins, evolocumab's C_{max} and area under the concentration curve (AUC) were reduced by 20%. However, the difference was not considered clinically significant and therefore, no dosing modifications are indicated.

Risk Evaluation

As of October 26th, 2015

Sentinel event advisories	Comments									
Look-alike/sound-alike error potentials	<ul style="list-style-type: none"> None 	NME Drug Name	Evolocumab 140 mg inj	Lexi-Comp	None	First DataBank	None	ISMP	None	Clinical Judgment Eculizumab Everolimus Alirocumab

Repatha	None	None	None	Ranexa Raplixa Repliva
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Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Other Considerations

The FDA has required several post-marketing trials to be conducted including:

1. A large, long-term randomized controlled trial to assess the incidence and severity of new onset diabetes, injection site reactions, hypersensitivity, immunogenicity and its associated consequences and the potential for neurologic adverse events in patients taking evolocumab.
2. A large, long-term trial to evaluate changes in neurocognitive functioning in patients receiving evolocumab.
3. An efficacy and safety study of evolocumab in patients with HeFH, ages 10 to <18 years. Suggested study design is an initial 6-month study followed by an open-label extension trial. Existing lipid lowering therapy must be stable and LDL >130 g/dL on treatment.
4. A prospective, observational study of pregnant women taking evolocumab to assess the effect on the fetus, infant and the child through the first 5 years of childhood. The intent of this observational study is to identify any adverse safety signals on pregnancy and childhood outcomes related to humoral immune suppression. Although details were not provided, the FDA indicates that the study should have validated or adjudicated outcomes, be properly powered and if differences are detected between evolocumab and control, justification for the observed differences provided.
5. Other adverse events that may require further examination with increased exposure to evolocumab and ongoing clinical trials are the higher number of cases of pancreatitis and proteinuria observed in the integrated trials program, as noted by the FDA reviewer.

Dosing and Administration¹

Dosing:

- In patients with HeFH or in those patients with established ASCVD (who require additional LDL lowering), the dose of evolocumab is 140 mg administered subcutaneously every 2 weeks or 420 mg once every month.
- If the dosing schedule is changed from every 2 weeks to once a month, or vice versa, the initial dose of the new regimen should be administered on the next scheduled date of the prior dosing regimen.
- In patients with HoFH, the dose of evolocumab is 420 mg administered subcutaneously once a month. Since response to evolocumab is dependent upon the presence of functional LDL receptors, LDL should be measured within 4 to 8 weeks of the initiation of therapy to assess response.
- If a dose of evolocumab is missed, the patient should be instructed to administer the missed dose as soon as possible if there are more than 7 days prior to their next dose OR omit the missed dose and resume dosing according to the original schedule.

Administration:

- If the 420 mg dose is prescribed, 3 evolocumab injections (140 mg each) must be administered subcutaneously within a 30-minute period.
- Patients and/or caregivers must be educated on the proper technique for preparation and administration of evolocumab.
- Evolocumab should be stored in the refrigerator and allowed to come to room temperature for at least 30 minutes prior to administration. Evolocumab can be stored at room temperature in its original packaging. However if stored outside of the refrigerator, it must be used within 30 days.
- Evolocumab is administered as a subcutaneous injection into the thigh, abdomen or upper arm. The injection should not be given into areas that are tender, bruised, red or indurated. The site of injection should be rotated with each injection.

- Other injectable drugs should not be administered at the same site as evolocumab.

For additional instructions on dosing and administration, refer to the manufacturers prescribing information.

Special Populations (Adults)¹

	Comments
Elderly	<ul style="list-style-type: none"> • No differences in safety or efficacy were noted in over 1420 patients ≥ 65 years and 171 ≥ 75 years who received evolocumab. However, a greater sensitivity of older patients to evolocumab cannot be dismissed.
Pregnancy	<ul style="list-style-type: none"> • No data identified. Before prescribing evolocumab, consider the benefits/risks in pregnant women and the risk to the fetus.
Lactation	<ul style="list-style-type: none"> • No available data. Therefore, consider the benefits of breastfeeding to the infant and the risk of the underlying condition to the mother along with the benefit/risks of evolocumab before prescribing to nursing mothers.
Females and Males of Reproductive Potential	<ul style="list-style-type: none"> • No available data.
Renal Impairment	<ul style="list-style-type: none"> • No dose adjustments are needed in patients with mild to moderate renal dysfunction. No data exist in patients with severe renal disease.
Hepatic Impairment	<ul style="list-style-type: none"> • No dose adjustments are needed in patients with mild to moderate hepatic dysfunction. No data exist in patients with severe liver disease.
Pharmacogenetics/genomics	<ul style="list-style-type: none"> • No data identified.

Projected Place in Therapy (this section may be edited prior to final approval)

- Evolocumab (Repatha®) is FDA approved as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional LDL lowering. It is also approved for use in addition to other LDL lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional LDL lowering.
- Heterozygous familial hypercholesterolemia (HeFH) is an inherited condition associated with very high levels of LDL and premature cardiovascular disease. It is much more common than homozygous familial hypercholesterolemia (HoFH), occurring in 1 in 300-500 patients.
- Homozygous familial hypercholesterolemia is a rare, inherited condition caused by mutations in the LDL receptor gene. It is estimated to occur in 1 in a million births. The LDL receptor defect/mutation results in very high levels of LDL cholesterol (LDL-C), development of severe cardiovascular disease at an early age and premature death.¹²⁻¹⁴ Existing lipid-lowering drugs do not sufficiently reduce LDL in these patients and statins are less effective since statins act in part by upregulating LDL receptors. Many of these patients require weekly or biweekly LDL apheresis to maintain lower LDL levels.
- One meta-analyses/systematic review of PCSK9 inhibitors, focusing on clinical outcomes, reported that PCSK9 inhibitors had a significant impact on clinical outcomes but the authors cite a number of limitations to the analysis, including study design, short study duration, small number of clinical events, etc.¹⁵ None of the studies in the meta-analysis was designed with clinical outcomes as an endpoint.
- At this time, the effect of evolocumab on CV morbidity and mortality is unknown. There is an ongoing trial (FOURIER) designed to examine the effect of evolocumab added to statins on clinical outcomes

in 27,500 patients with established CV disease. Study completion is expected in late 2017 or early 2018. *Cardiobrief Update 12-21-15: Results of Fourier may be presented at the annual American Heart Association meeting in November 2016.*²⁰

- In a prespecified analysis of positively adjudicated CV events in the OSLER 1 and 2 studies, 29 CV events were reported in the Evo (0.95%) vs. 31 events in the placebo group (2.18%), HR 0.47, 95% CI 0.28-0.78, p=0.003, ARR 1.23%, NNT 81.3.⁷ The number of individual events occurring by 52 weeks as well as combined events was small.
- In the 52 week DESCARTES trial enrolling patients with varying levels of baseline CV risk, the number of positively adjudicated CV events was also small (Evo: n=6 [1%]; PBO: n=2 [0.7%]) and no clear differences were reported.⁵
- Statins should remain first-line for primary or secondary prevention. In secondary prevention, moderate dose statins reduce all-cause mortality, nonfatal MI, coronary heart disease (CHD) death, fatal and nonfatal stroke. High dose statins reduce nonfatal events in patients at greatest risk vs. moderate dose statins. Statins should be maximized prior to considering combination therapy.¹⁶
- Evidence supports a modest reduction in major cardiovascular events with the addition of ezetimibe to simvastatin 40 mg daily in patients with acute coronary syndrome (IMPROVE-IT study).¹⁷ Although the reduction was limited to nonfatal events over a median of six years of treatment, there are no prospective clinical outcome data for the PCSK9 inhibitors at this time.
- Existing guidelines for reducing cardiovascular risk no longer recommend treating to specific LDL targets but instead managing higher risk patients with high dose statins (VA/DoD 2014 and American College of Cardiology/American Heart Association [ACC/AHA 2013]).¹⁸⁻¹⁹ Therefore, in those patients with established ASCVD who are receiving high dose statins, existing evidence is lacking to provide clear, evidence-based guidance on which patients would be the optimal candidates for PCSK9 inhibitors.
- The FDA is requiring several post-marketing trials including a large, long-term trial to determine the incidence and severity of a number of plausible adverse events with evolocumab including new-onset diabetes, injection site reactions, hypersensitivity, immunogenicity and its consequences and adverse events related to neurologic events.
- **Because of the inadequate clinical outcome and long-term safety data with evolocumab, use of evolocumab should be limited to patients with a diagnosis of HeFH, who have not achieved at least a 50% reduction in LDL from untreated baseline despite treatment with and confirmed adherence to maximum dose statins in addition to at least one other lipid lowering therapy (ezetimibe +/- bile acid sequestrants). Additionally, may be considered in those patients with a diagnosis of HoFH who are receiving and are adherent to maximum lipid lowering therapy (e.g., statins, ezetimibe, LDL apheresis, etc.) who require additional LDL lowering. In clinical trials, the LDL lowering response was lower in patients with HoFH and no response was observed in patients who were LDL receptor negative.**

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