

## Class Update – PCSK9 Inhibitors

**Date of Review:** January 2018

**Date of Last Review:** November 2016

### **Current Status of PDL Class:**

See **Appendix 1**.

### **Research Questions:**

1. Is there any new comparative evidence for Proprotein Convertase Subtilisin Kexin type 9 (PCSK9) Inhibitors in reducing cardiovascular (CV) outcomes or mortality in adult patients being treated for the primary or secondary prevention of cardiovascular disease (CVD)?
2. Is there any new comparative evidence for harms of PCSK9 inhibitors in patients being treated for the primary or secondary prevention of CV disease?
3. Are there subpopulations of patients based on demographics (e.g., age, sex, race, and diagnoses) for which one PCSK9 inhibitor is more effective or associated with more harm than other non-statin agents?

### **Conclusions:**

- One high quality systematic review evaluated the effects of PCSK9 inhibitors as a class on lipid parameters and the incidence of CVD.<sup>1</sup>
  - There is moderate quality evidence for a reduction in low-density lipoprotein cholesterol [LDL-C] at 24 weeks with PCSK9 inhibitors compared to placebo (-54%; 95% Confidence Interval [CI] 58.6 to 49.1), compared to ezetimibe (30.2%; 95% CI 34.2 to 26.2) and compared to ezetimibe plus statin (39.2%; 95% CI 56.15 to 22.26).
  - There is moderate quality evidence of a modest reduction in cardiovascular disease [CVD] events with PCSK9 inhibitors compared to placebo (odds ratio [OR] 0.86; 95% CI 0.8 to 0.92; absolute risk reduction [ARR] 0.9%; number needed to treat [NNT] 112) from 6 to 36 months of follow up.
  - Low quality evidence suggests a beneficial effect on cardiovascular [CV] outcomes with PCSK9 inhibitors compared to ezetimibe and statins (OR 0.45; 95% CI 0.27 to 0.75; ARR 1.1%, NNT 91) with significant uncertainty.
  - There was no significant difference in mortality between PCSK9 inhibitors and placebo (OR 1.02; 95% CI 0.91 to 1.14) with follow up of 6 to 36 months.
  - There is low quality evidence of an increase in adverse events with PCSK9 inhibitors compared to placebo (OR 1.08; 95% CI 1.04 to 1.12; absolute risk increase [ARI] 1.5%; number needed to harm [NNH] 67). There was no significant difference in any one individual adverse event (myalgia, influenza, cancer, elevated creatinine) and the effect of PCSK9 inhibitors on the risk of an event was modest, with changes in risk often less than 1%. The increase in adverse events was largely driven by two trials evaluating bococizumab, which was discontinued due to immunogenicity
- There is moderate quality evidence from one large, good quality trial with a median duration of follow-up of 26 months that evolocumab added on to statin therapy reduces non-fatal CV events compared to placebo with a modest magnitude of benefit (9.8% vs. 11.3%, respectively, ARR 1.5%; NNT 67) in those patients with clinically evident CVD at high risk for recurrence.<sup>2</sup>

- There is moderate quality evidence that evolocumab added on to statin therapy does not reduce the risk of mortality (3.2% vs. 3.1%) or CV death (1.8% vs. 1.7%) compared to placebo, respectively, and there was a numerically high risk of both with treatment compared to placebo.<sup>2</sup>
- There is low quality evidence of no difference in serious adverse events, musculoskeletal, or new onset diabetes between evolocumab and placebo.
- There remains conflicting evidence on the risk of neurocognitive adverse events with PCSK9 inhibitors and the overall incidence is low (< 1%). A recent systematic review found no difference in neurocognitive adverse events with PCSK9 inhibitors compared to standard of care (0.8% vs. 0.5%; OR 1.29; 95% CI 0.64 to 2.59) with mild between-study heterogeneity. However, a subgroup analysis using only the two larger outcome trials with longer duration of follow-up did demonstrate a significant increase in neurocognitive adverse events (1% vs. 0.4%; OR 2.81; 95% CI 1.32 to 5.99) with PCSK9 inhibitors compared to standard of care with a wide confidence interval.<sup>3</sup> These events were self-reported with no objective analysis.
- There is insufficient evidence to directly compare the effectiveness or safety of evolocumab and alirocumab.
- There remains insufficient evidence that alirocumab is effective in preventing CV events. Ongoing trials will help evaluate effectiveness once completed.
- There is insufficient evidence evaluating PCSK9 inhibitors on quality of life outcomes.

#### **Recommendations:**

- Continue to require prior authorization for approval of evolocumab and alirocumab (**Appendix 4**) to approve for high CV risk patients that have been included in clinical studies.
- No changes to PDL recommended. Evaluate costs in executive session.

#### **Previous Conclusions:**

- Moderate quality evidence shows proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are efficacious at reducing low-density lipoprotein cholesterol (LDL-C) levels by over 50% from baseline in patients with familial hypercholesterolemia already on a statin and ezetimibe and in non-familial hypercholesterolemia who cannot achieve adequate LDL-C lowering.
- However, evidence is insufficient at this time to support the use of PCSK9 inhibitors to reduce adverse CV outcomes including all-cause mortality.
- In patients with homozygous familial hypercholesterolemia already on a statin and ezetimibe, there is insufficient evidence to use alirocumab
- There is insufficient evidence that directly compares efficacy and harms between PCSK9 inhibitors.
- Moderate quality evidence from short term trials suggests PCSK9 inhibitors are associated with increased neurocognitive adverse events compared to placebo.<sup>8</sup> The FDA has directed developers of PCSK9 inhibitors to monitor for neurocognitive adverse effects in ongoing clinical trials. A higher frequency of neurocognitive adverse events was observed with both evolocumab (0.9% versus 0.3% for placebo) and alirocumab (1.2% versus 0.5% for placebo)
- There is insufficient evidence to differentiate between differences in harms between PCSK9 inhibitors. It is unknown if significantly lowering LDL-C will adversely affect gastrointestinal, metabolic and neurocognitive functions.

#### **Previous Recommendations:**

- Designate alirocumab and evolocumab as non-preferred in the “Other Dyslipidemia Drugs” class. Preferred status cannot be made at this time due to limited evidence of long-term CV benefit and harms.
- Restrict use of PCSK9 Inhibitors to the following populations: 1) non-familial hypercholesterolemia unable to achieve at least 50% LCL-C reduction despite high-intensity statin therapy and ezetimibe; 2) familial hypercholesterolemia; or 3) persistent myopathy or myalgia with several adequate trials of statin therapy.

---

**Methods:**

A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted from November 2016 to November 2017. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews, evidence-based guidelines, and randomized controlled trials (RCTs) evaluating clinical cardiovascular (CV) outcomes. Randomized controlled trials of surrogate outcomes will be emphasized if evidence is lacking or insufficient from those preferred sources.

**Background:**

The association between hypercholesteremia and CVD is well established. Statins have been the primary treatment option for prevention of CVD and have been shown to decrease CV events and mortality in patients with CVD and patients at high CV risk.

The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) Task Force on Practice Guidelines advocate for a substantial shift in strategies to assess and manage elevated cholesterol to reduce CVD.<sup>4</sup> Recommendations were derived from randomized trials, meta-analyses, and observational studies that were considered high quality using National Heart, Lung and Blood Institute (NHLBI) criteria.<sup>4</sup> The previous Adult Treatment Panel (ATP) III guidelines focused on reducing LDL-C and non-high density lipoprotein cholesterol (non-HDL-C) to specific target levels. The updated ACC/AHA guidelines recommend adjusting the intensity of statin therapy to reduce CVD risk in patients most likely to benefit from therapy using a risk estimator.<sup>11</sup> According to the ACC/AHA, non-statin therapies do not provide acceptable CVD risk reduction benefits.<sup>4</sup> For high risk patients including those with atherosclerotic CVD, LDL greater than or equal to 190 mg/dl and diabetics who are statin intolerant or unable to achieve sufficient response to statins, non-statin options such as niacin, fibric acid derivatives, ezetimibe, or omega-3 fatty acids can be considered to further lower LDL-C.<sup>4</sup> However, the benefit of CVD risk reduction with non-statin therapy should be evaluated against the risks of adverse effects and drug-drug interactions.<sup>4</sup> Since the 2013 guidelines, the IMPROVE-IT trial demonstrated a modest CV benefit with ezetimibe add-on therapy. The PCSK9 inhibitors were not part of the ACC/AHA practice guidelines since they were not yet approved in 2013.

PCSK9 promotes the degradation of the LDL receptor, resulting in an increase in plasma LDL. Inhibition of PCSK9 may enhance the lipid-lowering effects of statin due to a statin-induced increase in PCSK9 expression.<sup>1</sup> There are currently two PCSK9 inhibitors available, evolocumab and alirocumab (**Table 1**). A third agent, bococizumab, was removed from the development phase due to significant immune reactions and a decreased efficacy seen over time. These are both monoclonal antibodies that have been studied in challenging populations including those intolerant to statins and those with familial hypercholesterolemia. They have been shown to result in significant additive LDL reduction (>50%) on top of statin therapy in high-risk patients. However, at the time of approval, there was insufficient evidence on their effect on CV outcomes. Data from observational studies and small randomized trials led to a FDA warning regarding the risk of cognitive deficits as a result from considerable lowering of LDL-C.<sup>5</sup>

**Table 1: FDA approved indications and dose for available PCSK9 inhibitors**

PCSK9 Inhibitor	Dose	FDA approved indications
Evolocumab <sup>6</sup>	140 mg SubQ every 2 weeks 420 mg SubQ every month	<ul style="list-style-type: none"> <li>• To reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established CVD</li> <li>• As adjunct therapy for adults with primary hyperlipidemia <ul style="list-style-type: none"> <li>○ heterozygous familial hypercholesterolemia</li> <li>○ homozygous familial hypercholesterolemia</li> </ul> </li> </ul>
Alirocumab <sup>7</sup>	75 mg SubQ every 2 weeks 300 mg SubQ every month	<ul style="list-style-type: none"> <li>• Adjunct therapy for adults with heterozygous familial hypercholesterolemia</li> <li>• Adjunct therapy for patients with clinical ASCVD requiring additional LDL-C lowering</li> </ul>

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; LDL-C = low density lipoprotein cholesterol; SubQ = subcutaneously

**Systematic Reviews Including Clinical Outcomes:**

1. A systematic review from Cochrane Collaboration evaluated short-term (24 weeks), medium-term (one year), and long term (five years) effects of the PCSK9 inhibitors on lipid parameters and the incidence of CVD.<sup>1</sup> Twenty industry funded RCTs including participants with CVD or at high risk of CV events were included (n=67,237) from a literature search through March 2016, of which 12 included alirocumab and only four included evolocumab. They were analyzed together as a class of medications. Three large RCTs published in March 2017 were also included. Of the study participants, 67,237 (30%) were female, 6984 (11%) did not have CVD, and 2513 had familial hypercholesterolemia (FH) (7%). The primary reason for study exclusion was follow-up time less than 24 weeks. Included studies were all industry funded and about one-third of the trials had unclear risk of bias due to insufficient detail on randomization or allocation concealment. Overall, most trials had a low risk of bias with a few exceptions (open-label OSLER trials).

There was moderate quality evidence for the PCSK9 inhibitors in percentage change from baseline of LDL-C at 24 weeks compared to placebo (mean difference in percentage change from baseline of 54%; 95% CI 58.6 to 49.1), compared to ezetimibe (mean difference 30.2%; 95% CI 34.2 to 26.23), and compared to ezetimibe and statins (mean difference 39.20%; 95% CI 56.15 to 22.26). At one year, six trials showed similar results in LDL-lowering compared to statins (-52.9%; 95% CI 60 to 45.7). Additionally, there was moderate quality evidence of a reduction in CVD events compared to placebo (OR 0.86; 95% CI 0.8 to 0.92; ARR 0.9%; NNT 112) from 6 to 36 months of follow up. There was a significant reduction in myocardial infarction (MI) (OR 0.77; 95% CI 0.69 to 0.85) and any stroke (OR 0.76; 95% CI 0.65 to 0.89). The absolute rates of MI and stroke were not provided. There was significant heterogeneity between studies. However, the authors concluded that consistency in direction of effect and differences in magnitude were similar enough to provide clinically relevant treatment effect estimates. Results were consistent when analyzed by the following subgroup populations: gender, age, baseline LDL, history of CVD, and history of diabetes. There was no dose-response seen on LDL-C lowering. Very low quality evidence suggests a stronger protective effect on CV risk compared to ezetimibe and statins (OR 0.45; 95% CI 0.27 to 0.75; ARR 1.1%, NNT 91) with significant uncertainty. There was no significant difference in mortality between PCSK9 inhibitors and placebo (OR 1.02; 95% CI 0.91 to 1.14). There was insufficient data on clinical outcomes to evaluate comparisons to ezetimibe, and data on quality of life were unavailable for all studies. Clinical outcome data comes largely from the FOURIER trial and two trials evaluating bococizumab which was never FDA approved (SPIRE-1 and SPIRE-2). Median follow-up was still less than three years in these large trials, and longer follow up data on efficacy and safety is still needed.

Lastly, low quality evidence shows an increase in adverse events with the PCSK9 inhibitors compared to placebo (OR 1.08; 95% CI 1.04 to 1.12; ARI 1.5%; NNH 67) and compared to ezetimibe and statins (OR 1.18; 95% CI 1.05 to 1.24; ARI 3.7%; NNT 27). There was no significant difference in any one individual adverse event (myalgia, influenza, cancer, elevated creatinine), and the effect of PCSK9 inhibitors on the risk of an event was modest, with changes in risk often less than 1%. The increase in adverse events was largely driven by two trials evaluating bococizumab, which was discontinued due to immunogenicity. There was no significant difference seen in neurological events (OR 1.04; 95% CI 0.88 to 1.24), risk of cancer or type 2 diabetes mellitus, but with limited follow-up duration to detect a difference. The authors concluded that over medium term follow up, PCSK9 inhibitors decrease CVD but may increase the risk of adverse events. Evidence of efficacy and safety compared to active treatments was low to very low quality with short follow-up times and few events. Estimated risk differences suggested only a modest change in absolute risk (less than 1%).

2. Another systematic review evaluated RCTs of alirocumab or evolocumab that reported  $\geq 1$  health outcome (CV events), lipid outcome, or harms.<sup>8</sup> A total of 17 studies were included from a literature search through September 2015. No studies were found to be poor quality. The results based on study population are as follows:
  - a. Heterozygous familial hypercholesterolemia and homozygous familial hypercholesterolemia (HeFH and HoFH): There was low strength evidence that alirocumab resulted in a higher LDL-C reduction compared to placebo (difference in LDL-C change of -8.0% to -57.4%) in HeFH in addition to maximally dosed statin and ezetimibe. No studies were identified with alirocumab in HoFH. There was high strength evidence that evolocumab resulted in a higher LDL-C reduction compared to placebo (difference in LDL-C change of -44.1% to -61.3%) in those with HeFH on a high-intensity statin plus ezetimibe. Lastly, there was low strength evidence that evolocumab achieved a higher LDL-C reduction in those with HoFH on a high intensity statin plus ezetimibe. There was no significant difference in serious adverse events, neurocognitive events, or withdrawals due to adverse events.
  - b. Statin-intolerant: There was no evidence for alirocumab in those who were statin intolerant. There was low strength evidence that evolocumab led to a greater reduction in LDL-C than placebo and that the combination of evolocumab plus ezetimibe led to a greater LDL-C reduction than placebo.
  - c. High CV risk: Moderate strength evidence suggests that alirocumab resulted in a higher proportion of patients reaching a LDL-C < 70 mg/dl than placebo (RR 1.70; 95% CI 1.46 to 1.95) and that there was no difference in serious adverse events. There was high strength evidence that alirocumab resulted in a higher proportion of patients reaching an LDL-C < 70 mg/dl (RR 9.65; 95% CI 7.7-12.0) and no difference in serious adverse events or discontinuations due to adverse events. There was moderate – and low-strength evidence of no difference in adjudicated CV events between alirocumab and placebo at 52 weeks.
3. A systematic review using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was conducted to assess long term safety of the PCSK9 inhibitors.<sup>3</sup> Only trials > 6 months in duration were included. A total of 11 studies (n=10656) were included; the majority including patients with unspecific hypercholesterolemia (7 trials). The risk of bias was assessed using the Cochrane tool and all included studies were determined to be low risk of bias. There was no difference in serious adverse events between PCSK9 inhibitors and standard of care (10.3% vs. 11%, respectively; OR 1.00; 95% CI 0.88 to 1.15). There was no difference in musculoskeletal adverse events with the PCSK9 inhibitors and standard of care (14.2% vs. 12.7%; OR 1.01; 95% CI 0.87 to 1.13) with mild between-study heterogeneity. Neurocognitive events, defined as delirium, cognitive and attention disorders, dementia, disturbances in thinking and mental impairment disorders) was reported in 8 studies and there was also no difference between PCSK9 inhibitors and standard of care (0.8% vs. 0.5%; OR 1.29; 95% CI 0.64 to 2.59) with mild between-study heterogeneity and low rates overall. However, a subgroup analysis using only the two larger outcome trials did demonstrate a significant increase in neurocognitive adverse events (1% vs. 0.4%; OR 2.81; 95% CI 1.32 to 5.99) with PCSK9 inhibitors compared to standard of care with a wide confidence interval.<sup>3</sup> These events were self-reported with no objective analysis.

---

**Guidelines:**

In 2016, the American College of Cardiology (ACC) published the first expert consensus decision pathway on the role of non-statin therapies for LDL-C lowering in the management of atherosclerotic cardiovascular disease (ASCVD) risk. A focused update was published in 2017 to include new evidence on the efficacy and safety of PCSK9 inhibitors, including data from the FOURIER trial.<sup>9</sup> However, this was an expert consensus document meant to provide guidance for clinicians in areas where evidence may be limited or evolving. Since this process did not involve formal systematic reviews, grading of the evidence, or synthesis of evidence it will not be used to make conclusions or recommendations.

The expert group recommends consideration of a PCSK9 inhibitor or ezetimibe for the following populations: 1) patients without clinical ASCVD and with baseline LDL-C greater than or equal to 190 mg/dl on statin therapy who do not achieve at least 50% LDL-C reduction, 2) patients with clinical ASCVD and baseline LDL-C greater than or equal to 190 mg/dl who do not achieve at least 50% LDL-C reduction on high intensity statin, 3) patients with clinical ASCVD and comorbidities (recent ASCVD, chronic kidney disease, symptomatic heart failure, current daily cigarette smoking, symptomatic peripheral artery disease, etc.) who do not achieve at least 50% LDL-C reduction on maximally tolerated statin therapy, 4) patients with stable clinical ASCVD without comorbidities on maximally tolerated statin AND ezetimibe therapy who do not achieve at least 50% LDL-C reduction.

**Safety Updates:**

None

**New formulations or indications:**

On December 1, 2017 FDA approved evolocumab to prevent MI, stroke, and coronary revascularization in adults with established CVD.<sup>6</sup> Approval was based on FDA review of clinical outcome data from the FOURIER Trial (**Table 2**). Evolocumab is now also approved for primary hyperlipidemia (including heterozygous familial hypercholesterolemia).

**Clinical Trials Evaluating CV outcomes:***Evolocumab*

The FOURIER trial is the first published trial that evaluated CV clinical outcomes as the primary outcome (**Table 2**).<sup>2</sup> It is a parallel group, double-blind, very large good quality RCT (n=27,654) that included adults with history of clinically evident CVD with LDL-C greater than or equal to 70 mg/dl or non-high density lipoprotein cholesterol (HDL-C) of at least 100 mg/dl with at least one major risk factor (diabetes, smoker, age ≥65 years, recent acute coronary syndrome [ACS]) or two minor risk factors (coronary revascularization, residual coronary artery disease [CAD], metabolic syndrome, LDL-C ≥130 mg/dl). Clinically evident ASCVD was defined as a history of MI, ischemic stroke, or symptomatic peripheral artery disease. Participants were randomized to evolocumab plus moderate- or high-intensity statin background therapy or placebo plus statin background therapy with or without ezetimibe. Patients with heart failure with reduced ejection fraction, uncontrolled hypertension, ventricular tachycardia, homozygous familial hypercholesterolemia (HoFH), or requiring LDL or plasma apheresis, estimated glomerular filtration rate (eGFR) less than 20ml/min, active liver disease, or elevated creatinine kinase (CK) were excluded from the trial. The primary outcome was a CV composite outcome including CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization. There was a low risk of bias overall, but was funded and supported by Amgen.

Baseline characteristics were similar between the two groups. The majority of the participants were from Europe (62.9%), and only 16.6% were from North America. Approximately 80% of participants had a history of a MI and 36% had diabetes at baseline. Only around 5% of those in each group were on ezetimibe,

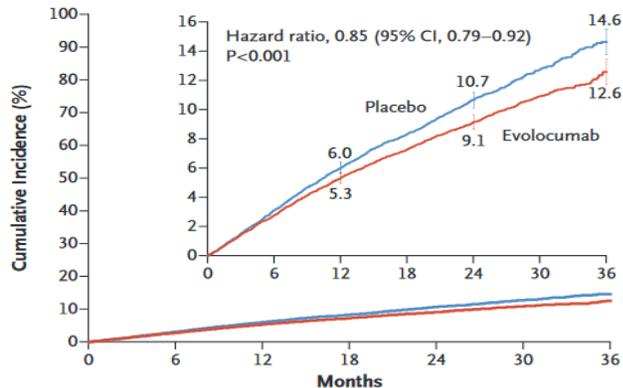
and almost 70% were on high intensity statin. The study population had a relatively well-controlled lipid profile with a median LDL-C of 92 mg/dl and triglycerides of 133 mg/dl. The median duration of follow-up was 26 months.

Consistent with other trials, LDL-C was significantly reduced with evolocumab compared to placebo, with a least-squares mean reduction of 59% compared to placebo (95% CI 55 to 57). At 48 weeks, LDL-C was reduced to less than or equal to 70 mg/dl in 87% of evolocumab-treated patients compared to 18% in the placebo group (ARR 69%; NNT 2). The median LDL-C after 48 weeks of evolocumab was 30 mg/dl. The primary CV composite outcome was significantly reduced with evolocumab compared to placebo (9.8% vs. 11.3%; HR 0.85; 95% CI 0.79 to 0.92; ARR 1.5%; NNT 67) with a modest absolute risk reduction of 1.5%. There was also a significant reduction in the composite of CV death, MI or stroke (5.9% vs. 7.4%; HR 0.80; 95% CI 0.73 to 0.88; ARR 1.5%; NNT 67). The magnitude of risk reduction increased over time beyond the first year (**Figure 1**). There was no significant reduction in individual outcomes including CV death or overall mortality, and there was numerically a higher rate of overall mortality (3.2% vs. 3.1%) and CV death (1.8% vs. 1.7%) in the evolocumab group compared to placebo. The primary composite outcome was largely driven by a difference in non-fatal events (MI, stroke, or coronary revascularization).

Results were consistent across subgroups, including age, sex, baseline atherosclerotic disease and baseline LDL-C. Subgroup analysis based on blood pressure or diabetes was not included. There was no significant difference in the primary CV outcome seen in those participants who were on ezetimibe. However, overall numbers were small in this subgroup and it is difficult to make any conclusive statement from this finding.

**Figure 1: Effect on Primary Outcome over Time<sup>2</sup>**

**A Primary Efficacy End Point**



No. at Risk	0	6	12	18	24	30	36
Placebo	13,780	13,278	12,825	11,871	7610	3690	686
Evolocumab	13,784	13,351	12,939	12,070	7771	3746	689

There was no significant difference in the percentage of patients with serious adverse events (24.8% vs. 24.7%) or those withdrawing due to adverse events (1.6% vs. 1.5%), with evolocumab versus placebo, respectively. There was no difference between myalgia, cataract, neurocognitive adverse events, or hemorrhagic stroke. Injection site reactions occurred more frequently in the evolocumab group compared to placebo (2.1% vs. 1.6%). There was no significant difference in new-onset diabetes (HR 1.05; 95% CI 0.94 to 1.17).

## Alirocumab

The effect of alirocumab on CV events is being studied in the ODYSSEY OUTCOMES trial and is estimated to be completed in December 2017.<sup>10</sup>

**Table 2: Summary of Clinical Trials Evaluating Clinical CV Outcomes**

Study	Comparison	Population	Primary Outcome	Results
FOURIER trial <sup>2</sup>  RCT, DB  48 weeks, 26 months follow-up	Evolocumab 140 mg Q2W or 420 mg QMO add on  Vs.  Placebo injection add on	Adults with history of clinically evidence CVD at high risk for a recurrent event with LDL-C ≥ 70 mg/dl or non-HDL-C ≥ 100 mg/dl (n=27,654)	Major CV events (CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization)	<p><u>Major CV events</u> Evolocumab: 1,344 (9.8%) Placebo: 1,563 (11.3%) HR 0.85; 95% CI 0.79 to 0.92 ARR 1.5%; NNT 67</p> <p><u>CV death, MI or stroke</u> Evolocumab: 816 (5.9%) Placebo: 1013 (7.4%) HR 0.80; 95% CI 0.73 to 0.88 ARR 1.5%; NNT 67</p> <p><u>Serious Adverse Events</u> Evolocumab: 3410 (24.8%) Placebo: 3404 (24.7%)</p> <p><u>Withdrawals due to Adverse Events:</u> Evolocumab: 628 (4.6%) Placebo: 581 (4.2%)</p>

Abbreviations: DB = double-blind; CVD = cardiovascular disease; CV = cardiovascular; LDL-C = low density lipoprotein cholesterol; MI = myocardial infarction; Q2W = every 2 weeks; QMO = every month; RCT = randomized controlled trial.

### Additional Randomized Controlled Trials:

A total of 30 citations were manually reviewed from the literature search. After manual review, 24 trials were excluded because of wrong study design (observational), outcome studied, or published prior to dates of interest. The remaining 6 trials are briefly described in the table below. Full abstracts are included in **Appendix 2**.

**Table 3. Description of Additional Randomized Clinical Trials.**

Study	Comparison	Population	Primary Outcome	Results	Quality Comments
ODYSSEY COMBO II <sup>11</sup>  DB, RCT, PG  104 weeks	Alirocumab 75 mg Q2 weeks titrated up to 150 mg Q2W+ ezetimibe 10 mg daily  Vs.  Placebo + Ezetimibe 10 mg daily	Participants with hypercholesterolemia, established CVD or CVD risk equivalents (e.g. chronic kidney disease), and on a maximally tolerated dose of statin	Change from baseline in LDL-C	<p><u>Change from baseline in LDL-C over 2 years:</u> Alirocumab: 49% Placebo: 17% LS mean difference -32%; 95% CI -38 to -26 P&lt;0.0001</p> <p><u>Discontinuations due to AE:</u> Alirocumab: 36(7.5%) Placebo: 13 (5.4%)</p>	Low risk of bias Funded by Sanofi and Regeneron Not powered for analysis of CV events

	Both add-on to statins	(n=720)			
ODYSSEY OPTIONS II <sup>12</sup>  DB, PC, PG, RCT  24 weeks	Alirocumab 75 mg Q2W titrated up to 150 mg Q2W add-on  Vs.  Ezetimibe 10 mg add-on  Vs.  Additional 10-20 mg rosuvastatin	History of CVD and LDL-C levels $\geq$ 70 mg/dl, or CVD risk factors and LDL-C $\geq$ 100 mg/dl receiving rosuvastatin 10 or 20 mg/day (n=305)	Change from baseline in LDL-C at week 24	<u>Change from baseline in LDL-C at week 24:</u> Alirocumab: 50.6% Ezetimibe: 14.4% Double-dose rosuvastatin: 16.4% P<0.0001 favoring alirocumab versus all other comparisons	Low risk of bias Funded by Sanofi and Regeneron
ODYSSEY HIGH FH <sup>13</sup>  DB, PG, RCT  78 weeks	Alirocumab 150 mg Q2 weeks vs. placebo  Both add-on to statin and possible other lipid lowering therapies	HeFH on maximally tolerated dose of statin with LDL-C $\geq$ 160 mg/dl	Change from baseline in LCL-C at week 24	<u>Change from baseline in LDL-C at week 24:</u> Alirocumab: -45.7% Placebo: -6.6% Difference of -39.1%; p<0.0001	Low risk of bias Funded by Sanofi and Regeneron
EBBINGHAUSE <sup>5</sup>  Subgroup analysis of FOURIER Trial	Evolocumab 140 mg Q2W or 420 QMo + statin  Vs.  Placebo + statin therapy	ASCVD and LDL $\geq$ 70 mg/dl on moderate- or high-intensity statin  Patients with dementia or cognitive dysfunction at baseline were excluded	Mean change from baseline in spatial working memory (SWM) index of executive function	<u>Mean change in SWM:</u> Evolocumab: -0.21 Placebo: -0.29 P<0.001 for noninferiority P=0.85 for superiority  <u>Cognitive adverse events:</u> Evolocumab: 11 (1.9%) Placebo: 8 (1.3%) P=NS	Short follow up to detect differences in cognitive function High risk patients for cognitive impairment excluded Tool used is validated but not used in clinical practice Funded by Amgen
ODYSSEY DM-INSULIN <sup>14</sup>  RCT, DB, PC, PG  24 weeks	Alirocumab titrated up to 150 mg Q2W  Vs.  Placebo	Insulin treated T2D or T1D and established ASCVD or at least one CV risk factor with LDL $\geq$ 70 mg/dl on maximally tolerated statin therapy	Change from baseline in LCL-C at week 24	<u>Change from baseline in LCL-C at week 24</u> Alirocumab: -48.2% Placebo: +0.8% Difference -49% (p<0.0001)	Extensive exclusion criteria Funded by Sanofi and Regeneron

GLAGOV <sup>15</sup> DB, RCT, PC 76 weeks	Evolocumab 420 mg QMO Vs. Placebo  Plus statin	Participants with angiographic coronary disease (n=968)	Nominal change in percent atheroma volume (PAV) from baseline	<u>Change in PAV from baseline</u> Evolocumab: -0.95% Placebo: +0.05% Difference -1.0%; 95% CI -1.8% to -0.64%; p<0.01	Unknown clinical significance of measured outcome Funded by Amgen
Ray et al. <sup>16</sup> Pooled analysis of 10 ODYSSEY trials	Alirocumab 75/150 mg Q 2 weeks Vs. Control On background statin	Participants with ASCVD or high CV Risk (3182 taking alirocumab, 1174 taking placebo, 618 taking ezetimibe).	Relationship between LDL and MACE	For every 39 mg/dL lower achieved LDL-C, the risk of MACE appeared to be 24% lower (adjusted hazard ratio, 0.76; 95% CI, 0.63–0.91; P=0.0025)	Post-hoc analyses

Abbreviations: AE = adverse events; ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; DB = double blind; CI = confidence interval; CV = cardiovascular; HDL-C = high density lipoprotein cholesterol; HEFH = heterozygous familial hypercholesterolemia; LDL-C = low density lipoprotein cholesterol; MC = multi-centered; mg = milligram; MACE = major adverse cardiovascular events; MI = myocardial infarction; PC = placebo controlled; PG = parallel group; Q2W = every 2 weeks; QMO = every month; RCT = randomized controlled trial; T1D = type 1 diabetes; T2D = type 2 diabetes.

## References:

1. Schmidt AF, Pearce LS, Wilkins JT, Overington JP, Hingorani AD, Casas JP. PCSK9 monoclonal antibodies for the primary and secondary prevention of cardiovascular disease. *The Cochrane database of systematic reviews*. 2017;4:Cd011748.
2. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. *New England Journal of Medicine*.376(18):1713-1722.
3. Khan AR, Bavishi C, Riaz H, et al. Increased Risk of Adverse Neurocognitive Outcomes With Proprotein Convertase Subtilisin-Kexin Type 9 Inhibitors. *Circulation Cardiovascular Quality & Outcomes*. 2017;10(1).
4. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63(25 Pt B):2889-2934.
5. Giugliano RP, Mach F, Zavitz K, et al. Cognitive Function in a Randomized Trial of Evolocumab. *New England Journal of Medicine*.377(7):633-643.
6. Repatha® U.S. Prescribing Information. Amgen.
7. Praluent® U.S. Prescribing Information. Sanofi
8. McDonagh M, Peterson K, Holzhammer B, Fazio S. A Systematic Review of PCSK9 Inhibitors Alirocumab and Evolocumab. *Journal of Managed Care & Specialty Pharmacy*.22(6):641-653q.
9. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol*. 2017;70(14):1785-1822.
10. Schwartz GG, Bessac L, Berdan LG, et al. Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes: rationale and design of the ODYSSEY outcomes trial. *Am Heart J*. 2014;168(5):682-689.
11. El Shahawy M, Cannon CP, Blom DJ, et al. Efficacy and Safety of Alirocumab Versus Ezetimibe Over 2 Years (from ODYSSEY COMBO II). *American Journal of Cardiology*.120(6):931-939.
12. Farnier M, Jones P, Severance R, et al. Efficacy and safety of adding alirocumab to rosuvastatin versus adding ezetimibe or doubling the rosuvastatin dose in high cardiovascular-risk patients: The ODYSSEY OPTIONS II randomized trial. *Atherosclerosis*.244:138-146.
13. Ginsberg HN, Rader DJ, Raal FJ, et al. Efficacy and Safety of Alirocumab in Patients with Heterozygous Familial Hypercholesterolemia and LDL-C of 160 mg/dl or Higher. *Cardiovascular Drugs & Therapy*.30(5):473-483.
14. Leiter LA, Cariou B, Muller-Wieland D, et al. Efficacy and safety of alirocumab in insulin-treated individuals with type 1 or type 2 diabetes and high cardiovascular risk: The ODYSSEY DM-INSULIN randomized trial. *Diabetes, obesity & metabolism*. 2017;19(12):1781-1792.
15. Nicholls SJ, Puri R, Anderson T, et al. Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients: The GLAGOV Randomized Clinical Trial. *JAMA*.316(22):2373-2384.
16. Ray KK, Ginsberg HN, Davidson MH, et al. Reductions in Atherogenic Lipids and Major Cardiovascular Events: A Pooled Analysis of 10 ODYSSEY Trials Comparing Alirocumab With Control. *Circulation*.134(24):1931-1943.

---

**Appendix 1:** Current Status of PDL Class.

**PCSK9 Inhibitors**

ROUTE	FORMULATION	BRAND	GENERIC	PDL
SQ	PEN INJCTR	PRALUENT PEN	ALIROCUMAB	N
SQ	WEAR INJCT	REPATHA PUSHTRONEX	EVOLOCUMAB	N
SQ	PEN INJCTR	REPATHA SURECLICK	EVOLOCUMAB	N
SQ	SYRINGE	REPATHA SYRINGE	EVOLOCUMAB	N

---

## Appendix 2: Abstracts of RCTs

1. El Shahawy M, Cannon CP, Blom DJ, et al. Efficacy and Safety of Alirocumab Versus Ezetimibe Over 2 Years (from ODYSSEY COMBO II). *Am J Cardiol*. 2017 Sep 15;120(6):931-939. doi: 10.1016/j.amjcard.2017.06.023. Epub 2017 Jun 28.

### Abstract

The proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab has been shown to substantially reduce low-density lipoprotein cholesterol (LDL-C). Demonstrating whether efficacy and safety are maintained over a long duration of exposure is vital for clinical decision-making. The COMBO II trial compared the efficacy and safety of alirocumab versus ezetimibe over 2 years. A prespecified first analysis was reported at 52 weeks. Here we report the final end-of-study data (on-treatment) and evaluate post hoc the safety profile with longer versus shorter duration of alirocumab exposure. Patients (n = 720) on maximally tolerated statin dose were treated with alirocumab (75/150 mg every 2 weeks) or ezetimibe (10 mg/day). Overall mean adherence for both treatment groups during the first and second year was >97%. At 2 years, LDL-C was reduced by 49% (alirocumab) versus 17% (ezetimibe;  $p < 0.0001$ ), and LDL-C <70 mg/dl was achieved by 73% of alirocumab-treated versus 40% of ezetimibe-treated patients. Overall safety was similar in both treatment groups at 2 years and during the first versus the second year. Local injection-site reactions were reported by 2.5% (alirocumab) versus 0.8% (ezetimibe) during the first year, and 0.2% versus 0.5% during the second year, indicating early occurrence during prolonged alirocumab exposure. Two consecutive calculated LDL-C values <25 mg/dl were observed in 28% of alirocumab-treated patients (vs 0.4% with ezetimibe). Persistent anti-drug antibody responses were observed in 1.3% (6 of 454) of alirocumab-treated versus 0.4% (1 of 231) of ezetimibe-treated patients. Neutralizing antibodies (that inhibit binding in vitro) were observed in 1.5% (7 of 454) of alirocumab-treated patients (0 with ezetimibe), mostly at isolated time points. Alirocumab sustained substantial LDL-C reductions and was well tolerated up to 2 years in the COMBO II trial.

2. Farnier M, Jones P, Severance R, Aversa M, Steinhagen-Thiessen E. Efficacy and safety of adding alirocumab to rosuvastatin versus adding ezetimibe or doubling the rosuvastatin dose in high cardiovascular-risk patients: The ODYSSEY OPTIONS II randomized trial. *Atherosclerosis*. 2016 Jan;244:138-46. doi: 10.1016/j.atherosclerosis.2015.11.010. Epub 2015 Nov 14.

### OBJECTIVE:

To compare lipid-lowering efficacy of adding alirocumab to rosuvastatin versus other treatment strategies (NCT01730053).

### METHODS:

Patients receiving baseline rosuvastatin regimens (10 or 20 mg) were randomized to: add-on alirocumab 75 mg every-2-weeks (Q2W) (1-mL subcutaneous injection via pre-filled pen); add-on ezetimibe 10 mg/day; or double-dose rosuvastatin. Patients had cardiovascular disease (CVD) and low-density lipoprotein cholesterol (LDL-C)  $\geq 70$  mg/dL (1.8 mmol/L) or CVD risk factors and LDL-C  $\geq 100$  mg/dL (2.6 mmol/L). In the alirocumab group, dose was blindly increased at Week 12 to 150 mg Q2W (also 1-mL volume) in patients not achieving their LDL-C target. Primary endpoint was percent change in calculated LDL-C from baseline to 24 weeks (intent-to-treat).

### RESULTS:

305 patients were randomized. In the baseline rosuvastatin 10 mg group, significantly greater LDL-C reductions were observed with add-on alirocumab (-50.6%) versus ezetimibe (-14.4%;  $p < 0.0001$ ) and double-dose rosuvastatin (-16.3%;  $p < 0.0001$ ). In the baseline rosuvastatin 20 mg group, LDL-C reduction with add-on

alirocumab was -36.3% compared with -11.0% with ezetimibe and -15.9% with double-dose rosuvastatin ( $p = 0.0136$  and  $0.0453$ , respectively; pre-specified threshold for significance  $p < 0.0125$ ). Overall, ~80% alicumab patients were maintained on 75 mg Q2W. Of alicumab-treated patients, 84.9% and 66.7% in the baseline rosuvastatin 10 and 20 mg groups, respectively, achieved risk-based LDL-C targets. Treatment-emergent adverse events occurred in 56.3% of alicumab patients versus 53.5% ezetimibe and 67.3% double-dose rosuvastatin (pooled data).

#### CONCLUSIONS:

The addition of alicumab to rosuvastatin provided incremental LDL-C lowering versus adding ezetimibe or doubling the rosuvastatin dose.

3. Ginsberg HN, Rader DJ, Raal FJ, Guyton JR, et al. Efficacy and Safety of Alirocumab in Patients with Heterozygous Familial Hypercholesterolemia and LDL-C of 160 mg/dl or Higher. *Cardiovasc Drugs Ther.* 2016 Oct;30(5):473-483.

#### PURPOSE:

Even with statins and other lipid-lowering therapy (LLT), many patients with heterozygous familial hypercholesterolemia (heFH) continue to have elevated low-density lipoprotein cholesterol (LDL-C) levels. ODYSSEY HIGH FH (NCT01617655) assessed the efficacy and safety of alicumab, a proprotein convertase subtilisin/kexin type 9 monoclonal antibody, versus placebo in patients with heFH and LDL-C  $\geq 160$  mg/dl despite maximally tolerated statin  $\pm$  other LLT.

#### METHODS:

Patients were randomized to subcutaneous alicumab 150 mg or placebo every 2 weeks (Q2W) for 78 weeks. The primary endpoint was percent change in LDL-C from baseline to week 24.

#### RESULTS:

Mean baseline LDL-C levels were 196.3 mg/dl in the alicumab ( $n = 71$ ) and 201.0 mg/dl in the placebo groups ( $n = 35$ ). Significant mean (standard error [SE]) reductions in LDL-C from baseline to week 24 were observed with alicumab ( $-45.7 [3.5] \%$ ) versus placebo ( $-6.6 [4.9] \%$ ), a difference of  $-39.1 (6.0) \%$  ( $P < 0.0001$ ). Absolute mean (SE) LDL-C levels were reduced from baseline by 90.8 (6.7) mg/dl with alicumab at week 24, with reductions maintained to week 78. Treatment-emergent adverse events were generally comparable between groups. Injection-site reactions were more frequent in the alicumab group (8.3 %) versus placebo (5.7 %); most were mild in severity and did not result in study medication discontinuation.

#### CONCLUSIONS:

In patients with heFH and very high LDL-C baseline levels despite maximally tolerated statin  $\pm$  other LLT, alicumab 150 mg Q2W demonstrated significant reductions in LDL-C levels with 41 % of patients achieving predefined LDL-C goals. Alicumab was generally well tolerated.

4. Giugliano RP1, Mach F, Zavitz K, Kurtz C, Im K, et al. Cognitive Function in a Randomized Trial of Evolocumab. *N Engl J Med.* 2017 Aug 17;377(7):633-643. doi: 10.1056/NEJMoa1701131.

#### Abstract

Background Findings from clinical trials of proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors have led to concern that these drugs or the low levels of low-density lipoprotein (LDL) cholesterol that result from their use are associated with cognitive deficits. Methods In a subgroup of patients from a randomized, placebo-controlled trial of evolocumab added to statin therapy, we prospectively assessed cognitive function using the Cambridge Neuropsychological Test Automated Battery. The primary end point was the score on the spatial working memory strategy index of executive function (scores

range from 4 to 28, with lower scores indicating a more efficient use of strategy and planning). Secondary end points were the scores for working memory (scores range from 0 to 279, with lower scores indicating fewer errors), episodic memory (scores range from 0 to 70, with lower scores indicating fewer errors), and psychomotor speed (scores range from 100 to 5100 msec, with faster times representing better performance). Assessments of cognitive function were performed at baseline, week 24, yearly, and at the end of the trial. The primary analysis was a noninferiority comparison of the mean change from baseline in the score on the spatial working memory strategy index of executive function between the patients who received evolocumab and those who received placebo; the noninferiority margin was set at 20% of the standard deviation of the score in the placebo group. Results A total of 1204 patients were followed for a median of 19 months; the mean ( $\pm$ SD) change from baseline over time in the raw score for the spatial working memory strategy index of executive function (primary end point) was  $-0.21\pm 2.62$  in the evolocumab group and  $-0.29\pm 2.81$  in the placebo group ( $P < 0.001$  for noninferiority;  $P = 0.85$  for superiority). There were no significant between-group differences in the secondary end points of scores for working memory (change in raw score,  $-0.52$  in the evolocumab group and  $-0.93$  in the placebo group), episodic memory (change in raw score,  $-1.53$  and  $-1.53$ , respectively), or psychomotor speed (change in raw score,  $5.2$  msec and  $0.9$  msec, respectively). In an exploratory analysis, there were no associations between LDL cholesterol levels and cognitive changes. Conclusions In a randomized trial involving patients who received either evolocumab or placebo in addition to statin therapy, no significant between-group difference in cognitive function was observed over a median of 19 months

5. Leiter LA, Cariou B, Müller-Wieland D, et al. and safety of alirocumab in insulin-treated individuals with type 1 or type 2 diabetes and high cardiovascular risk: The ODYSSEY DM-INSULIN randomized trial. *Diabetes Obes Metab.* 2017 Dec;19(12):1781-1792. doi: 10.1111/dom.13114. Epub 2017 Oct 10.

#### AIMS:

To investigate the efficacy and safety of alirocumab in participants with type 2 (T2D) or type 1 diabetes (T1D) treated with insulin who have elevated LDL cholesterol levels despite maximally tolerated statin therapy.

#### METHODS:

Participants at high cardiovascular risk with T2D ( $n = 441$ ) or T1D ( $n = 76$ ) and LDL cholesterol levels  $\geq 1.8$  mmol/L ( $\geq 70$  mg/dL) were randomized 2:1 to alirocumab:placebo administered subcutaneously every 2 weeks, for 24 weeks' double-blind treatment. Alirocumab-treated participants received 75 mg every 2 weeks, with blinded dose increase to 150 mg every 2 weeks at week 12 if week 8 LDL cholesterol levels were  $\geq 1.8$  mmol/L. Primary endpoints were percentage change in calculated LDL cholesterol from baseline to week 24, and safety assessments.

#### RESULTS:

Alirocumab reduced LDL cholesterol from baseline to week 24 by a mean  $\pm$  standard error of  $49.0\% \pm 2.7\%$  and  $47.8\% \pm 6.5\%$  vs placebo (both  $P < .0001$ ) in participants with T2D and T1D, respectively. Significant reductions were observed in non-HDL cholesterol ( $P < .0001$ ), apolipoprotein B ( $P < .0001$ ) and lipoprotein (a) ( $P \leq .0039$ ). At week 24, 76.4% and 70.2% of the alirocumab group achieved LDL cholesterol  $< 1.8$  mmol/L in the T2D and T1D populations ( $P < .0001$ ), respectively. Glycated haemoglobin and fasting plasma glucose levels remained stable for the study duration. Treatment-emergent adverse events were observed in 64.5% of alirocumab- vs 64.1% of placebo-treated individuals (overall population).

#### CONCLUSIONS:

Alirocumab produced significant LDL cholesterol reductions in participants with insulin-treated diabetes regardless of diabetes type, and was generally well tolerated. Concomitant administration of alirocumab and insulin did not raise any safety concerns

6. Nicholls SJ, Puri R, Anderson T, Ballantyne CM, et al. Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients: The GLAGOV Randomized Clinical Trial. *JAMA*. 2016 Dec 13;316(22):2373-2384. doi: 10.1001/jama.2016.16951.

**IMPORTANCE:**

Reducing levels of low-density lipoprotein cholesterol (LDL-C) with intensive statin therapy reduces progression of coronary atherosclerosis in proportion to achieved LDL-C levels. Proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors produce incremental LDL-C lowering in statin-treated patients; however, the effects of these drugs on coronary atherosclerosis have not been evaluated.

**OBJECTIVE:**

To determine the effects of PCSK9 inhibition with evolocumab on progression of coronary atherosclerosis in statin-treated patients.

**DESIGN, SETTING, AND PARTICIPANTS:**

The GLAGOV multicenter, double-blind, placebo-controlled, randomized clinical trial (enrollment May 3, 2013, to January 12, 2015) conducted at 197 academic and community hospitals in North America, Europe, South America, Asia, Australia, and South Africa and enrolling 968 patients presenting for coronary angiography.

**INTERVENTIONS:**

Participants with angiographic coronary disease were randomized to receive monthly evolocumab (420 mg) (n = 484) or placebo (n = 484) via subcutaneous injection for 76 weeks, in addition to statins.

**MAIN OUTCOMES AND MEASURES:**

The primary efficacy measure was the nominal change in percent atheroma volume (PAV) from baseline to week 78, measured by serial intravascular ultrasonography (IVUS) imaging. Secondary efficacy measures were nominal change in normalized total atheroma volume (TAV) and percentage of patients demonstrating plaque regression. Safety and tolerability were also evaluated.

**RESULTS:**

Among the 968 treated patients (mean age, 59.8 years [SD, 9.2]; 269 [27.8%] women; mean LDL-C level, 92.5 mg/dL [SD, 27.2]), 846 had evaluable imaging at follow-up. Compared with placebo, the evolocumab group achieved lower mean, time-weighted LDL-C levels (93.0 vs 36.6 mg/dL; difference, -56.5 mg/dL [95% CI, -59.7 to -53.4]; P < .001). The primary efficacy parameter, PAV, increased 0.05% with placebo and decreased 0.95% with evolocumab (difference, -1.0% [95% CI, -1.8% to -0.64%]; P < .001). The secondary efficacy parameter, normalized TAV, decreased 0.9 mm<sup>3</sup> with placebo and 5.8 mm<sup>3</sup> with evolocumab (difference, -4.9 mm<sup>3</sup> [95% CI, -7.3 to -2.5]; P < .001). Evolocumab induced plaque regression in a greater percentage of patients than placebo (64.3% vs 47.3%; difference, 17.0% [95% CI, 10.4% to 23.6%]; P < .001 for PAV and 61.5% vs 48.9%; difference, 12.5% [95% CI, 5.9% to 19.2%]; P < .001 for TAV).

**CONCLUSIONS AND RELEVANCE:**

Among patients with angiographic coronary disease treated with statins, addition of evolocumab, compared with placebo, resulted in a greater decrease in PAV after 76 weeks of treatment. Further studies are needed to assess the effects of PCSK9 inhibition on clinical outcomes.

7. Ray KK, Ginsberg HN, Davidson MH, et al. Reductions in Atherogenic Lipids and Major Cardiovascular Events: A Pooled Analysis of 10 ODYSSEY Trials Comparing Alirocumab with Control. *Circulation*. 2016 Dec 13;134(24):1931-1943. Epub 2016 Oct 24.

**BACKGROUND:**

A continuous relationship between reductions in low-density lipoprotein cholesterol (LDL-C) and major adverse cardiovascular events (MACE) has been observed in statin and ezetimibe outcomes trials down to achieved levels of 54 mg/dL. However, it is uncertain whether this relationship extends to LDL-C levels <50

mg/dL. We assessed the relationship between additional LDL-C, non-high-density lipoprotein cholesterol, and apolipoprotein B100 reductions and MACE among patients within the ODYSSEY trials that compared alirocumab with controls (placebo/ezetimibe), mainly as add-on therapy to maximally tolerated statin.

#### METHODS:

Data were pooled from 10 double-blind trials (6699 patient-years of follow-up). Randomization was to alirocumab 75/150 mg every 2 weeks or control for 24 to 104 weeks, added to background statin therapy in 8 trials. This analysis included 4974 patients (3182 taking alirocumab, 1174 taking placebo, 618 taking ezetimibe). In a post hoc analysis, the relationship between average on-treatment lipid levels and percent reductions in lipids from baseline were correlated with MACE (coronary heart disease death, nonfatal myocardial infarction, ischemic stroke, or unstable angina requiring hospitalization) in multivariable analyses.

#### RESULTS:

Overall, 33.1% of the pooled cohort achieved average LDL-C <50 mg/dL (44.7%-52.6% allocated to alirocumab, 6.5% allocated to ezetimibe, and 0% allocated to placebo). In total, 104 patients experienced MACE (median time to event, 36 weeks). For every 39 mg/dL lower achieved LDL-C, the risk of MACE appeared to be 24% lower (adjusted hazard ratio, 0.76; 95% confidence interval, 0.63-0.91; P=0.0025). Percent reductions in LDL-C from baseline were inversely correlated with MACE rates (hazard ratio, 0.71; 95% confidence interval, 0.57-0.89 per additional 50% reduction from baseline; P=0.003). Strengths of association materially similar to those described for LDL-C were observed with achieved non-high-density lipoprotein cholesterol and apolipoprotein B100 levels or percentage reductions.

#### CONCLUSIONS:

In a post hoc analysis from 10 ODYSSEY trials, greater percentage reductions in LDL-C and lower on-treatment LDL-C were associated with a lower incidence of MACE, including very low levels of LDL-C (<50 mg/dL). These findings require further validation in the ongoing prospective ODYSSEY OUTCOMES trial.

### **Appendix 3: Medline Search Strategy**

Ovid MEDLINE(R) without Revisions 1996 to November week 4, 2017

1 evolocumab223

2 alirocumab.mp 272

3 PCSK9 inhibitors.mp 290

4 1 or 2 or 3

5 Stroke/ or Cardiovascular Diseases/ or Coronary Disease/ or Myocardial Infarction/ or Coronary Artery Disease/ 545407

6 4 and 5 and 7

limit 14 to (humans and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews) and last 3 years)30

## PCSK9 Inhibitors

**Goal:**

- Restrict use of PCSK9 inhibitors to populations in which the drugs have demonstrated efficacy.

**Length of Authorization:**

- Up to 12 months

**Requires PA:**

- All PCSK9 inhibitors

**Covered Alternatives:**

- Preferred alternatives listed at [www.orpdl.org/drugs/](http://www.orpdl.org/drugs/)

Approval Criteria		
1. Is this a request for renewal of a previously approved prior authorization?	Yes: Go to Renewal Criteria	No: Go to #2
2. What diagnosis is being treated?	Record ICD10 code; go to #3	

## Approval Criteria

3. Does the patient have clinical atherosclerotic cardiovascular disease, defined as documented history of  $\geq 1$  of the following:
- Myocardial infarction
  - Unstable angina
  - Coronary revascularization procedure (PCI or CABG)
  - Diagnosis of clinically significant coronary heart disease by coronary angiography, stress test using treadmill, stress echocardiography or nuclear imaging

Or a coronary heart disease (CHD) risk-equivalent, defined as documented history of  $\geq 1$  of the following:

- Peripheral arterial disease
- Ischemic stroke of atherothrombotic origin
- Chronic kidney disease (CrCl 30-60 mL/min)
- Diabetes mellitus PLUS  $\geq 2$  additional risk factors:
  - Hypertension; ankle-brachial index  $\leq 0.90$ ; micro- or macro-albuminuria; retinopathy; or family history of early coronary heart disease?

Yes: Go to #4

No: Go to #8

## Approval Criteria

<p>4. Has the patient taken a daily high-intensity statin (see table below) and ezetimibe 10 mg daily for at least 12 months with &lt;50% LDL-C reduction?</p> <p>Prescriber to submit chart documentation of:</p> <ol style="list-style-type: none"> <li>1) Doses and dates initiated of statin and ezetimibe;</li> <li>2) Baseline LDL-C (untreated);</li> <li>3) Recent LDL-C (within last 12 weeks).</li> </ol>	<p>Yes: Confirm documentation; go to #5</p> <ol style="list-style-type: none"> <li>1. Statin: Dose: Date Initiated:</li> <li>2. Ezetimibe 10 mg daily Date Initiated:</li> </ol> <p>Baseline LDL-C _____ mg/dL Date: _____</p> <p>Recent LDL-C _____ mg/dL Date: _____</p>	<p>No: Go to #6</p>
<p>5. Is the patient adherent with a high-intensity statin and ezetimibe?</p>	<p>Yes: Approve for up to 12 months</p> <p>Note: pharmacy profile may be reviewed to verify &gt;80% adherence (both lipid-lowering prescriptions refilled 5 months' supply in last 6 months)</p>	<p>No: Pass to RPh; deny for medical appropriateness</p>
<p>6. Does the patient have a history of rhabdomyolysis caused by a statin; or alternatively, a history of creatinine kinase (CK) levels &gt;10-times upper limit of normal with muscle symptoms determined to be caused by a statin?</p> <p>Note: Prescriber must provide chart documentation of diagnosis or CK levels. A recent LDL-C level (within last 12 weeks) must also be submitted.</p>	<p>Yes: Confirm chart documentation of diagnosis or labs and approve for up to 12 months</p> <p>Recent LDL-C _____ mg/dL Date: _____</p>	<p>No: Go to #7</p>

## Approval Criteria

7. Is there chart documentation the patient experienced persistent myalgia or myopathy on 3 separate trials (each trial  $\geq 8$  weeks' duration) of moderate- or high-intensity statin (see table below), separated by an adequate washout period of  $\geq 2$  weeks?

Note: Prescriber must provide chart documentation of myalgia/myopathy from each statin trial and provide chart documentation of recent LDL-C (within last 12 weeks).

Yes: Document statin trials and approve for up to 12 months

1. Statin:  
Dose:  
Date Initiated:  
Date D/C:  
Cause of D/C:

2. Statin:  
Dose:  
Date Initiated:  
Date D/C:  
Cause of D/C:

3. Statin:  
Dose:  
Date Initiated:  
Date D/C:  
Cause of D/C:

Recent LDL-C \_\_\_\_\_ mg/dL  
Date: \_\_\_\_\_

No: Pass to RPh; deny for medical appropriateness.

7.8. Does the patient have a diagnosis of homozygous or heterozygous familial hypercholesterolemia and already takes a maximally tolerated statin and/or ezetimibe?

Note: Prescriber must provide chart documentation of diagnosis and recent LDL-C (within last 12 weeks).

Yes: Document diagnosis and approve for up to 12 months

Recent LDL-C \_\_\_\_\_ mg/dL  
Date: \_\_\_\_\_

No: Pass to RPh; deny for medical appropriateness.

Renewal Criteria		
1. What is the most recent LDL-C (within last 12 weeks)?	Recent LDL-C _____ mg/dL Date: _____ ; go to #2	
2. Is the patient adherent with PCSK9 inhibitor therapy?	Yes: Approve for up to 12 months  Note: pharmacy profile may be reviewed to verify >80% adherence (PCSK9 inhibitor prescription refilled 10 months' supply in last 12 months)	No: Pass to RPh; deny for medical appropriateness

**High- and Moderate-intensity Statins.** Stone NJ, et al. 2013 ACC/AHA Blood Cholesterol Guideline.

High-intensity Statins (≥50% LDL-C Reduction)		Moderate-intensity Statins (30 to <50% LDL-C Reduction)	
Atorvastatin 40-80 mg	Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Fluvastatin 80 mg Lovastatin 40 mg	Pitavastatin 2-4 mg Pravastatin 40-80 mg Simvastatin 20-40 mg Rosuvastatin 5-10 mg

References:

1. NICE Clinical Guideline 181. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. Available at: [guidance.nice.org.uk/cg181](http://guidance.nice.org.uk/cg181). Accessed 18 September 2015.
2. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;129(25 Suppl 2):S1-45. doi: 10.1161/01.cir.0000437738.63853.7a.

P&T / DUR Review: 1/18 (MH), 11/16 (DM); 11/15 (AG)  
Implementation: TBD: 1/1/17