



PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE

PCSK9 INHIBITORS

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1. What are PCSK9 inhibitors?

These are newly approved medications for treating high cholesterol levels. They differ from previous treatments for high cholesterol in that they have a unique method for lowering cholesterol. Their mechanism of action is to block the action of an enzyme. PCSK9, or proprotein convertase subtilisin/kexin 9, is a protease that binds to low-density lipoprotein (LDL) receptors. This binding reduces the activity of the LDL receptors, thereby decreasing LDL metabolism. This leads to increased LDL cholesterol levels. By inhibiting the effects of PCSK9, the receptors are more active and remove more LDL from the blood. PCSK9 inhibitors are human monoclonal antibodies. Monoclonal antibodies would be destroyed in the stomach, so these medications must be given by injection.

2. What are the available compounds on the market?

Alirocumab injection (Praluent), is FDA approved for “use in addition to diet and maximally tolerated statin therapy in adult patients with heterozygous familial hypercholesterolemia (HeFH) or patients with clinical atherosclerotic cardiovascular disease such as heart attacks or strokes, who require additional lowering of LDL cholesterol.”

The FDA has described the evidence about alirocumab as follows: “The efficacy and safety of Praluent were evaluated in five placebo-controlled trials, involving 2,476 participants exposed to Praluent. All participants had HeFH or were otherwise at high risk for heart attack or stroke, and were taking maximally tolerated doses of a statin, with or without other lipid-modifying therapies. Participants taking Praluent had an average reduction in LDL cholesterol ranging from 36 to 59 percent, compared to placebo.”

(<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm455883.htm>)

Evolocumab injection (Repatha), is another FDA approved PCSK9 inhibitor. It is “indicated for use in addition to diet and maximally-tolerated statin therapy in adult patients with heterozygous familial hypercholesterolemia (HeFH), homozygous familial hypercholesterolemia (HoFH), or clinical atherosclerotic cardiovascular disease (ASCVD), such as heart attacks or strokes, who require additional lowering of LDL cholesterol.” The evidence used by the FDA to approve this medication included: “The efficacy and safety of Repatha were evaluated in one 52-week placebo-controlled trial and eight 12-week placebo-controlled trials in participants with primary hyperlipidemia, including two that specifically enrolled participants with HeFH and one that enrolled participants with HoFH. In one of the 12-week studies, 329 participants with HeFH, who required additional lowering of LDL cholesterol despite statins with or without other lipid-lowering therapies, were randomized to receive Repatha or placebo for 12 weeks. Participants taking Repatha had an average reduction in LDL cholesterol of approximately 60 percent, compared to placebo.”

(<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm460082.htm>)

For outcomes on adverse and cardiovascular events, one study combined data from two randomized trials totaling 4465 patients. Patients were followed for a median of 11.1 months.

“As compared with standard therapy alone, evolocumab reduced the level of LDL cholesterol by 61%, from a median of 120 mg per deciliter to 48 mg per deciliter ($P<0.001$). Most adverse events occurred with similar frequency in the two groups, although neurocognitive events were reported more frequently in the evolocumab group. The risk of adverse events, including neurocognitive events, did not vary significantly according to the achieved level of LDL cholesterol. The rate of cardiovascular events at 1 year was reduced from 2.18% in the standard-therapy group to 0.95% in the evolocumab group (hazard ratio in the evolocumab group, 0.47; 95% confidence interval, 0.28 to 0.78; $P = 0.003$).” (Sabatine et al., N Engl J Med 2015; 372:1500-1509)

3. What are some of the ongoing PCSK9 studies that aim to examine long-term clinical outcomes? A search on ClinicalTrials.gov on 8/31/2015 shows five ongoing studies¹ :

NCT01764633 - A Double-blind, Randomized, Placebo-controlled, Multicenter Study Assessing the Impact of Additional LDL-Cholesterol Reduction on Major Cardiovascular Events When Evolocumab (AMG 145) is Used in Combination With Statin Therapy In Patients With Clinically Evident Cardiovascular Disease

Primary outcome measures - time to cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, or coronary revascularization [Time Frame: 5 years]

Estimated study completion: 2/2018

Sample size: 27,564

NCT01975389 - Phase 3 Multi Center, Double Blind, Randomized, Placebo Controlled, Parallel Group Evaluation Of The Efficacy, Safety, And Tolerability Of Bococizumab (pf 0495061), In Reducing The Occurrence Of Major Cardiovascular Events In High Risk Subjects

This study focuses on “high risk subjects who are receiving background lipid lowering therapy and have cholesterol laboratory values of $LDL-C \geq 100 \text{ mg/dL}$ (2.6 mmol/L) or $non-HDL-C \geq 130 \text{ mg/dL}$ (3.4 mmol/L).”

Primary outcome measures - Cardiovascular event [Time Frame: The time from Randomization to the first adjudicated and confirmed occurrence of a primary endpoint major cardiovascular event, up to Month 60] - Confirmed occurrence of a major cardiovascular event, a composite endpoint which includes CV death, non fatal MI, non fatal stroke, and hospitalization for unstable angina needing urgent revascularization

Estimated study completion: 3/2018

Sample size: 9,000

NCT01975376 – a similar study as above but focuses on “high risk subjects who are receiving background lipid lowering therapy and have cholesterol laboratory values of $LDL-C \geq 70 \text{ mg/dL}$

¹ Based on the ongoing studies described in ClinicalTrials.gov, note that there is a third compound (Bococizumab) under evaluation.

(1.8 mmol/L) and < 100 mg/dL (2.6 mmol/L) or non-HDL-C >/= 100 mg /dl (2.6 mmol/L) and <130 mg/dL (3.4 mmol/L)."

Estimated study completion: 6/2018

Sample size: 17,000

[NCT01854918](#) - A Multicenter, Controlled, Open-label Extension (OLE) Study to Assess the Long-term Safety and Efficacy of AMG 145-2 [evolocumab]

Primary outcome measures - Subject incidence of adverse events [Time Frame: 156 weeks]

Estimated study completion: 5/2018

Sample size: 4428

[NCT01663402](#) - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Effect of Alirocumab (SAR236553/REGN727) on the Occurrence of Cardiovascular Events in Patients Who Have Recently Experienced an Acute Coronary Syndrome

Primary outcome measures - Time from randomization to first occurrence of one of the following clinical events: CHD death, any non-fatal MI, fatal and non-fatal ischemic stroke, unstable angina requiring hospitalization [Time Frame: Up to Month 64]

Estimated study completion: 12/2017

Sample size: 18,000

4. Summary

Two new drugs targeting a new mechanism of LDL metabolism have been approved by the FDA based on efficacious results in reducing LDL cholesterol levels in high risk patients or patients who are already on maximal dosages of statins. The prior studies evaluated only LDL cholesterol levels as an outcome. Most studies evaluating actual clinical outcomes (clinical events attributable to atherosclerotic cardiovascular disease) will not be completed until 2018.

These medications are unique, in that they are administered by injection rather than by mouth. Thus, they differ from all other medications for lowering cholesterol levels. There currently is no evidence about the long-term tolerability and patient acceptance of the PCSK9 inhibitors. There also is little evidence about long-term side effects or harms that may occur infrequently.

Comparative benefits and harms of these new medications are not known at this time.