PCSK9 Inhibitors: Mechanism of Action, Efficacy, and Safety

Eli M. Roth MD,[1] Michael H. Davidson, MD[2]
[1]Sterling Research Group, Cincinnati, OH; [2]Department of Cardiology, University of Chicago Medicine, Chicago, IL

Low-density lipoprotein (LDL) receptors on the surface of liver hepatocytes are the primary way that humans regulate serum LDL cholesterol levels. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a proteolytic enzyme that indirectly regulates serum LDL cholesterol (LDL-C) by causing the destruction of LDL receptors. Less LDL receptors result in increased LDL-C in the bloodstream but inhibiting or binding the circulating PCSK9 results in increased LDL receptors with the resultant decrease in serum LDL-C. Two PCSK9 inhibitors are currently approved for use: alirocumab and evolocumab. Both are fully human monoclonal antibodies that bind free PCSK9. Herein we discuss the mechanism of action, efficacy, and safety of PCSK9 inhibitors.

[Rev Cardiovasc Med. *2018;19(suppl 1):S31-S46 doi: 10.3909/ricm19S1S0002*]

KEY WORDS

PCSK9 • Low-density lipoprotein receptors • Monoclonal antibodies • Familial hypercholesterolemia

Low-density lipoprotein (LDL) receptors on the surface of liver hepatocytes are the primary mechanism that regulate serum LDL cholesterol (LDL-C) levels. LDL receptors are present on most cells, but the majority are on the surface of the hepatocyte, which is thought to be responsible for removing up to 70% of the circulating LDL particles that are removed daily from the blood.[1] LDL receptors on the surface of the hepatocyte are transmembrane proteins that attract and bind LDL particles that are circulating in the serum. Once an LDL particle binds to the LDL receptor, the complex enters the hepatocyte through a clathrin-coated pit, which transforms into an endosome. In the endosome, the LDL particle and the LDL receptor separate; the LDL receptor recycles to the cell surface and the LDL particle enters a lysosome for degradation. It takes approximately 10 minutes for the LDL receptor to enter the cell and recycle back to the cell surface, and each LDL receptor is thought to recycle approximately 150 times during its lifecycle.[2] This enables each unencumbered LDL receptor the potential to remove 150 molecules of LDL-C from circulation during its lifetime. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a proteolytic enzyme that indirectly regulates serum LDL-C by regulating the number of LDL receptors on cell surfaces. PCSK9 is an important regulator of hepatic LDL-C levels.

Although PCSK9 is mainly of hepatic origin, extrahepatic tissues such as the kidney, intestine, and central nervous system contribute to PCSK9 production and, potentially, local regulation of LDL receptor expression. If PCSK9 binds to the LDL receptor before the LDL particle and LDL receptor enter the hepatocyte, it prevents the LDL particle and LDL receptor from separating in the endosome and the entire complex enters the lysosome and is degraded (Figure 1). Thus, PCSK9 causes premature degradation of the LDL receptor, leading to fewer LDL receptors on the cell surface, and resulting in increased serum LDL-C levels because less LDL-C is returned to the liver for catabolism. Studies have shown that patients with loss-of-function mutations in PCSK9 leading to lower PCSK9 levels have lower-than-average LDL-C levels; conversely, those with gain-of-function mutations leading to higher PCSK9 levels have above-average LDL-C levels, which can mimic LDL-C levels seen in those with familial hypercholesterolemia (FH). Thus, decreasing the amount of free PCSK9 that is available to bind to the LDL receptor will result in less LDL receptor degradation, more LDL receptors on the hepatocyte surface, and less circulating LDL-C.[3]

PCSK9 Inhibitors

Two PCSK9 inhibitors are currently approved for use: alirocumab and evolocumab. Both are fully human monoclonal antibodies (mAbs) that bind free PCSK9, which prevents PCSK9 from attaching to the LDL receptor. Less free PCSK9 results in more LDL receptor recycling, a greater density of LDL receptors on the surface of the hepatocyte, and significant reductions in circulating LDL-C, consistent with the previously described mechanism of action. These mAbs are highly specific for interacting only with PCSK9, thus eliminating concerns about drug-drug interactions, including those with other injectable biologic agents. Also, because mAbs are large proteins, there is generally no concern about crossing the intact blood-brain barrier. PCSK9 inhibitors are metabolized by the reticuloendothelial system

Two PCSK9 inhibitors are currently approved for use: alirocumab and evolocumab. Both are fully human monoclonal antibodies (mAbs) that bind free PCSK9, which prevents PCSK9 from attaching to the LDL receptor.

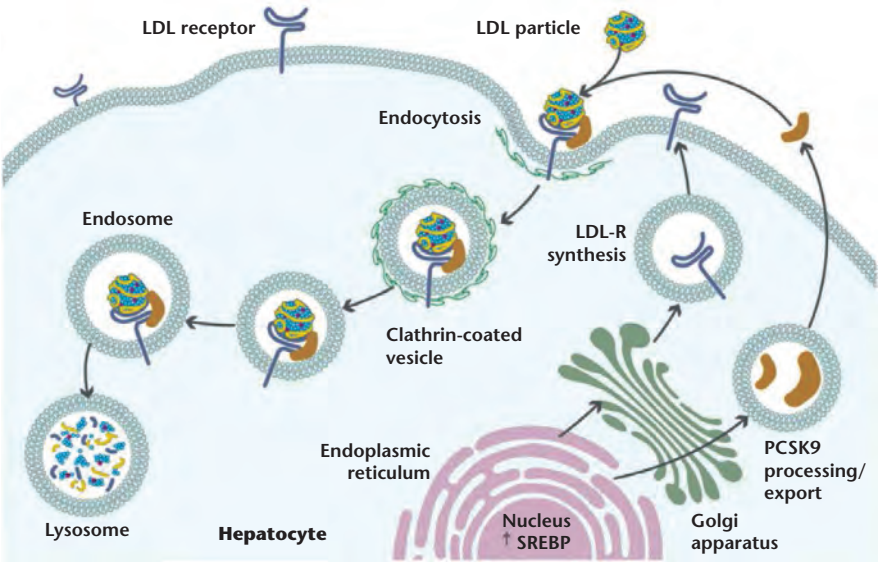

Figure 1A. Effect of PCSK9 on LDL receptor life cycle. LDL, low-density lipoprotein; LDL-R, low-density lipoprotein receptor; PCSK9, proprotein convertase subtilisin/kexin type 9; SREBP, sterol regulatory element binding protein. Reprinted with permission from Lambert G et al.[38]

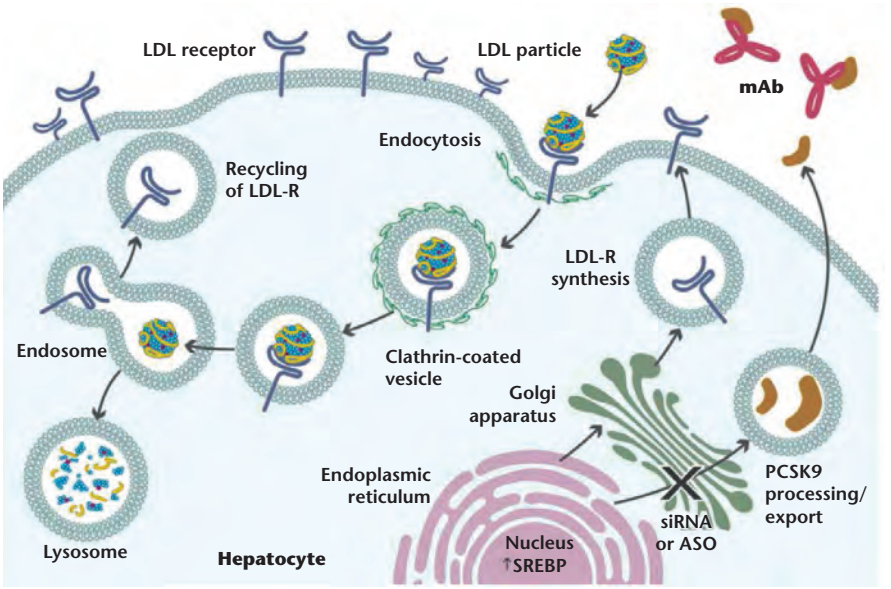

Figure 1B. LDL receptor life cycle with PCSK9 inhibited. ASO, antisense oligonucleotide; LDL, low-density lipoprotein; LDL-R, low-density lipoprotein receptor; mAb, monoclonal antibody; PCSK9, proprotein convertase subtilisin/kexin type 9; siRNA, small interfering RNA; SREBP, sterol regulatory element binding protein. Reprinted with permission from Lambert G et al.[38]

where proteins are broken down to small peptides and amino acids. There is no metabolism or excretion through the liver or kidney, eliminating concerns in many patients with concomitant disease states. A minor downside to the mAbs is the need for subcutaneous injection, but a benefit is a long half-life, thus frequency of injection is once every 2 or 4 weeks. Both PCSK9 inhibitors have extensive phase II and III clinical trial programs for efficacy and safety. Evolocumab has data from a cardiovascular outcomes trial (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk [FOURIER]),[4] and alirocumab has outcomes data (Study to Evaluate the Effect of Alirocumab on the Occurrence of Cardiovascular Events in Patients Who Have Experienced an Acute Coronary Syndrome [ODYSSEY OUTCOMES])[5] that was presented in March 2018. The efficacy and safety data for both mAbs are similar.

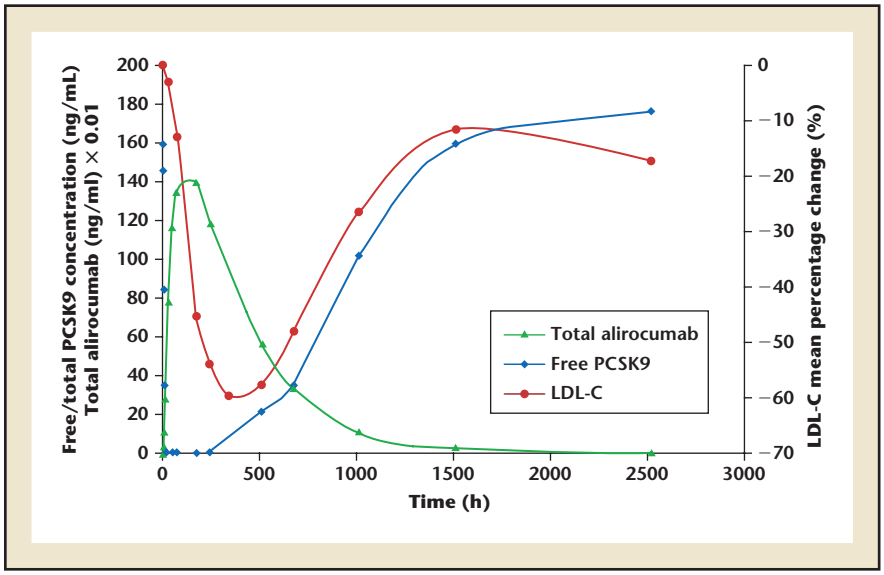

Figure 2. Pharmacokinetic relationship of alirocumab, PCSK9, and LDL-C after a subcutaneous dose. LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9. Reprinted with permission from Roth EM and Diller P.[3]

Pharmacokinetics of PCSK9 Inhibitors

Alirocumab and evolocumab are fully human mAbs that specifically target and bind to PCSK9. When bound to circulating PCSK9, the mAb blocks the active binding site to the LDL receptor; therefore, PCSK9 can no longer function by attaching to the LDL receptor and cause destruction of the LDL receptor and prevent its recycling to the cell surface. PCSK9 is continually produced in the endoplasmic reticulum of the hepatocyte, modified in the Golgi body of the cell, and diffuses across the cell membrane into the vascular space.[3] When the PCSK9 inhibitor mAb is given subcutaneously, it is rapidly absorbed into the serum and binds to its target, the free PCSK9. Free PCSK9 levels drop to zero within 4 to 6 hours of subcutaneous injection. As PCSK9 levels decrease, LDL receptor levels increase after a few days. Once LDL receptor levels increase, there is a resultant decrease in LDL cholesterol levels due to increased LDL particle uptake by the hepatocytes after several days, as seen in Figure 2. If there is available free mAb to bind to the newly produced PCSK9, free PCSK9 levels will remain at zero. Once all the mAb is consumed and bound to PCSK9, free PCSK9 levels begin to rise, and LDL receptor levels on the hepatocyte begin to decrease, with a resulting increase in LDL-C. Again, there is a time lag between each of these steps, as PCSK9 levels begins to return to baseline.

PCSK9 is continually produced in the endoplasmic reticulum, modified in the Golgi body of the cell, and diffuses across the cell membrane into the vascular space.

It is important to understand that, once free PCSK9 levels reach zero, no additional LDL-C lowering can be obtained by giving more of the PCSK9 inhibitor mAb. A higher dose of mAb will increase the duration of effect of the mAb but not the magnitude of effect (LDL-C lowering). The more mAb injected subcutaneously (and thus available within the serum), the longer it can continue to bind the newly formed PCSK9 and keep levels of free PCSK9 at zero. Alirocumab and evolocumab both have every 2-week (q2w) and every 4-week (q4w) dosing. The q4w doses are twice the q2w dose for alirocumab (2 150-mg subcutaneous injections) and three times the 140 mg q2w dose for evolocumab (420 mg by a 9-min infusion device). One should also remember that the degree of apparent LDL-C lowering is dependent on the dose of mAb given and the time of serum LDL cholesterol testing, particularly with q4w dosing. Once free PCSK9 levels start to rise from zero, after time there will be an increase in LDL-C. An LDL-C

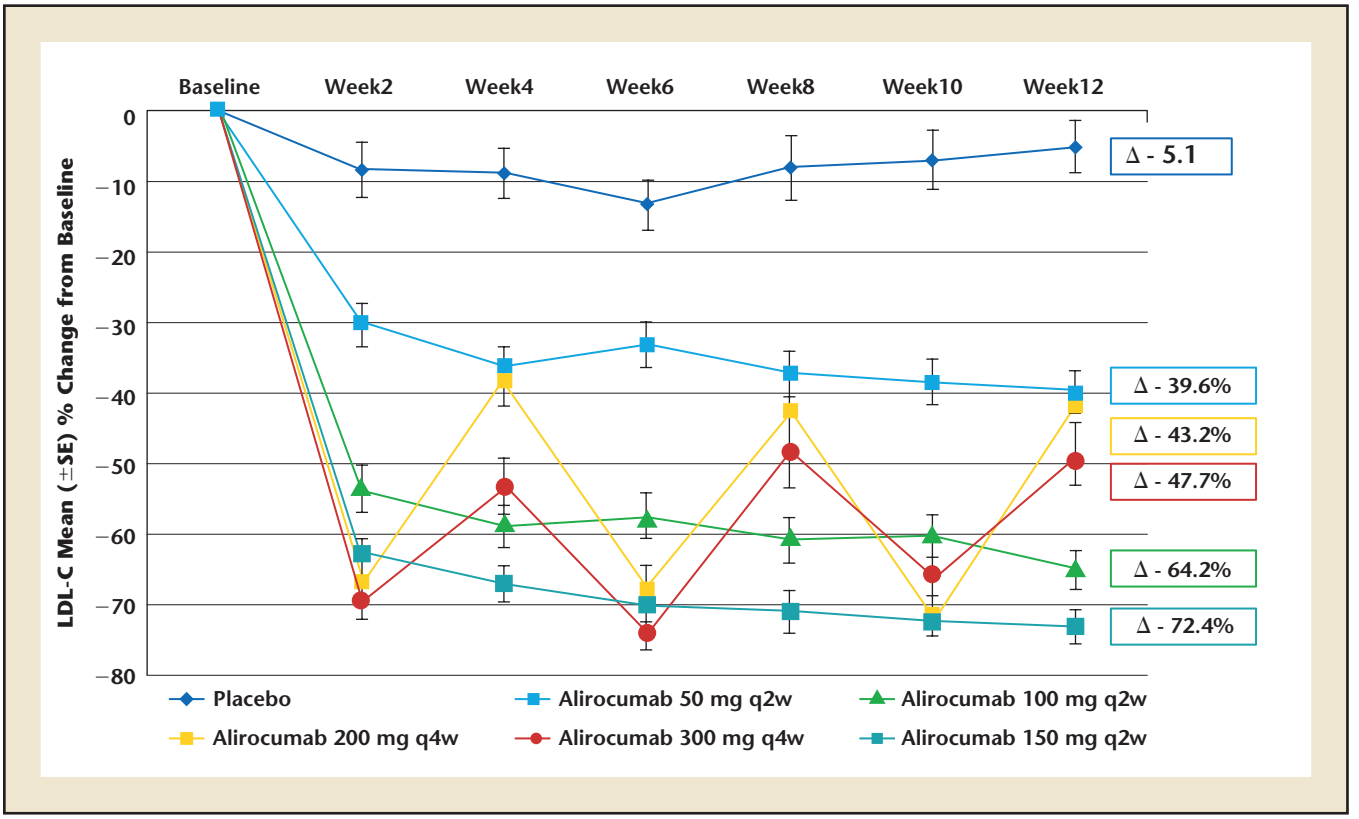

Figure 3. Changes in LDL-C measured every 2 weeks from baseline to week 12 across a dose range of alirocumab administered subcutaneously every 2 weeks and every 4 weeks. LDL-C, low-density lipoprotein cholesterol; q2w, every 2 weeks; q4w, every 4 weeks; SE, standard error. Reprinted with permission from McKenney JM.[6]

measurement is an indication of the current LDL-C level at a specific time point, not the average LDL-C level during the dosing interval. An example of this is shown in Figure 3 for various doses of alirocumab.[6] For patients on 300-mg q4w dosing of alirocumab, if LDL-C lowering is not adequate then a change to 150 mg q2w dosing is recommended.

Statins inhibit 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting step in intracellular cholesterol production. The decreased intracellular cholesterol content of the liver stimulates an increase in hepatic sterol regulatory element binding protein 2 (SREBP2) synthesis, which causes an increase in LDL receptor production and a resultant decrease in LDL-C. SREBP2 seems to have as one of its key actions, maintaining hepatic cholesterol levels. However, SREBP2 also causes an increase in PCSK9 production, countering the LDL-C–reducing impact of its other effect (greater LDL receptor synthesis). Statins not only lower LDL-C by increasing LDL receptors, but they also increase PCSK9 production and serum free PCSK9 levels, which handicaps those LDL receptors by leading to an up-regulation.[6] Data show that not only statins, but also ezetimibe and fenofibrate, cause an increase in PCSK9.[7] For statins, the increase in PCSK9 appears to be dose related: the higher the statin dose, the greater the increase in PCSK9. Because statins increase the PCSK9 level, the duration of effect of a dose of PCSK9i mAb is shortened when statins are administered with a PCSK9 inhibitor due to increased availability of PCSK9 as substrate. This effect is not enough to affect the dosing of a PCSK9 inhibitor. However, the efficacy of the PCSK9 inhibitor is increased because there is a synergistic effect of the statin and PCSK9 inhibitor on LDL-C lowering.

> ***Statins not only lower LDL cholesterol by increasing LDL receptors, but they also increase PCSK9 production and serum free PCSK9 levels…***

PCSK9 Inhibitor Clinical Trial Programs

Phase II and III clinical trial studies for alirocumab and evolocumab are shown in Table 1. Both mAbs underwent extensive phase II and III testing. Phase I studies (not shown) were small proof-of-concept and dose-ranging studies that gave

TABLE 1

Phase II and III Studies for Alirocumab and Evolocumab

Study	Phase	Control (n)	Dose, mg (n)	Length, wk	Population
Alirocumab					
CL-1003	II	Pl (15)	150 (16)	12	HeFH
DFI 11565	II	Pl (31)	150 (31)	12	Non-FH
DFI 11566	II	Pl (31)	150 (61)	12	Non-FH
DFI 2361	II	Pl (25)	75 (25), 150 (25)	12	Non-FH
ODYSSEY Long Term	III	Pl (788)	150 (1550)	78	HeFH + high CV risk
ODYSSEY HIGH FH	III	Pl (35)	150 (72)	78	HeFH
ODYSSEY FH I + ODYSSEY FH II	III	Pl (244)	75→150 (489)	78	HeFH
ODYSSEY COMBO I	III	Pl (107)	75→150 (207)	52	High CV risk
ODYSSEY COMBO II	III	Ez (241)	75→150 (479)	104	High CV risk
ODYSSEY OPTIONS I + II	III	Ez (202)	75→150 (207)	24	High CV Risk
ODYSSEY MONO	III	Ez (51)	75→150 (52)	24	Monotherapy
ODYSSEY ALTERNATIVE	III	Ez (124)	75→150 (126)	24	Statin intolerant
ODYSSEY OUTCOMES	III	Pl (9156)	75→150 (9156)	132	ACS (4-52 wk post-event)
Evolocumab					
MENDEL	II	Pl (90) Ez (45)	Multiple (271)	12	Monotherapy
YUKAWA	II	Pl (102)	Multiple (207)	12	Combination therapy
LAPLACE-TIMI 57	II	Pl (155)	Multiple (474)	12	Combination therapy
RUTHERFORD	II	Pl (56)	Multiple (112)	12	HeFH
GAUSS	II	None	Multiple (160)	12	Statin intolerant
MENDEL-2	III	Pl (164) Ez (154)	140 (153), 420 (153)	12	Monotherapy
LAPLACE-2	III	Pl (558) Ez (221)	140 (555), 420 (562)	12	Combination therapy
DESCARTES	III	Pl (302)	420 (599)	52	Risk-based therapy
RUTHERFORD 2	III	Pl (109)	140 (110), 420 (110)		
GAUSS-2	III	Ez (102)	140 (103), 420 (102)	12	Statin intolerant
OSLER-1	III	SOC (442)	420 (882)	>52	Phase II studies, open-label extension
OSLER-2	III	SOC (1047)	420 (2094)	>52	Phase III studies, open-label extension
FOURIER	III	Pl (13,780)	140 or 420 (13, 784)	112	High CV risk

ACS, acute coronary syndrome; CV, cardiovascular; DESCARTES, Durable Effect of PCSK9 Antibody Compared with Placebo Study; Ez, ezetimibe; FH, familial hypercholesterolemia; FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk; GAUSS, Goal Achievement after Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects; HeFH, heterozygous familial hypercholesterolemia; LAPLACE, LDL-C Assessment with PCSK9 Monoclonal Antibody Inhibition Combined With Statin Therapy; MENDEL, Monoclonal Antibody Against PCSK9 to Reduce Elevated LDL-C in Subjects Currently Not Receiving Drug Therapy for Easing Lipid Levels; ODYSSEY ALTERNATIVE, Study of Alirocumab in Patients With Primary Hypercholesterolemia and Moderate, High, or Very High Cardiovascular Risk, Who Are Intolerant to Statins; ODYSSEY COMBO I, Efficacy and Safety of Alirocumab Versus Placebo on Top of Lipid-Modifying Therapy in Patients With High Cardiovascular Risk and Hypercholesterolemia; ODYSSEY COMBO II, Efficacy and Safety of Alirocumab Versus Ezetimibe on Top of Statin in High Cardiovascular Risk Patients With Hypercholesterolemia; ODYSSEY FH I, Efficacy and Safety of Alirocumab Versus Placebo on Top of Lipid-Modifying Therapy in Patients With Heterozygous Familial Hypercholesterolemia Not Adequately Controlled With Their Lipid-Modifying Therapy; ODYSSEY FH II, Study of Alirocumab in Patients With heFH Who Are Not Adequately Controlled With Their LMT; ODYSSEY HIGH FH, Efficacy and Safety of Alirocumab Versus Placebo on Top of Lipid-Modifying Therapy in Patients With Heterozygous Familial Hypercholesterolemia; ODYSSEY Long Term, Efficacy and Safety of alirocumab in reducing lipids and cardiovascular events; ODYSSEY MONO, Long-term Safety and Tolerability of Alirocumab Versus Placebo on Top of Lipid-Modifying Therapy in High Cardiovascular Risk Patients With Hypercholesterolemia; Efficacy and Safety of Alirocumab Versus Ezetimibe in Patients With Hypercholesterolemia; ODYSSEY OPTIONS I, Study of the Efficacy and Safety of Alirocumab in Combination With Other Lipid-modifying Treatment; ODYSSEY OPTIONS II, Study of Alirocumab added-on to Rosuvastatin Versus Other Lipid Modifying Treatments; ODYSSEY OUTCOMES, Study to Evaluate the Effect of Alirocumab on the Occurrence of Cardiovascular Events in Patients Who Have Experienced an Acute Coronary Syndrome; OSLER, Open-Label Study of Long-Term Evaluation against LDL Cholesterol; Pl, placebo; SOC, standard of care; RUTHERFORD, Reduction of LDL-C With PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder Study; YUKAWA, Study of LDL-Cholesterol Reduction Using a Monoclonal PCSK9 Antibody in Japanese Patients With Advanced Cardiovascular Risk.

direction for the phase II studies. The phase II studies were larger studies also looking at dose ranging and various patient categories such as high cardiovascular risk, heterozygous familial hypercholesterolemia (HeFH), and statin intolerance. The phase II studies included multiple doses administered q2w and q4w; the data helped determine the doses for phase III studies. Alirocumab trials focused on both a 75-mg and 150-mg q2w dose for phase III studies and a 300 mg q4w dose was added after initial US Food and Drug Administration (FDA) approval of the q2w doses. Evolocumab trials focused on 140-mg q2w and 420-mg q4w dosing, which were shown to essentially be equivalent in terms of efficacy.[8] As previously noted, a large cardiovascular outcomes study on evolocumab was published (FOURIER), which has led to a new indication for adults with cardiovascular disease to reduce the risk of myocardial infarction (MI), stroke, and coronary revascularization.[4] A large cardiovascular outcomes study on alirocumab, ODYSSEY OUTCOMES was reported in March 2018 and will also most likely lead to new indications in the future.

Efficacy of the PCSK9 Inhibitors

The efficacy of the PCSK9 inhibitors to reduce LDL-C is related to the dose of the PCSK9 inhibitor, the baseline free PCSK9 level, the baseline LDL-C level, and the timing of the LDL-C measurement relative to the time of administration of the PCSK9 inhibitor. Most of the phase II and III clinical trials were performed with the maximally tolerated dose of statin in the background. A recent publication focusing on alirocumab, a summary of eight phase III trials with 4629 patients on various doses of statins but with similar baseline LDL-C values, showed that there was no association between statin type or dose as background therapy and the percent change in LDL-C at week 24 from baseline.[9] Similarly, in a phase II trial comparing alirocumab, 150 mg in combination with either 10 mg or 80 mg of atorvastatin, the 80-mg dose in combination with the alirocumab only provided a 7% additional decrease in LDL-C compared with alirocumab plus the 10-mg atorvastatin dose.[10] The statin "rule of 6s" suggests there should have been an 18% difference. In the Durable Effect of PCSK9 Antibody Compared with Placebo Study (DESCARTES), a 52-week trial of evolocumab, 420 mg q4w in patients with four different lipid-lowering therapy (LLT) groups: diet alone; atorvastatin, 10 mg; atorvastatin, 80 mg; and atorvastatin, 80 mg plus ezetimibe, 10 mg, LDL-C–lowering efficacy was not significantly different within the four groups when measured at week 12.[11] Also, the LDL-C Assessment with PCSK9 Monoclonal Antibody Inhibition Combined With Statin Therapy (LAPLACE)-2 trial of evolocumab with moderate- and high-intensity statins showed no difference in efficacy based on LLT.[12] When looking at the efficacy of alirocumab, 150 mg q2w and evolocumab, 140 mg q2w, and taking into consideration study variables, the efficacy was similar. Either PCSK9 inhibitors (alirocumab, 150 mg and evolocumab, 140 mg) will lower LDL-C approximately 55% to 65% compared with baseline when there is a statin in the concomitant therapy. The percent reduction in LDL-C without a statin on board is generally less but is biased by a higher baseline value that serves as the denominator for the percent LDL-C reduction.

Efficacy of Alirocumab

In eight phase III clinical trials, the 75-mg q2w dose of alirocumab was used as the starting dose and up-titration to 150 mg q2w at week 12 (denoted by 75/150 mg) was allowed if the week 8 prespecified LDL-C goal of <70 or <100 mg/dL (based on risk) was not achieved or the LDL-C decrease was <30%. The anticipated decrease in LDL-C was expected to be 50% with the 75-mg dose of alirocumab based on modeling from phase II trial data. The 75- and 150-mg studies can be grouped into HeFH studies, of which there are two (Efficacy and Safety of Alirocumab [SAR236553/REGN727] Versus Placebo on Top of Lipid-Modifying Therapy in Patients With Heterozygous Familial Hypercholesterolemia Not Adequately Controlled With Their Lipid-Modifying Therapy [ODYSSEY FH I] & Study of Alirocumab [REGN727/SAR236553] in Patients With HeFH Who Are Not Adequately Controlled With Their LMT [ODYSSEY FH II]),[13] and non-FH studies, of which there are six (Efficacy and Safety of Alirocumab [SAR236553/REGN727] Versus Placebo on Top of Lipid-Modifying Therapy in Patients With High Cardiovascular Risk and Hypercholesterolemia [ODYSSEY COMBO I] & Efficacy and Safety of Alirocumab [SAR236553/REGN727] Versus Ezetimibe on Top of Statin in High Cardiovascular Risk Patients With Hypercholesterolemia [ODYSSEY COMBO II], Study of the Efficacy and Safety of Alirocumab [REGN727/SAR236553] in Combination With Other Lipid-modifying Treatment [ODYSSEY OPTIONS I], Study of Alirocumab [REGN727/SAR236553] added-on to Rosuvastatin Versus Other Lipid Modifying Treatments [ODYSSEY OPTIONS II], Efficacy and Safety of Alirocumab [SAR236553/REGN727]

Versus Ezetimibe in Patients With Hypercholesterolemia [ODYSSEY MONO], and Study of Alirocumab [REGN727/SAR236553] in Patients With Primary Hypercholesterolemia and Moderate, High, or Very High Cardiovascular Risk, Who Are Intolerant to Statins [ODYSSEY ALTERNATIVE]).[14-19] Differences in efficacy of these studies are based on the baseline LDL-C level, as previously noted. Approximately 40% of patients in the two FH studies needed to be up-titrated to 150 mg of alirocumab q2w based on the criteria above. Baseline LDL-C levels in the FH studies were high compared with the other studies (144.7 mg/dL and 134.6 mg/dL for ODYSSEY FH I & ODYSSEY FH II, respectively). Percent reductions in LDL-C compared with placebo at week 24 were −57.9% and −51.4% for ODYSSEY FH I and ODYSSEY FH II, respectively. Absolute reductions for alirocumab were 71 mg/dL for ODYSSEY FH I and 66 mg/dL for ODYSSEY FH II. It is not possible to separate the 75-mg dose from the 75- and 150-mg doses at week 24, but it is known that baseline LDL-C and baseline free PCSK9 level are factors statistically associated with a need for dose increase.[20] Because HeFH patients have a high baseline LDL-C level despite being on high-dose statins plus other LLTs (thus having a higher baseline free PCSK9 level), the need to increase the alirocumab dose to 150 mg q2w is not surprising. Data have been generated to show that up-titrating from 75 mg to 150 mg of alirocumab results in an additional 14% reduction in LDL-C.[21]

The non-FH studies using 75 and 150 mg of alirocumab overall had lower baseline LDL-C (except the statin intolerant study, ODYSSEY ALTERNATIVE) and a smaller percent of patients needing up-titration of alirocumab to 150 mg q2w. ODYSSEY COMBO I randomized 316 patients to alirocumab, 75/150 mg, versus placebo. Baseline least square mean (LSM) LDL-C was 102.2 and the LSM LDL-C reduction at week 52 was −48.2%. Up-titration to 150 mg q2w occurred at week 12 in 16.8% of patients. ODYSSEY COMBO II was a similar study with 720 patients randomized to alirocumab 75/150 mg doses versus ezetimibe. Baseline LSM LDL-C was 107.3 mg/dL and LSM LDL-C reduction was −50.6%. Up-titration to 150 mg q2w occurred at week 12 in 18.2% of patients. ODYSSEY OPTIONS I and II were two complicated 24-week studies, ODYSSEY OPTIONS I (n = 355) started out with two doses of atorvastatin and added alirocumab or ezetimibe, or changed to rosuvastatin. ODYSSEY OPTIONS II (n = 305) started with two doses of rosuvastatin and added alirocumab or ezetimibe, or up-titrated the rosuvastatin. Reductions in LDL-C with alirocumab in ODYSSEY OPTIONS I were −44.1% (atorvastatin, 20 mg) and −54.0% (atorvastatin, 40 mg), and up-titration to 150 mg occurred in 8.0% of patients on atorvastatin, 20 mg and in 20.9% of patients on atorvastatin, 40 mg. Reductions in LDL-C with alirocumab in ODYSSEY OPTIONS II were −50.6% (rosuvastatin, 10 mg) and −36.3% (rosuvastatin, 20 mg), and up-titration to 150 mg occurred in 15.9% of patients on rosuvastatin, 10 mg and in 20.8% of patients on rosuvastatin, 20 mg. ODYSSEY MONO was a 24-week study that enrolled 103 low-risk patients not on statins who had a baseline LDL-C value of 139.7 mg/dL. Alirocumab, 75/150 mg lowered LDL-C by −47.2%; 27% of patients needed up-titration because of an LDL cholesterol >70 mg/dL but only 2% had LDL-C levels >100 mg/dL. ODYSSEY ALTERNATIVE was a 24-week study for statin intolerant patients with a baseline LDL-C of 191.1 mg/dL. LDL-C was reduced by −47.3% (absolute LDL-C change of 90.4 mg/dL) and 49.5% of patients needed up-titration to 150 mg q2w.

Two phase III studies, Efficacy and Safety of Alirocumab (SAR236553/REGN727) Versus Placebo on Top of Lipid-Modifying Therapy in Patients With Heterozygous Familial Hypercholesterolemia (ODYSSEY HIGH FH) and Long-term Safety and Tolerability of Alirocumab (SAR236553/REGN727) Versus Placebo on Top of Lipid-Modifying Therapy in High Cardiovascular Risk Patients With Hypercholesterolemia (ODYSSEY Long Term),[22,23] used alirocumab, 150 mg q2w for the entire study. Baseline LDL-C for the ODYSSEY HIGH FH study was high compared with the other studies, at 196.3 mg/dL. Percent reduction in LDL-C compared with placebo at week 24 was −39.1% for ODYSSEY HIGH FH and the absolute reduction in LDL-C was 90 mg/dL. The ODYSSEY Long Term study was 78 weeks in duration with 2341 patients, including 415 patients with HeFH. Mean LDL-C at baseline was 122 mg/dL. The mean percentage change in calculated LDL-C level from baseline to week 24 was −61.0% with alirocumab versus 0.8% with placebo. At week 78, at the end of study, the mean reduction in LDL-C was −58.0% in the intent-to-treat analysis. On average, alirocumab, 75 mg q2w provides LDL-C reductions of 45% to 50% and alirocumab, 150 mg q2w achieves 60% to 65% reductions in LDL-C.

Alirocumab, 300 mg q4w was studied in the Study to Evaluate the Efficacy and Safety of an Every Four Weeks Treatment Regimen of Alirocumab (REGN727/SAR236553)

in Patients With Primary Hypercholesterolemia (ODYSSEY CHOICE 1) study.[24] Those patients who received alirocumab, 300 mg q4w were eligible for a dosage change to 150 mg q2w if they did not achieve LDL-C goals or had <30% decrease in LDL-C level. The study included 146 patients not on a statin and 312 patients on a statin who were randomized to alirocumab, 300 mg q4w. The LSM change in LDL cholesterol in the nonstatin patients was −52.7% and was −58.8% in the statin-treated patients at week 24. The average LDL-C reduction from baseline to weeks 21 to 24 was −56.9% in patients not receiving a statin and −65.8% in patients on statin therapy. At week 12, the dosing was adjusted to alirocumab, 150 mg q2w in 14.7% of patients on no statin and 19.3% of patients on a concomitant statin.

Efficacy of Evolocumab

The two available doses of evolocumab, 140 mg q2w and 420 mg q4w have been shown to have essentially the same efficacy.[8] The phase III evolocumab studies used these doses exclusively, whereas the phase II studies used multiple dosing strategies. Therefore, the only efficacy variable in the phase III evolocumab studies is patient population, which includes HeFH patients, homozygous FH (HoFH) patients, hypercholesterolemic patients on statins, and patients on monotherapy without statins. The DESCARTES trial[11] examined hypercholesterolemic patients without FH and randomized them to diet alone (no statin), atorvastatin, 10 mg once daily, atorvastatin, 80 mg once daily, or atorvastatin, 80 mg once daily plus ezetimibe, 10 mg once daily, and then added evolocumab, 420 mg q4w or placebo. At the end of 52 weeks, the LDL-C reductions compared with placebo for the groups were as follows: diet alone: −55.7% ± 4.2%; atorvastatin, 10 mg: −61.6% ± 2.6%; atorvastatin, 80 mg: −56.8% ± 5.3%; and atorvastatin, 80 mg + ezetimibe, 10 mg: −48.5% ± 5.2%. In the Goal Achievement after Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects (GAUSS)-2 trial of 307 statin-intolerant patients, evolocumab, 140 mg q2w or evolocumab 420 mg q4w reduced LDL-C at 12 weeks by a mean of 53% to 56%.[25] The Reduction of LDL-C With PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder Study-2 (RUTHERFORD-2) trial enrolled 329 patients with HeFH who were on statins and demonstrated a reduction in LDL-C of −59.2% for the q2w group and −61.3% for the q4w group.[26] The LDL-C reduction for the 420-mg q4w group, using the mean of weeks 10 and 12, was −65.6%. The Trial Evaluating PCSK9 Antibody in Subjects with LDL Receptor Abnormalities (TESLA) Part B trial enrolled 50 HoFH patients and treated 49 of them with evolocumab, 420 mg q4w or placebo in a 2:1 ratio in addition to their other LLTs.[27] LDL receptor defects in HoFH patients can be either receptor-negative mutations (<2% of normal LDL uptake) or receptor-defective mutations (2%–25% of normal LDL uptake). HoFH patients can have two receptor-negative mutations or be complex heterozygotes with two different receptor-defective mutations, or one receptor-negative mutation with a receptor-defective mutation. Complex heterozygotes will respond better to PCSK9 inhibitors than true homozygotes. Patients with two receptor-defective mutations had a mean LDL-C response of −31.8% with a range of −44.9% to −18.8%. Patients with defective/negative status had a mean LDL-C response of −21.0% with a range of −30.7% to −11.2%). Patients with two receptor-negative mutations, which is rare, do not respond to a PCSK9 inhibitor. Overall LDL-C reduction compared with placebo in TESLA Part B was −30.9% at week 12. Patients with HeFH have one normal receptor allele and one allele that is defective or negative. Because they have at least half the normal LDL receptor, they respond to a PCSK9 inhibitor normally, as seen by the LDL-C reduction in the RUTHERFORD-2 trial. The GAUSS-2 study enrolled statin-intolerant patients but 18% were on a low-dose statin. After 12 weeks, the mean percent reduction in LDL-C from baseline as a mean of weeks 10 and 12 was −56.1% with evolocumab, 140 mg q2w and −55.3% for evolocumab, 420 mg q4w. This correlates well with the −55.7% decrease in LDL-C in the diet-alone group in the DESCARTES trial.

Effect of Alirocumab and Evolocumab on Other Lipid Parameters

Both PCSK9 inhibitors have positive effects on lipid parameters in addition to LDL-C.[4,9,11,23-27] On average, both alirocumab and evolocumab lower non–high-density lipoprotein (HDL) cholesterol and apolipoprotein B (ApoB) by approximately 80% to 85% of their LDL-C–lowering ability (if LDL-C is reduced 60%, ApoB is reduced 48%–51%). Triglycerides are lowered approximately 8% to 15% at usual levels, and at higher percentages when triglycerides are elevated. HDL cholesterol (HDL-C) is typically raised by approximately 6% to 10% and lipoprotein(a) (Lp[a]) is lowered approximately 20% to 30% depending on PCSK9 inhibitor dose. Clinically, the changes in HDL, triglyceride, and Lp(a) values are in a favorable direction for

cardiovascular disease prevention but are probably relatively minor factors. The lowering of ApoB and non-HDL by significant amounts assures that atherogenic lipid particles have been significantly reduced, which should favorably impact cardiovascular disease prevention.

Safety of Alirocumab

Alirocumab safety is currently best summarized by a safety analysis combining 4 phase II and 10 phase III trials with 5234 patients followed for 8 to 104 weeks.[28] Alirocumab was received by 3340 patients (4029 patient-years of exposure), 1276 patients were treated with placebo, and 618 patients received ezetimibe within these studies. Most patients were in studies for >52 weeks and 64% were observed for up to 76 weeks. Significantly more safety data (approximately 27,000 patient-years of exposure) will be available after the ODYSSEY OUTCOMES trial presented in March 2018 is published. At the time of publication of this article, no trial results have been published, but the top-line safety data presented for ODYSSEY OUTCOMES does not differ from the information presented here. Table 2 shows overall adverse events (AEs) and AEs that occurred in ≥5% of patients. The table divides the placebo-controlled pool and the ezetimibe-controlled pool into separate columns. When examining AEs, it is important to remember that most patients were on high-dose statin therapy with or without other LLTs as background therapy.

Any treatment-emergent AEs (TEAEs) were similar for alirocumab versus the control group for both placebo and ezetimibe, as seen in Table 2. Serious AEs in the placebo-controlled pool occurred in 15.6% of the alirocumab group versus 16.1% in the placebo group. Serious AEs in the ezetimibe-controlled pool occurred in 17.0%

TABLE 2

Overall Frequencies of Adverse Events and Events in ≥5% of Patients

Variable	Placebo-controlled Pool		Ezetimibe-controlled Pool	
	Alirocumab (n = 2,476)	Placebo (n = 1,276)	Alirocumab (n = 864)	Ezetimibe (n = 618)
Any TEAE	1,942 (78.4%)	1,004 (78.7%)	657 (76.0%)	457 (73.9%)
SAE	387 (15.6%)	205 (16.1%)	147 (17.0%)	86 (13.9%)
Leading to treatment discontinuation	148 (6.0%)	71 (5.6%)	84 (9.7%)	66 (10.7%)
Leading to death	16 (0.6%)	13 (1.0%)	6 (0.7%)	9 (1.5%)
TEAEs in ≥5% of patients				
Nasopharyngitis	301 (12.2%)	147 (11.5%)	52 (6.0%)	41 (6.6%)
Upper respiratory tract infection	165 (6.7%)	97 (7.6%)	62 (7.2%)	40 (6.5%)
Influenza	147 (5.9%)	63 (4.9%)	37 (4.3%)	23 (3.7%)
Urinary tract infection	129 (5.2%)	65 (5.1%)	21 (2.4%)	25 (4.0%)
Back pain	126 (5.1%)	71 (5.6%)	33 (3.8%)	26 (4.2%)
Arthralgia	119 (4.8%)	79 (6.2%)	42 (4.9%)	26 (4.2%)
Myalgia	112 (4.5%)	47 (3.7%)	62 (7.2%)	48 (7.8%)
Diarrhea	128 (5.2%)	61 (4.8%)	30 (3.5%)	21 (3.4%)
Headache	126 (5.1%)	67 (5.3%)	43 (5.0%)	24 (3.9%)
Accidental overdose	35 (1.4%)	17 (1.3%)	54 (6.3%)	24 (3.9%)

SAE, serious adverse event; TEAE, treatment-emergent adverse event.
Data from Jones PH et al.[28]

of alirocumab-treated patients versus 13.9% in the ezetimibe group. Treatment discontinuation was similar in both pools: 6.0% for alirocumab versus 5.6% for placebo and 9.7% for alirocumab versus 10.7% for ezetimibe. The number of deaths was small in each group and probably meaningless from a statistical perspective, although the number was slightly less in the alirocumab groups. The most common AEs for both the placebo group and ezetimibe-controlled pool were nasopharyngitis, upper respiratory tract infection, and influenza, which were slightly higher than placebo. These typically are the most common AEs in studies because they are the most common events that occur in the general population and are usually unrelated to the study drug. AEs of special interest are seen in Table 3 and include local injection site reactions, general allergic events, neurologic events, neurocognitive disorders, ophthalmological events, hepatic disorders, musculoskeletal events, and new-onset diabetes or new diabetic complications. Hazard ratios versus control are given for each of these categories for both the placebo-controlled pool and the ezetimibe-controlled pool. The only AE of special interest that appears related to alirocumab is local injection site reaction. This has been true in multiple individual studies and is also seen with evolocumab. Injection site reactions with alirocumab have typically been mild and transient, and have rarely caused treatment discontinuation. Other than injection site reactions, the incidence of alirocumab AEs appear similar to those in the control group throughout the individual studies and pooled analyses. The safety of alirocumab in patients with prediabetes versus those with normoglycemia at baseline was analyzed in 10 phase III studies recently; with a follow-up of 24 to 104 weeks, there was no effect on glycemia or safety profile with alirocumab.[29] In another study recruiting over 500 insulin-dependent type I and II diabetics treated with alirocumab, 150 mg q2w or placebo for 24 weeks, there was no difference in TEAEs and no apparent effect on glycemic control.[30]

Safety of Evolocumab

The evolocumab clinical trial program involved mostly shorter 12-week studies with low patient-year exposures. Exceptions were the phase III DESCARTES study (n = 902), which was 52 weeks, the Open-Label Study of Long-Term Evaluation against LDL Cholesterol 1 (OSLER-1) trial (n = 1324), which was an open-label extension of the phase II studies, the OSLER-2 trial (n = 3141), which was an open-label extension of the phase III studies, and FOURIER (n = 27,564), the large cardiovascular outcomes trial. A review of 12 phase II and III evolocumab trials plus the data from the first year of OSLER-1 and -2 determined that the frequency of AEs for evolocumab were similar to those in the control and standard-of-care groups (Table 4).[31] These safety data represent approximately 5500 patient-years of exposure. All AEs, serious AEs, AEs leading to study drug discontinuation, and injection site reactions were similar between the control and evolocumab groups in the phase II and III trials. The most common AEs were nasopharyngitis, upper respiratory infection, influenza, and headache—similar to what was seen in the alirocumab clinical trials. There are limited published safety data for the FOURIER trial. The exposure to evolocumab was approximately 25,300 patient-years. Again, the evolocumab and placebo groups had similar rates of AEs. Any AE occurred in 77.4% of evolocumab patients and 77.4% of placebo patients, serious AEs occurred in 24.8% of the evolocumab group and 24.7% of the placebo group, and AEs leading to study drug discontinuation were 1.6% for evolocumab and 1.5% for placebo. Muscle-related events were 5.0% for the evolocumab group and 4.8% for the placebo group, and new-onset diabetes occurred in 8.1% of the evolocumab group and 7.7% of the placebo group.

A recent paper on evolocumab safety reviewed these trials and the associated safety data.[32] Additionally, specific AEs of interest, including cognitive function, low LDL cholesterol levels, new-onset diabetes, steroid hormones and vitamin E levels, muscle AEs, and injection site reactions, were reviewed. Cognitive function was evaluated in the Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects (EBBINGHAUS) study, a substudy of FOURIER in 1974 patients with 19.8 months of follow-up. Evolocumab appeared to have no effect on cognitive function compared with placebo. Low LDL cholesterol levels are best addressed by the FOURIER trial, which had a median LDL-C of 30 mg/dL in those patients receiving evolocumab. A recent review of LDL-C levels attained at week 4 in the FOURIER trial found no relationship between low LDL-C and AEs over the 2.2-year median duration of the study.[3] Remarkably, 2669 patients

A recent review of LDL-C levels attained at week 4 in the FOURIER trial found no relationship between low LDL-C and AEs over the 2.2-year median duration of the study.

TABLE 3

Adverse Events of Interest[a]

Variable	Placebo-controlled Pool		Ezetimibe-controlled Pool	
	Alirocumab (n = 2,476)	Placebo (n = 1,276)	Alirocumab (n = 864)	Ezetimibe (n = 618)
Local injection site reactions	183 (7.4%)	67 (5.3%)	27 (3.1%)	14 (2.3%)
Rate per 100 patient-years[b]	5.8	4.1	2.5	2.2
HR vs control (95% CI)	1.47 (1.11 to 1.95)		1.49 (0.78 to 2.86)	
Leading to discontinuation	5 (0.2)	4 (0.3)	3 (0.3)	2 (0.3)
General allergic events	237 (9.6%)	105 (8.2%)	67 (7.8%)	38 (6.1%)
Rate per 100 patient-years[b]	7.5	6.5	6.3	6.1
HR vs control (95% CI)	1.15 (0.92 to 1.45)		1.23 (0.82 to 1.85)	
SAEs	12 (0.5%)	5 (0.4%)	2 (0.2%)	2 (0.3%)
Leading to discontinuation	15 (0.6%)	3 (0.2%)	7 (0.8%)	2 (0.3%)
Neurologic events	99 (4.0%)	52 (4.1%)	35 (4.1%)	19 (3.1%)
Rate per 100 patient-years[b]	3.0	3.1	3.2	3.0
HR vs control (95% CI)	0.98 (0.70 to 1.37)		1.27 (0.72 to 2.24)	
SAEs	6 (0.2%)	3 (0.2%)	4 (0.5%)	2 (0.3%)
Leading to discontinuation	6 (0.2%)	2 (0.2%)	4 (0.5%)	3 (0.5%)
Neurocognitive disorders	22 (0.9%)	9 (0.7%)	10 (1.2%)	8 (1.3%)
Rate per 100 patient-years[b]	0.7	0.5	0.9	1.2
HR vs control (95% CI)	1.24 (0.57 to 2.68)		0.81 (0.32 to 2.08)	
SAEs	3 (0.1%)	2 (0.2%)	1 (0.1%)	1 (0.2%)
Leading to discontinuation	0	2 (0.2%)	1 (0.1%)	3 (0.5%)
Ophthalmological events	54 (2.2%)	20 (1.6%)	10 (1.2%)	5 (0.8%)
HR vs control (95% CI)	137 (0.82 to 2.29)		1.11 (0.38 to 3.27)	
Hepatic disorders	72 (2.9%)	29 (2.3%)	23 (2.7%)	16 (2.6%)
HR vs control (95% CI)	1.28 (0.83 to 1.97)		0.84 (0.44 to 1.59)	
Musculoskeletal events[c]	415 (16.8%)	215 (16.8%)	41 (32.5%)	52 (41.9%)
HR vs control (95% CI)	0.99 (0.84 to 1.17)		0.69 (0.46 to 1.04)	
Patients without diabetes at baseline[d]	n = 1,761	n = 908	n = 581	n = 427
Diabetes mellitus or diabetic complications AEs	27 (1.5%)	22 (2.4%)	19 (3.3%)	11 (2.6%)
HR vs control (95% CI)	0.61 (0.35 to 1.08)		0.91 (0.43 to 1.93)	
Patients with diabetes at baseline[d]	n = 715	n = 368	n = 283	n= 191
Diabetes mellitus or diabetic complications AEs	85 (11.9%)	40 (10.9%)	21 (7.4%)	18 (9.4%)
HR vs control (95% CI)	1.07 (0.73 to 1.55)		0.72 (0.38 to 1.35)	

[a]Pool of phase II and III studies. Certain categories of AEs were assessed based on identified, potential, and theoretical risks for the new drug class collected during the clinical trial program.
[b]Number of patients with an event divided by total patients-years.
[c]Ezetimibe-controlled pool data are for the ODYSSEY ALTERNATIVE study only (n = 126 alirocumab, 124 ezetimibe), due to the high rate of events in this study of patients with documented stain intolerance who would otherwise skew results if pooled with the other ezetimibe-controlled trials.
[d]Baseline diabetes defined based on medical history.
AE, adverse event; CI, confidence interval; HR, hazard ratio; SAE, serious adverse event; TEAE, treatment-emergent adverse event; ODYSSEY ALTERNATIVE, Study of Alirocumab in Patients With Primary Hypercholesterolemia and Moderate, High, or Very High Cardiovascular Risk, Who Are Intolerant to Statins.
Data from Jones PH et al.[28]

TABLE 4

Adverse Events From 12 phase II and III Studies and the First-year Data From the OSLER Study

	Parent Studies		Extension Studies Year 1	
Adverse events	Control $n = 2080$	Evolocumab $n = 3946$	SOC $n = 1489$	Evolocumab $n = 2976$
Any AE, *n* (%)	1031 (49.6)	2016 (51.1)	982 (66.0)	2084 (70.0)
SAE, *n* (%)	43 (2.1)	110 (2.8)	116 (7.8)	231 (7.8)
AE → D/C	48 (2.3)	75 (1.9)	N/A	75 (2.5)
Injection site reactions	50 (2.4)	131 (3.3)	N/A	131 (4.1)
Common AEs				
Nasopharyngitis	99 (4.8)	231 (5.9)	142 (9.5)	281 (9.4)
URI	56 (2.7)	127 (3.2)	74 (5.0)	162 (5.4)
Headache	66 (3.2)	120 (3.0)	32 (2.1)	107 (3.6)
Influenza	41 (2.0)	83 (2.1)	45 (3.0)	108 (3.6)
Myalgia	55 (2.6)	98 (2.5)	43 (2.9)	90 (3.0)
Arthralgia	45 (2.2)	91 (2.3)	48 (3.2)	144 (4.8)
Muscle spasms	37 (1.8)	68 (1.7)	30 (2.0)	75 (2.5)
Musculoskeletal pain	24 (1.2)	43 (1.1)	30 (2.0)	62 (2.1)

AE, adverse event; D/C, study drug discontinuation; SAE, serious adverse event; OSLER, Open-Label Study of Long-term Evaluation Against LDL-C; SOC, standard of care; URI, upper respiratory tract infection.
Data from Roth EM.[32]

had an on-treatment LDL-C value <19.3 mg/dL and a median LDL-C of 13.9 mg/dL, and 25% of the subgroup had an LDL-C level <10.8 mg/dL. Despite these extremely low LDL-C levels, this group of patients had levels of AEs similar to the patients with higher LDL-C within the study. New-onset diabetes in all the evolocumab studies to date has not appeared to be different than new-onset diabetes in the control group. Among 16,676 patients without diabetes at baseline, the incidence of new-onset diabetes during the FOURIER trial was 8.1% in patients assigned to evolocumab versus 7.7% in those on placebo. However, almost all patients were on statin therapy, which has been shown to increase the incidence of new-onset diabetes, mainly in those patients who already have impaired fasting glucose levels. This may mask the effect of PCSK9 inhibition on new-onset diabetes. Mendelian randomization studies have suggested that PCSK9 inhibition increases glucose levels similar to and additive to statin therapy, but this has not been seen in either the alirocumab or evolocumab clinical trials to date.[34] The relevance of any increase in glucose levels has not been determined and may be an epiphenomenon. Injection site reactions in FOURIER were 2.1% for evolocumab and 1.6% for placebo ($P < .001$). Injection site reactions for evolocumab in the phase II and III trials were not different than control values but they were typically 12-week studies, so patient exposure was limited. FOURIER was the longest evolocumab trial with the greatest number of participants; injection site reactions being statistically significant in the evolocumab group is consistent with what was seen in the alirocumab studies. Steroid hormone and vitamin E levels were not affected by evolocumab treatment, even with very low LDL-C levels. Additionally, no significant difference was seen in evolocumab versus control for muscle AEs, or in laboratory findings related to muscle or liver abnormalities.[32]

Antidrug Antibodies

mAbs can elicit an immune response because they are a foreign protein. The body forms antidrug antibodies (ADAs) as a defense against an unknown protein. ADAs can lead to AEs such as injection site reactions and more

serious allergic reactions. Certain ADAs can also bind to the mAb in such a way as to block its binding site and stop it from interacting with its target, PCSK9 in the case of alirocumab and evolocumab, potentially affecting LDL-C reduction. This subset of ADAs is called neutralizing antibodies (nAbs). The FDA indicates that it is important to monitor ADAs in clinical trials, and that ADA assays should be sensitive enough to have false-positive results, insuring detection of all ADAs present in the serum. Assay type for ADA measurement and frequency of assessments varied between the alirocumab and evolocumab studies, making direct trial comparisons illegitimate. Alirocumab has a 5.1% incidence of ADAs in alirocumab-treated patients, and 1.4% of patients have nAbs. There has been no apparent loss of efficacy in those patients with alirocumab ADAs or nAbs.[35] Placebo-treated and control subjects in the alirocumab studies have a 1% incidence of ADAs. Evolocumab has very low rates of ADA detection in the shorter 12-week studies, and the FOURIER study showed 0.3% of evolocumab patients with ADAs and none with nAbs. There were no ADAs detected in the placebo group. Injection site reactions in FOURIER were statistically greater in the evolocumab group than the placebo group, which is consistent with the alirocumab data from longer clinical trials. The low rates of ADAs in evolocumab-treated patients may indicate a less immunogenic mAb than alirocumab, but more likely represents a difference in ADA detection assay sensitivities, frequency of testing, and trial duration.

FOURIER: Outcomes Data for Evolocumab

The FOURIER study enrolled 27,564 high-risk, stable patients with prior MI, stroke, or symptomatic peripheral arterial disease (PAD) and randomized them to evolocumab, 140 mg q2w or 420 mg q4w versus placebo if LDL-C levels were ≥70 mg/dL or non–HDL-C levels were ≥100 mg/dL.[4] Baseline median LDL-C was 92 mg/dL on LLT (99%+ on statins) and the median LDL-C with the addition of evolocumab was 30 mg/dL with an interquartile range of 19 to 46 mg/dL. The primary endpoint of cardiovascular death, MI, stroke, hospitalization for unstable angina (UA), or coronary revascularization showed a 15% relative risk reduction for evolocumab compared with placebo. Absolute risk reduction was 2%, 14.6% event rate for placebo, and 12.6% event rate for evolocumab. Individual components of the primary endpoint showed 27% risk reduction for MI (4.4% vs 6.3%), 21% risk reduction for stroke (2.2% vs 2.6%), and 22% risk reduction for coronary revascularization (7.0 vs 9.2). There was no risk reduction for hospitalization for UA (2.2% vs 2.3%) or cardiovascular death (2.5% vs 2.4%). The secondary composite endpoint of cardiovascular death, MI, or stroke showed a 20% relative risk reduction (7.9% vs 9.9%). The trial was an endpoint trial and ended earlier than anticipated because the event rate was double the predicted rate. As a result, median time of follow-up was 26 months, which is relatively short for a cardiovascular outcomes trial. Regarding safety, only injection site reactions (which overall were mild) occurred more frequently in the evolocumab group compared with the placebo group.

ODYSSEY OUTCOMES: Preliminary Outcomes Data for Alirocumab

Topline results were presented at the American College of Cardiology meeting on March 10, 2018, only 7 days after unblinded trial results were available. ODYSSEY OUTCOMES randomized 18,924 patients, 1 to 12 months post–ACS event, who were on high-intensity or maximum tolerated statin and still had an LDL-C ≥ 70 mg/dL or non-HDL-C ≥ 100 mg/dL or apolipoprotein B ≥ 80 mg/dL. LDL-C criteria ≥ 70 mg/dL was the basis for eligibility of 92.5% of randomized participants and 88.6% of those assigned to alirocumab; 89.2% of placebo participants were on high-intensity statin (defined as 40-80 mg of atorvastatin or 20-40 mg of rosuvastatin). An additional 8.8% of alirocumab patients and 9.2% of placebo patients were on low- to moderate-intensity statin. Baseline LDL-C was 87 mg/dL for both groups and a high percentage of both groups were additionally treated with aspirin, P2Y12 inhibitor, beta-blocker, and ACE-I/ARB. The median time from index ACS event to randomization was 2.6 months for both alirocumab and placebo patients. The types of ACS events were essentially equal in the alirocumab and placebo groups, with 48% non-ST-elevation MI, 35% ST-elevation MI, and 17% unstable angina.

Bococizumab was a humanized PCSK9 inhibitor mAb; development was stopped because of significant injection site reactions and decreasing efficacy over time due to high rates of ADAs.

The study was designed to maximize the number of patients in the alirocumab group with LDL-C ≥ 15 mg/dL, but < 50 mg/dL while minimizing the number of patients with sustained levels of LDL-C

< 15 mg/dL (which was quite different than the FOURIER Trial). This was achieved by starting all alirocumab-randomized patients on alirocumab 75 mg q2w from randomization to the month 1 visit. If the month 1 LDL-C was ≥ 50 mg/dL, then alirocumab was increased to 150 mg q2w. If at any future visit the LDL was ≥ 50 mg/dL, then alirocumab was increased to 150 mg q2w if the patient was on 75 mg q2w or continued at 150 mg q2w if they were already on 150 mg q2w. If LDL-C was < 25 mg/dL on two consecutive visits and the patient was on 150 mg q2w, there was blinded down-titration to 75 mg q2w at the next visit and safety monitoring occurred by an independent physician to make sure low LDL-C did not create any specific safety issues. If the patient was on 75 mg q2w and had at least one of the two values ≥ 15 mg/dL, then safety monitoring was instituted, and they continued 75 mg q2w. If, however, both LDL-C values were below 15 mg/dL, then the patient was permanently discontinued from alirocumab for the remainder of the trial. Alirocumab discontinuation occurred in 7.7% of the alirocumab patients and 0% of the placebo patients. Additionally, 14.2% of the alirocumab patients had premature treatment discontinuation for various reasons versus 15.8% of placebo patients. The median time of follow-up was 2.8 years and 44% of patients were followed 3 years or longer. Baseline LDL-C was 87 mg/dL for both groups and the alirocumab group showed an approximate 60% decrease in LDL-C versus no significant change in LDL-C for the placebo group within the first year of the study.

Primary outcome was the composite of CHD death, non-fatal MI, ischemic stroke, and unstable angina requiring hospitalization which occurred in 9.5% of alirocumab patients and 11.1% of placebo patients for a relative risk reduction of 15% ($P = 0.0003$) and an absolute risk reduction of 1.6%. Individual components of the composite for alirocumab versus placebo, respectively, were CHD death, 2.2% versus 2.3% ($P = 0.38$); non-fatal MI, 6.6% versus 7.6% ($P = 0.006$); ischemic stroke, 1.2% versus 1.6% ($P = 0.01$); and unstable angina, 0.4% versus 0.6% ($P = 0.02$). There was no statistical decrease in CHD death or CV death although the numerical trend was in favor of alirocumab. All-cause death showed a 15% decrease with alirocumab ($P = 0.026$), but because of hierarchical testing and failure of CHD and CV death to show benefit, this must be considered a nominal *P* value similar to a post-hoc analysis. A prespecified subgroup analysis looking at effect of baseline LDL-C value on outcomes showed a 24% reduction in the primary endpoint in the alirocumab group with baseline LDL-C ≥ 100 mg/dL versus non-statistically significant reductions in the <80 mg/dL and 80 to 99 mg/dL subgroups. A post-hoc analysis for all-cause death also showed a 29% decrease in the alirocumab group with baseline LDL-C ≥ 100 mg/dL versus no reductions in the <80 mg/dL and 80 to 99 mg/dL subgroups. Safety-wise there was no difference in the alirocumab versus placebo group for treatment emergent adverse events or abnormal laboratory findings. Similar event occurrence was seen for diabetes worsening or diabetes complications, new onset diabetes, neurocognitive events, cataracts, or hemorrhagic strokes. Only injection site reactions occurred more frequently in the alirocumab group, which has been seen in most of the previous studies as well. There will be significantly more safety and efficacy data available in the future that will provide additional insights and results from the ODYSSEY OUTCOMES trial.

SPIRE II: Outcomes Trial of Bococizumab

Bococizumab was a humanized PCSK9 inhibitor mAb; development was stopped because of significant injection site reactions and decreasing efficacy over time due to high rates of ADAs. *Humanized* means the antibody contained approximately 3% mouse protein. However, at the time of discontinuation, an ongoing cardiovascular outcomes study with 10,621 patients, The Evaluation of Bococizumab (PF-04950615; RN316) in Reducing the Occurrence of Major Cardiovascular Events in High Risk Subjects (SPIRE-2), showed positive outcomes.[36] Patients in SPIRE-2 needed an LDL-C value ≥100 mg/dL or a non-HDL-C value ≥130 mg/dL and cardiovascular disease, HeFH, or multiple risk factors for cardiovascular disease to be eligible for study enrollment. Baseline LDL-C was 134 mg/dL and LDL-C reduction at 14 weeks was −56%, but with attenuation was −41.8% at 52 weeks and −38.3% at 104 weeks. The primary study endpoint was nonfatal MI, nonfatal stroke, hospitalization for UA requiring urgent revascularization, and cardiovascular death. The primary endpoint occurred in 179 bococizumab patients and 224 placebo patients for a hazard ratio of 0.79, or a 21% decrease in events in the bococizumab group. Median follow-up at the time of study discontinuation was only 12 months. Despite discontinuation of the bococizumab drug development, SPIRE-2 is the second PCSK9 inhibitor study to show cardiovascular benefits. It should be noted that SPIRE-1 was a lower-risk population study with 16,817 patients, baseline LDL-C of 94 mg/dL, and

median follow-up of only 7 months when discontinued showed no cardiovascular outcomes benefit, as was expected by the short follow-up of a lower-risk population.

Comparison of Study Design of ODYSSEY OUTCOMES and FOURIER

It is important to understand some of the differences between ODYSSEY OUTCOMES and the FOURIER trial. The population in ODYSSEY OUTCOMES were patients 4 to 52 weeks after acute coronary syndrome (ACS), whereas FOURIER enrolled stable patients with a history of MI, stroke, PAD, and cardiovascular risk factors. Median follow-up for FOURIER was 26 months with a range of 1 to 3.5 years, and in ODYSSEY OUTCOMES the median follow-up was 33 months with a range of 2 to 5 years. In FOURIER, 70% of patients were on high-intensity statins, whereas in ODYSSEY OUTCOMES that number is 90%. ODYSSEY OUTCOMES randomized 18,924 patients versus 27,564 patients in FOURIER. ODYSSEY OUTCOMES had 2.9% of patients with stroke versus 19.3% in FOURIER, 3.7% with PAD versus 13.2%, and 100% with ACS (median 2.6 months since event) versus 81% with nonacute MI in FOURIER. Median baseline LDL-C in ODYSSEY OUTCOMES was 87 mg/dL versus 92.0 mg/dL for FOURIER. Patients in FOURIER received evolocumab, 140 mg q2w or 420 mg q4w, but in ODYSSEY OUTCOMES all patients start at 75 mg q2w for the first month and alirocumab dosage of 75 or 150 mg or permanent discontinuation were related to measured LDL-C levels during the study as previously outlined. Finally, ODYSSEY OUTCOMES is looking at coronary heart disease death, which is a narrower definition than cardiovascular death in FOURIER. Additionally, the ODYSSEY OUTCOMES diagnosis of UA is quite strict compared with FOURIER, and coronary revascularization is not included in the ODYSSEY OUTCOMES primary endpoint. Knowing these differences makes a simple comparison of the results of FOURIER and ODYSSEY OUTCOMES improper and unreliable.

Conclusions

Alirocumab and evolocumab, fully human mAbs targeting PCSK9, both significantly lower LDL-C and have AEs similar to those of placebo. Their LDL-C-lowering efficacy ranges from 45% to 65% depending on dose, frequency, and patient population. These two PCSK9 inhibitors have helped clinicians achieve historically low LDL-C levels. We have positive cardiovascular outcomes data for both. Subcutaneous injection of these drugs has been accepted by patients and injection easily accomplished with autoinjectors. Current indications for alirocumab are HeFH or patients with atherosclerotic cardiovascular disease on maximally tolerated statins who need additional LDL cholesterol lowering. Evolocumab received new FDA indications in December 2017 to reduce the risk of MI, stroke, and coronary revascularization in adults with established cardiovascular disease; and, as an adjunct to diet, alone or in combination with other lipid-lowering therapies, for treatment of adults with primary hyperlipidemia (including HeFH) to

MAIN POINTS

- Low-density lipoprotein (LDL) receptors on the surface of liver hepatocytes are the primary way that humans regulate serum LDL cholesterol (LDL-C) levels.
- Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a proteolytic enzyme that indirectly regulates serum LDL-C by regulating the number of LDL receptors on cell surfaces. PCSK9 is an important regulator of serum LDL-C.
- Two PCSK9 inhibitors are currently approved for use: alirocumab and evolocumab. Both are fully human monoclonal antibodies (mAbs) that bind free PCSK9, which prevents PCSK9 from attaching to the LDL receptor.
- The efficacy of the PCSK9 inhibitors to reduce LDL-C is related to the dose of the PCSK9 inhibitor, the baseline free PCSK9 level, the baseline LDL-C level, and the timing of the LDL-C measurement.
- Alirocumab and evolocumab both significantly lower LDL-C and have adverse events similar to those of placebo. Their LDL-C–lowering efficacy ranges from 45% to 65% depending on dose, frequency, and patient population.

reduce LDL-C. Evolocumab also has an indication for HoFH based on the TESLA Part B study. Limiting factors in the use of these two drugs include high cost and difficulty obtaining insurance provider approval for their use. However, over time, the approval process has improved and hopefully with positive outcomes and other data, appropriate utilization will increase, and costs will decrease. The PCSK9 inhibitors represent the most significant progress in lipid therapy since the introduction of statins 30 years ago. The knowledge gained from the PCSK9 inhibitor cardiovascular outcomes trials will expand our lipid knowledge and help shape future lipid guidelines. ■

Dr. Roth has served as a consultant for Sanofi; is a member of the Speakers Bureau for Amgen, Regeneron, and Sanofi; and has received honoraria from Regeneron and Sanofi. Dr. Davidson has served as an consultant and on the Speakers Bureau for Amgen, Regeneron, Sanofi, and Akcea.

References

1. Dietschy JM, Turley SD, Spady DK. Role of liver in the maintenance of cholesterol and low density lipoprotein homeostasis in different animal species, including humans. *J Lipid Res.* 1993;34:1637-1659.
2. Goldstein JL, Brown MS. The LDL receptor. *Arterioscler Thromb Vasc Biol.* 2009;29:431-438.
3. Roth EM, Diller P. Alirocumab for hyperlipidemia: physiology of PCSK9 inhibition, pharmacodynamics and Phase I and II clinical trial results of a PCSK9 monoclonal antibody. *Future Cardiol.* 2014;10:183-199.
4. Sabatine MS, Giugliano RP, Keech AC, et al; FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med.* 2017;376:1713-1722.
5. 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;168:682-689.
6. McKenney JM. Understanding PCSK9 and anti-PCSK9 therapies. *J Clin Lipidol.* 2015;9:170-186.
7. Rey J, Poitiers F, Paehler T, et al. Relationship between low-density lipoprotein cholesterol, free proprotein convertase subtilisin/kexin type 9, and alirocumab levels after different lipid-lowering strategies [published online June 10, 2016]. *J Am Heart Assoc.* doi: 10.1161/JAHA.116.003323.
8. Stein EA, Koren M, Honarpour N, et al. Clinical equivalence of evolocumab 140 mg every two weeks and 420 mg monthly dosing regimens: a pooled analysis of 3146 patients in phase 3 studies. *JACC.* 2015;65(10S):A1368.
9. Catapano AL, Lee LV, Louie MJ, et al. Efficacy of alirocumab according to background statin type and dose: pooled analysis of 8 ODYSSEY Phase 3 clinical trials. *Sci Rep.* 2017;7:45788.
10. Roth EM, McKenney JM, Hanotin C, et al. Atorvastatin with or without an antibody to PCSK9 in primary hypercholesterolemia. *N Engl J Med.* 2012;367:1891-1900.
11. BlomDJ, Hala T, Bolognese M, et al ; DESCARTES Investigators. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. *N Engl J Med.* 2014;370:1809-1819.
12. Robinson JG, Nedergaard BS, Rogers WJ, et al; LAPLACE-2 Investigators. Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. *JAMA.* 2014;311:1870-1882.
13. Kastelein JJ, Ginsberg HN, Langslet G, et al. ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia. *Eur Heart J.* 2015;36:2996-3003.
14. Kereiakes DJ, Robinson JG, Cannon CP, et al. Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy: the ODYSSEY COMBO I study. *Am Heart J.* 2015;169:906-915.
15. Cannon CP, Cariou B, Blom D, et al; ODYSSEY COMBO II Investigators. Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated doses of statins: the ODYSSEY COMBO II randomized controlled trial. *Eur Heart J.* 2015;36:1186-1194.
16. Bays H, Gaudet D, Weiss R, et al. Alirocumab as add-on to atorvastatin versus other lipid treatment strategies: ODYSSEY OPTIONS I randomized trial. *J Clin Endocrinol Metab.* 2015;100:3140-3148.
17. 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.* 2016;244:138-146.
18. Roth EM, McKenney JM. ODYSSEY MONO: effect of alirocumab 75 mg subcutaneously every 2 weeks as monotherapy versus ezetimibe over 24 weeks. *Future Cardiol.* 2015;11:27-37.
19. Moriarty PM, Jacobson TA, Bruckert E, et al. Efficacy and safety of alirocumab, a monoclonal antibody to PCSK9, in statin-intolerant patients: design and rationale of ODYSSEY ALTERNATIVE, a randomized Phase 3 trial. *J Clin Lipidol.* 2014;8:554-561.
20. Vallejo-Vaz A, Roth EM, Hovingh GK, et al. Predictive factors for alirocumab dose increase in patients with hypercholesterolaemia and high cardiovascular risk: analyses from the ODYSSEY COMBO I and II trials. Poster presented at: European Society of Cardiology Annual Meeting; August 26-30 2017: Barcelona, Spain.
21. Kastelein JJ, Kereiakes DJ, Cannon CP, et al. Effect of alirocumab dose increase on LDL lowering and lipid goal attainment in patients with dyslipidemia. *Coron Artery Dis.* 2017;28:190-197.
22. 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. *Cardiovasc Drugs Ther.* 2016;30:473-483.
23. Robinson JG, Farnier M, Krempf M, et al; ODYSSEY LONG TERM Investigators. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med.* 2015;372:1489-1499.
24. Roth EM, Moriarty PM, Bergeron J, et al; ODYSSEY CHOICE I investigators. A phase III randomized trial evaluating alirocumab 300 mg every 4 weeks as monotherapy or add-on to statin: ODYSSEY CHOICE I. *Atherosclerosis.* 2016;254:254-262.
25. Stroes E, Colquhoun D, Sullivan D, et al; GAUSS-2 Investigators. Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. *J Am Coll Cardiol.* 2014;63:2541-2548.
26. Raal FJ, Stein EA, Dufour R, et al; RUTHERFORD-2 Investigators. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2015;385:331-340.
27. Raal FJ, Honarpour N, Blom DJ, et al; TESLA Investigators. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2015;385:341-350.
28. Jones PH, Bays HE, Chaudhari U, et al. Safety of alirocumab (a PCSK9 monoclonal antibody) from 14 randomized trials. *Am J Cardiol.* 2016;118:1805-1811.
29. Leiter LA, Müller-Wieland D, Baccara-Dinet MT, et al. Efficacy and safety of alirocumab in people with prediabetes vs those with normoglycaemia at baseline: a pooled analysis of 10 phase III ODYSSEY clinical trials. *Diabet Med.* 2017;35:121-130.
30. Leiter LA, Cariou B, Müller-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 Obes Metab.* 2017;19:1781-1792.
31. Toth PP, Descamps O, Genest J, et al; PROFICIO Investigators. Pooled safety analysis of evolocumab in over 6000 patients from double-blind and open label extension studies. *Circulation.* 2017;135:1819-1831.
32. Roth EM. A safety evaluation of evolocumab. *Expert Opin Drug Saf.* 2017;16:1-8.
33. Giugliano RP, Pedersen TR, Park JG, et al; FOURIER Investigators. Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial. *Lancet.* 2017;390:1962-1971.
34. Ference BA, Robinson JG, Brook RD, et al. Variation in PCSK9 and HMGCR and risk of cardiovascular disease and diabetes. *N Engl J Med.* 2016;375:2144-2153.
35. Roth EM, Goldberg AC, Catapano AL, et al. Antidrug antibodies in patients treated with alirocumab. *N Engl J Med.* 2017;376:1589-1590.
36. Ridker PM, Revkin J, Amarenco P, et al; SPIRE Cardiovascular Outcome Investigators. Cardiovascular efficacy and safety of bococizumab in high-risk patients. *N Engl J Med.* 2017;376:1527-1539.
37. 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;168:682-689.
38. Lambert G, Sjouke B, Choque B, et al. The PCSK9 decade. *J Lipid Res.* 2012;53:2515-2524.