What is the potential place in therapy of the PCSK9 inhibitors, evolocumab and alirocumab, for hypercholesterolemia?

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Introduction

According to recently published heart disease and stroke statistics, it is estimated that 73.5 million adults in the United States (US) have dyslipidemia in the form of elevated low-density lipoprotein cholesterol (LDL-C).[1] Individuals with hypercholesterolemia, in general, are at twice the risk of atherosclerotic cardiovascular disease (ASCVD) compared to those with normal cholesterol levels.[2] The World Health Organization recognizes ASCVD as the leading cause of death worldwide.[3] Risk factors for ASCVD include total cholesterol greater than 170 mg/dL, high-density lipoprotein cholesterol (HDL-C) less than 50 mg/dL, hypertension with a systolic blood pressure greater than 110 mmHg, diabetes, and smoking.[4]

Heterozygous familial hypercholesterolemia (HeFH) and homozygous familial hypercholesterolemia (HoFH) are conditions that result in elevated LDL-C levels ranging from 190 mg/dL to 400 mg/dL or higher.[5] Patients with FH are at high risk for heart attack and sudden cardiac death due to elevated LDL-C levels despite optimal statin therapy. One in 200 to 500 people worldwide have HeFH, while only 1 in 160,000 to 1,000,000 people worldwide have HoFH. According to the European Atherosclerosis Society, less than 1% of FH is diagnosed in most countries.[6] Although HeFH is a relatively common condition accounting for 60-80% of FH, patients with this genetic abnormality are under-diagnosed and subsequently under-treated with lipid-lowering therapy (LLT).[6,7]

In 2013, the American College of Cardiology and American Heart Association (ACC/AHA) released new guidelines for the management of blood cholesterol to reduce ASCVD risk.[4] Unlike the previous recommendations from the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III, the ACC/AHA does not recommend treating to a target cholesterol level.[8] In addition, treating to the lowest possible LDL-C level or treating based on lifetime ASCVD risk is not advocated as there are no long-term data to support association with a reduction in ASCVD risk.[4] The ACC/AHA have developed a novel, pooled cohort equation which calculates an individual patient's ASCVD risk score. This score estimates the patient's 10-year risk of cardiovascular (CV) disease or stroke, and it can be used to determine the appropriate intensity of statin therapy. For patients with primary hyperlipidemia and statin intolerance due to adverse events (AEs) such as myalgia, the ACC/AHA recommends use of non-statin cholesterol-lowering drugs, such as oral ezetimibe, which have demonstrated a reduction in ASCVD events.

It is known that individuals with inherited deficiencies in proprotein convertase subtilisin/kexin type 9 (PCSK9) have low LDL-C, and as a result, a reduced ASCVD risk.[9] PCSK9 binds to and facilitates LDL-C receptor degradation in the liver, which leads to elevated levels of circulating LDL-C in the blood. Due to its role in LDL-C metabolism, it has been proposed that inhibition of PCSK9 and the resulting increase in hepatic LDL-C receptors may lower LDL-C as well as morbidity in hyperlipidemia patients, regardless of a patient's genotype.[10] Currently, 2 targeted monoclonal antibodies, evolocumab and alirocumab, are approved for treatment of FH and high-risk hyperlipidemia respectively.[11,12] Both are approved as an adjunct to diet and maximally tolerated statin therapy for treatment of HeFH or clinical ASCVD, in adult patients requiring further

LDL-C reduction. Evolocumab is also approved as an adjunct to diet and other LLT (e.g., statins, ezetimibe, LDL-C apheresis) in patients aged ≥12 years with HoFH requiring further LDL-C reduction.

There are no published, long-term trials investigating the clinical outcomes or ASCVD reduction caused by these drugs. However, long-term trials investigating the safety of these agents after 52 weeks have been completed.[13-15] Available data suggest that the drugs are efficacious in the reduction of LDL-C; however, they are costly, specialty medications. This may present a challenge to healthcare payers, particularly in consideration of the prevalence of hypercholesterolemia.[16] Given these issues, as well as the novelty of these agents, it is important to determine the role of the PCSK9 inhibitors in LLT.

Literature Review

A search of the literature revealed several studies involving the use of evolocumab and alirocumab in patients with various types of hypercholesterolemia: HeFH or HoFH, hypercholesterolemia in statin-intolerant patients, and drug-resistant hypercholesterolemia. According to a retrospective cohort study by Zhang et al that spanned over 8 years, 10-20% of patients from 2 Massachusetts hospitals could not tolerate statin therapy, leading to either temporary or permanent discontinuation.[17] Patients who are unable to tolerate statins may remain at an elevated ASCVD risk if nonstatin therapy fails to produce adequate LDL-C-lowering. The ACC/AHA recommend nonstatin therapy for statin-intolerant patients, as well as for individuals with severe or refractory hypercholesterolemia in combination with optimal statin therapy.[4] Ezetimibe is a widely used, nonstatin LLT agent that serves as a comparator arm in many of the studies examining PCSK9 inhibitors.

In phase III trials, evolocumab was administered subcutaneously (SC) at 140 mg (2 mL doses) every 2 weeks (q2w) or 420 mg (three, 2 mL or two, 3 mL doses) every 4 weeks (q4w).[12,18,19] Phase III clinical trials investigating alirocumab were implemented utilizing 3 different dosing strategies that were available as 1 mL-prefilled autoinjection pen: 75 mg SC q2w, 150 mg SC q2w, and 150 mg SC q4w.[20,21]

Evolocumab

Amgen Inc. conducted investigations of evolocumab through its *P*rogram to *R*educe LDL-C cholesterol and Cardiovascular *O*utcomes *F*ollowing *I*nhibition of P*C*SK9 *I*n Different P*o*pulations (PROFICIO).[22] Within phase 3 of this program, there were 16 total trials evaluating the use of evolocumab in combination with statins or as monotherapy for patients with hypercholesterolemia, statin-intolerant hypercholesterolemia, or FH. To date, 10 phase III clinical trials from this program have been completed.[13,14,19,23-30] Published results were found for 8 of these studies (see Table 1).[13,14,19,23-28]

Of the 8 available trials, 2 investigated the safety and efficacy of evolocumab as an adjunctive agent to stable statin therapy in patients with hypercholesterolemia (LAPLACE-2 and YUKAWA-2),[24,27,28] 1 examined evolocumab in the context of statin-intolerance (GAUSS-2),[23] 1 as monotherapy in patients with hypercholesterolemia (MENDEL-2),[25] and 2 as an adjunctive agent to stable statin therapy in patients with FH (RUTHERFORD-2 and TESLA part B).[19,26] Two trials have been completed that establish the sustained efficacy of evolocumab after approximately 1 year of therapy (OSLER-2 and DESCARTES).[13,14]

With the exception of TESLA, OSLER-2, and DESCARTES, the co-primary efficacy endpoints of all studies in Table 1 were the percent change from baseline in LDL-C at the mean of weeks 10 to 12 and at week 12.[13,14,19,23-28] Instead of examining the mean percent change from baseline in LDL-C at weeks 10 to 12, the investigators of the TESLA trial solely observed change from baseline at week 12.[19] Due to the longer study durations in OSLER-2 and DESCARTES, the investigators of these trials looked at the percent change from baseline in LDL-C at weeks 48 and 52 respectively.[13,14] The following safety endpoints were shared among all 8 trials: the incidence of treatment-emergent AEs (TEAEs), incidence of serious TEAEs, incidence of anti-

Table 1. Available results from phase III clinical trials investigating evolocumab.

Study*	Design/ Duration	Population	Intervention(s)**	Percent *reduction* in LDL-C from baseline	Conclusions
DESCARTES[14]	R, DB, PC 52 weeks	n=901 patients with HC; aged 18-75 years with LDL-C ≥75 mg/dL and fasting TG ≤400 mg/dL, while receiving statin therapy with or without ezetimibe	Run-in period (open-label): Background LLT for 4-12 weeks Blinded phase: Evolocumab 420 mg q4w PB -8 total treatment groups	At week 12: 57.5±1.6% (p<0.001) At week 52: Overall least-squares mean reduction taking into account change in PB group: 57.0±2.1% (p<0.001)	Evolocumab added to diet alone, to low-dose atorvastatin, or to high-dose atorvastatin with or without ezetimibe significantly reduced LDL-C levels in HC patients with varying CV risks.
GAUSS-2[23]	R, DB, DD AC 12 weeks	n=307 patients with HC and statin intolerance; aged 18 to 80 years with LDL-C 100-190 mg/dL on no or low-dose statin therapy	Evolocumab 140 mg q2w Evolocumab 420 mg q4w Ezetimibe 10 mg QD PB -4 total treatment groups	At the mean of weeks 10-12: Evolocumab 140 mg q2w: 56.1% (95% CI: 52.5% to 59.7%) Evolocumab 420 mg q4w: 55.3% (95% CI: 52.3% to 58.3%) -Mean % reductions in LDL-C from baseline and treatment differences at week 12 were similar (p<0.001)	Evolocumab significantly reduced LDL-C with favorable tolerability in HC patients that were statin-intolerant. Treatment may address the unmet clinical need of high-risk, statin-intolerant patients with elevated LDL-C despite nonstatin therapy.
LAPLACE-2[24]	R, DB, PC, AC 12 weeks	n=2067 patients with HC and mixed dyslipidemia on moderate- or high-intensity statin therapy with elevated LDL-C stratified to intensity of statin therapy: ≥80 mg/dL (intensive statin at screening), ≥100 mg/dL (nonintensive statin at screening), or ≥150 mg/dL (no statin at screening)	Run-in period (open-label): Background LLT (moderate or high intensity statin therapy) for 4 weeks Blinded phase: Patients taking rosuvastatin or simvastatin during run-in period were randomized to: Evolocumab 140 mg q2w Evolocumab 420 mg q4w, PB -4 total treatment groups Patients taking atorvastatin were randomized to: Evolocumab 140 mg q2w Evolocumab 420 mg q4w PB Ezetimibe 10 mg QD -24 total treatment groups	At the mean of weeks 10-12 for both moderate- and high-intensity statin-treated groups: Evolocumab 140mg q2w: 66% (95% CI: 58% to 73%) to 75% (95% CI: 65% to 84%) vs. PB Evolocumab 420mg q4w: 63% (95% CI: 54% to 71%) to 75% (95% CI: 67% to 83%) vs. PB -Mean % reductions in LDL-C from baseline at week 12 were similar (p<0.001)	Evolocumab added to moderate- or high-intensity statin therapy in HC and mixed dyslipidemia patients resulted in additional LDL-C lowering.

Study*	Design/ Duration	Population	Intervention(s)**	Percent *reduction* in LDL-C from baseline	Conclusions
MENDEL-2[25]	R, DB, PC, AC 12 weeks	n=614 patients with HC not on statin therapy; aged 18-80 years with fasting LDL-C 100-190 mg/dL, TG ≤400 mg/dL, and Framingham risk score ≤10%	Evolocumab 140 mg q2w Evolocumab 420 mg q4w Ezetimibe 10 mg QD PB -6 total treatment groups (stratified by LDL-C <130 mg/dL vs. ≥130 mg/dL)	At the mean of weeks 10-12: Evolocumab 140 mg q2w: 56.9% (95% CI: 54.8% to 59%) PB: 0.4% (95% CI: -3.3% to 2.4) Ezetimibe: 17.5% (95% CI: 14.7% to 20.4%) Evolocumab 420 mg q4w: 58.5% (95% CI: 56.8% to 60.8%) PB: 1.4% (95% CI: -4.1% to 1.3%) Ezetimibe: 19.1% (95% CI: 16.2% to 21.9%) -Mean % reductions in LDL-C from baseline at week 12 were similar (p<0.001)	Evolocumab as monotherapy significantly reduced LDL-C levels in HC patients not on statin therapy compared with PB or ezetimibe.
RUTHERFORD-2[26]	R, DB, PC 12 weeks	n=331 patients with HeFH; aged 18-80 years with LDL-C ≥75 mg/dL on stable, statin therapy ≥4 weeks with or without ezetimibe	Evolocumab 140 mg q2w Evolocumab 420 mg q4w PB -4 total treatment groups	At the mean of weeks 10-12: Evolocumab 140 mg q2w: 60.2% (95% CI: 54.5% to 65.8%) vs. PB Evolocumab 420 mg q4w: 65.6% (95% CI: 59.8% to 71.3%) vs. PB -Mean % reductions in LDL-C from baseline at week 12 were similar (p<0.001)	Evolocumab has efficacy in the HeFH patient population. Both dosing modalities were well tolerated and resulted in similar, rapid 60% reductions in LDL-C compared with PB.

Study*	Design/ Duration	Population	Intervention(s)**	Percent *reduction* in LDL-C from baseline	Conclusions
OSLER-2[13]	R, OL, AC Median duration of follow-up: 11.1 months	n=3141 patients who were enrolled in 7 phase III parent trials[14,24-29] and who agreed to participate in this extension study	Evolocumab 140mg q2w Evolocumab 420mg q4w Standard therapy -2 total treatment groups (stratified by parent trial and study-drug dose frequency in the parent trial) Note: evolocumab dosing in treatment group was based on patient choice; standard therapy was based on local guidelines for the treatment of LDL-C.	At week 12: Evolocumab arm: 61% (95% CI: 59% to 63%) vs. PB At week 48: Evolocumab arm: 58.4% (p<0.001)	Compared to standard therapy alone, patients treated with evolocumab combined with standard therapy for approximately 1 year experienced significantly reduced LDL-C levels and a reduced incidence of CV events.
TESLA (PART B)[19]	R, DB, PC 12 weeks	n=49 HoFH patients; aged ≥20 years; on stable LLT ≥ 4 weeks with LDL-C ≥130 mg/dL, TG ≤400 mg/dL, and body weight ≥40 kg. Patients were also not receiving lipoprotein apheresis.	Evolocumab 420 mg q4w PB -2 total treatment groups (stratified by LDL-C at screening of <425 mg/dL vs. ≥ 425 mg/dL)	At week 12: 30.9% (95% CI: 18% to 43.9%; p<0.0001) vs. PB	Evolocumab 420 mg q4w was well tolerated and significantly reduced LDL-C compared with PB for patients with HoFH receiving stable, background LLT and not on apheresis.
YUKAWA-2[27,28]	R, DB, PC 12 weeks	n=404 Japanese patients with HC or mixed dyslipidemia; aged 20-80 years at high CV risk with LDL-C ≥100 mg/dL and fasting TG ≤400 mg/dL	Two-step randomization: Background LLT (atorvastatin 5 mg or 20 mg) for 4 weeks followed by randomization to: Evolocumab 140 mg q2w Evolocumab 420 mg q4w PB -8 total treatment groups	At the mean of weeks 10-12 and at week 12: 67-76% compared to PB (p=not reported)	Either dosing modality of evolocumab in combination with low or high-dose statin therapy accomplished significant LDL-C reductions compared to PB in Japanese patients with high CV risk and high LDL-C.

*Expanded study names are as follows: DESCARTES=Durable Effect of PCSK9 Antibody Compared with Placebo Study; GAUSS-2=Goal Achievement after Utilizing an anti-PCSK9 antibody in Statin Intolerant subjects; LAPLACE-2=LDL-C Assessment with PCSK9 Monoclonal Antibody Inhibition Combined With Statin Therapy; MENDEL-2=Monoclonal Antibody Against PCSK9 to Reduce Elevated LDL-C in Patients Currently Not Receiving Drug Therapy For Easing Lipid Levels-2; RUTHERFORD-2=The Reduction of LDL-C With PCSK9 Inhibition in Heterozygous Familiar Hypercholesterolemia Disorder-2; TESLA Part B=Trial Evaluating PCSK9 Antibody in Subjects with LDL-C Receptor Abnormalities Part B; YUKAWA-2=Study of LDL-C Reduction Using a Monoclonal PCSK9 Antibody in Japanese Patients with Advanced Cardiovascular Risk

**All doses of evolocumab were administered subcutaneously; all doses of ezetimibe were administered orally.

AC=active-controlled; AE=adverse event; CI=confidence interval; CK=creatine kinase; CV=cardiovascular; DB=double-blind; DD=double-dummy; ECG=electrocardiography; HC=hypercholesterolemia; HeFH=heterozygous familial hypercholesterolemia; HoFH=homozygous familial hypercholesterolemia; LDL-C=low-density lipoprotein cholesterol; LLT=lipid-lowering therapy; OL=open-label; PB=placebo; PC=placebo-controlled; q2w=every 2 weeks; q4w=every 4 weeks; QD=daily; R=randomized; TG = triglycerides

evolocumab antibodies, elevations in creatine kinase (CK) or liver function tests (LFTs), and the incidence of adjudicated CV events.[13,14,19,23-28] TESLA and YUKAWA-2 also included measurement of electrocardiogram (ECG) parameters in their safety endpoints.[19,27,28]

After reviewing the data from these studies, it was found that both evolocumab dosing regimens resulted in greater LDL-C reductions compared to all other therapies that were incorporated in the other treatment arms.[13,14,19,23-28] Of these trials, patients with primary hypercholesterolemia, statin-intolerant hypercholesterolemia, HeFH, and HoFH are represented. The addition of evolocumab to optimal statin therapy resulted in reductions in LDL-C from baseline of 57% to 76% depending on the specific time frame for evaluation of the endpoint and evolocumab dosing strategy used within each study. When used as monotherapy for patients with hypercholesterolemia, or added to a low-dose statin regimen in statin-intolerant patients, evolocumab 140 mg SC q2w and evolocumab 420 mg SC q4w both achieved LDL-C reductions from baseline of 52% to 58.5% after 12 weeks of therapy.[23,25] Although it seems that the LDL-C-lowering effect of evolocumab was greater with baseline statin therapy, this was not the case. The patient populations within each trial were diverse, which precludes definitive conclusions on the LDL-C-lowering effects. On average, evolocumab reduced LDL-C by 52% to 76% in patients with hypercholesterolemia regardless of baseline statin therapy.

Compared to ezetimibe, both evolocumab-dosing strategies resulted in 37% to 45% greater reductions in LDL-C from baseline.[13,23-25] The recent results of the IMPROVE-IT trial demonstrated that the addition of ezetimibe to a statin significantly reduced ASCVD events through additional LDL-C reduction compared to statin monotherapy.[31] From this, it can be deduced that the addition of evolocumab to statin therapy in hypercholesterolemia patients will result in greater reductions in LDL-C, greater reductions in ASCVD events, and improved clinical outcomes compared to ezetimibe plus statin therapy. Ongoing, long-term trials investigating the incidence of ASCVD events will confirm or refute these points.

The following trials are analyzed further in order to demonstrate the efficacy of evolocumab in FH. RUTHERFORD-2 and TESLA studied evolocumab in patients with HeFH and HoFH, respectively.[19,26] The design, interventions, and results of these 2 trials are depicted in Table 1. Patients with HeFH included in RUTHERFORD-2 had LDL-C concentrations ≥100 mg/dL despite intense LLT with a statin. These patients experienced mean reductions in LDL-C from baseline of 60.2% to 65.6% at weeks 10 to 12 with evolocumab 140 mg SC q2w and evolocumab 420 mg SC q4w, respectively. These results were unrelated to patient age, gender, body-mass index, baseline LDL-C, intensity of statin therapy, or concomitant use of ezetimibe, further demonstrating the efficacy of evolocumab in HeFH. In addition, these results are similar to the LDL-C reductions seen in patients with primary hypercholesterolemia. Patients with HoFH from the TESLA trial, on average, experienced a 30.9% reduction in LDL-C from baseline with 12 weeks of evolocumab 420 mg SC q4w therapy.[19] Although these reductions were significant, they were of less magnitude compared to the reductions seen in patients with HeFH or primary hypercholesterolemia. This may be attributed to the severity of hypercholesterolemia and nature of the LDL-C receptor mutation caused by this genetic disorder. Although LDL-C reductions were seen in varying degrees, these 2 trials established the efficacy of evolocumab in FH.[19,26]

With regard to safety and tolerability of evolocumab, musculoskeletal symptoms, arthralgia, headache, nasopharyngitis, influenza, pain in the extremities, and back pain were cumulatively reported as the most common AEs.[13,14,19,23-28] There were similar incidences of neurocognitive AEs and lower incidences of injection-site reactions with evolocumab compared to placebo. The incidences of serious TEAEs were ≤4% in all of the 12 week trials,[19,23-26] and ≤5.5% in DESCARTES.[14] In OSLER-2, the incidence of serious TEAEs for both the evolocumab group and standard-therapy group was reported as 7.5%.[13] These serious TEAEs rarely led to evolocumab treatment discontinuation in all trials.[13,14,19,23-28] With the exception of 0.3% of patients in the evolocumab group in OSLER-2,[13] no new anti-evolocumab neutralizing-antibodies were detected after study completion.[13,14,19,23-28] A statistically insignificant number of patients developed new, anti-evolocumab binding-

antibodies; however, the development of these antibodies did not result in treatment discontinuation or serious TEAEs. During the studies, 2 deaths occurred while on evolocumab therapy.[14] These occurred due to heart failure and myocardial infarction in the DESCARTES trial. Lastly, the incidences of abnormal elevations in CK and LFTs were insignificant throughout the studies as they were either similar or lower than the rates reported in the comparator arm(s).[13,14,19,23-28]

In summary, these trials were successful in determining the efficacy and safety of evolocumab in multiple patient populations.[13,14,19,23-28] This monoclonal antibody was well-tolerated and produced significant reductions in LDL-C. More long-term trials similar to OSLER-2 are needed to substantiate the premise that additional reductions in LDL-C will result in reduced ASCVD events.[13]

Alirocumab

As stated previously, there are multiple trials evaluating the use of alirocumab in the context of FH, drug-resistant hypercholesterolemia, or statin intolerance. Funded by Sanofi and Regeneron Pharmaceuticals, Inc., the ODYSSEY phase III clinical trial program consists of 14 studies, 12 of which have been completed to date.[32] Findings from 9 of these studies have been accessed through meeting abstracts, presentation slides, or published articles in medical journals. Available data from these studies are outlined in Table 2.[15,20,21,33-38]

Of the 9 available trials, 6 investigated the safety and efficacy of alirocumab in patients with hypercholesterolemia on optimal and stable statin therapy (ODYSSEY COMBO I, COMBO II, HIGH FH, LONG-TERM, OPTIONS I, and OPTIONS II);[15,20,21,35-37] 4 investigated the use of alirocumab in patients with HeFH (ODYSSEY HIGH FH, ODYSSEY LONG-TERM, OPTIONS I, and OPTIONS II);[15,20,21,37] 2 investigated the use of alirocumab in patients with statin-intolerance (ODYSSEY ALTERNATIVE and ODYSSEY CHOICE II);[33,34] and 1 compared the use of alirocumab to ezetimibe as monotherapy for the treatment of hypercholesterolemia (ODYSSEY MONO).[38] Four of these trials investigated the sustained efficacy of alirocumab after ≥52 weeks of therapy (ODYSSEY COMBO I, COMBO II, ODYSSEY HIGH FH, and LONG-TERM).[15,35-37]

The primary endpoint of the ODYSSEY studies was percent reduction in LDL-C from baseline to week 24.[15,20,21,33-38] The safety endpoints of all studies were as follows: incidence of TEAEs, serious TEAEs, serious TEAEs leading to death or treatment discontinuation, laboratory abnormalities, ECG abnormalities, vital sign abnormalities, and adjudicated CV events.

All 9 trials were successful in demonstrating a statistically significant reduction in LDL-C from baseline with alirocumab therapy.[15,20,21,33-38] Those receiving treatment included patients with primary hypercholesterolemia, statin-intolerant hypercholesterolemia, and HeFH. The results from these trials showed that alirocumab was efficacious compared to both placebo and ezetimibe therapy. The addition of alirocumab to optimal statin therapy generally resulted in reductions in LDL-C from baseline of 45% to 61%.[15,20,21,33-37] Compared to ezetimibe, alirocumab achieved 30% greater reductions.[33,38] When used as monotherapy in hypercholesterolemia patients for LLT with or without statin-intolerance, reductions in LDL-C from baseline of 45% to 47.2 % were observed.[33,34,38] According to these data, addition of alirocumab to optimal statin therapy resulted in significantly greater LDL-C reductions compared to statin monotherapy. This finding appears to be consistent throughout the trials (see Table 2).[15,20,21,33-38] Regardless of baseline LLT, alirocumab was efficacious in further reducing LDL-C levels, which supports its use in high-risk patients with hypercholesterolemia.

The ODYSSEY LONG-TERM, HIGH FH, and OPTIONS studies investigated alirocumab in the HeFH patient population.[15,20,21,37] By design, patients within the ODYSSEY OPTIONS study did not have their statin therapy optimized prior to the addition of alirocumab.[20,21] Therefore, the results of these 2 studies may not accurately reflect the true LDL-C reduction potential of alirocumab. Patients in the ODYSSEY LONG-TERM and HIGH FH trials were on optimized statin therapy, and these results can be extrapolated to the HeFH patient population.[15,37]

Table 2. Available results from phase III clinical trials investigating alirocumab.

Study	Design/ Duration	Population	Intervention(s)*	Percent *reduction* in LDL-C from baseline at week 24	Conclusions
ODYSSEY ALTERNATIVE[33¶]	R, DB, DD, AC 24 weeks	n=314 patients with HC and statin-intolerance; with LDL-C ≥70 mg/dL for very-high ASCVD risk, or LDL-C ≥100 for moderate-to-high ASCVD risk	Run-in period: PB DB treatment period: Alirocumab 75 mg q2w Ezetimibe 10 mg QD Atorvastatin 20 mg QD -3 total treatment groups	Using the least squares method: Alirocumab: 45.0% (p=not reported) Ezetimibe: 14.6% (p=not reported) Treatment difference: 30.4% p<0.0001	In statin-intolerant patients with baseline LDL-C levels ≥190 mg/dL, alirocumab produced significantly greater LDL-C reductions allowing a greater percentage of patients to achieve their LDL-C goals compared to ezetimibe. In addition, alirocumab was better tolerated in comparison to atorvastatin.
ODYSSEY CHOICE II[34€]	R, DB, PC 24 weeks	n=233 patients with HC and statin-intolerance managed with either diet, fenofibrate, or ezetimibe	Alirocumab 75 mg q2w Alirocumab 150 mg q4w PB -3 total treatment groups	Results not available	This trial established that alirocumab has efficacy in statin-intolerant patients utilizing the following background LLT: fenofibrate, ezetimibe, or diet. It also established alirocumab 150 mg q4w as an efficacious dosing strategy.
ODYSSEY COMBO I[35❖]	R, DB, PC 52 weeks	n=316 patients with HC; established CHD or CHD risk equivalents and LDL-C ≥70 mg/dL or ≥100 mg/dL respectively; on optimal statin therapy with or without other LLT	Alirocumab 75 mg q2w PB -2 total treatment groups	45.9% (95% CI: 39.3% to 52.5%) vs. PB (p<0.0001)	Despite optimal statin therapy, alirocumab treatment resulted in additional and significantly greater reductions in LDL-C in high CV risk patients compared to PB. Subsequently, alirocumab treatment allowed more patients to achieve their LDL-C goals.
ODYSSEY COMBO II[36¶]	R, DB, DD, AC 52 weeks for efficacy analysis 102 weeks for safety analysis	n=720 patients with HC at high CV risk; on optimal statin therapy; with LDL-C ≥70 mg/dL for those with established CVD or LDL-C ≥100 mg/dL for those without established CVD	Alirocumab 75 mg q2w Ezetimibe 10 mg QD PB -2 total treatment groups	Using the least squares method: Alirocumab: 50.6% (p=not reported) Ezetimibe: 20.7% (p=not reported) Treatment difference: 29.8% (p<0.0001)	In high CV risk patients on optimal standard-of-care therapy, the addition of alirocumab resulted in significantly greater reductions in LDL-C compared to ezetimibe. Seventy-seven percent of patients achieved an LDL-C goal of <70 mg/dL, and 80% did not require up-titration in

Study	Design/ Duration	Population	Intervention(s)*	Percent *reduction* in LDL-C from baseline at week 24	Conclusions
					alirocumab dose.
ODYSSEY HIGH FH[37¶]	R, DB, PB 52 weeks for efficacy analysis 102 weeks for safety analysis	n=107 patients with HeFH on optimal statin therapy with or without other LLT; LDL-C ≥160 mg/dL	Alirocumab 150 mg q2w PB -2 total treatment groups	Using the least squares method: Alirocumab: 45.7% (p=not reported) PB: 6.6% (p=not reported) Treatment difference: 39.1% (p<0.0001)	Despite optimal statin therapy, alirocumab produced significantly greater LDL-C reductions at week 24 compared to PB and subsequently allowed more patients to achieve an LDL-C goal <70 mg/dL despite baseline LDL-C >190 mg/dL.
ODYSSEY LONG-TERM[15❖]	R, DB, PC 78 weeks	n=2341 patients with HeFH or HC at high CV risk on optimal statin therapy; LDL-C ≥70 mg/dL	Alirocumab 150 mg q2w PB -2 total treatment groups	Alirocumab: 61.0% ± 0.7% PB: 0.8% ± 1.0% Treatment difference: 61.9% ± 1.3%	When added to optimal statin therapy, alirocumab achieved significantly greater reductions in LDL-C compared to PB. In addition, this trial's post hc analysis provided evidence of a reduction in the rate of major CV events with alirocumab therapy.
ODYSSEY MONO[38€]	R, DB, DD, AC 24 weeks	n=103 patients with HC; estimated 10-year fatal CVD risk score ≥1% and <5%; not on statin therapy or other LLT; LDL-C levels 100-190 mg/dL	Alirocumab 75 mg q2w Ezetimibe 10 mg QD -2 total treatment groups	Using the least squares method: Alirocumab: 47.2% ± 3.0% (p<0.0001) Ezetimibe: 15.6% ± 3.1% (p<0.0001)	This was the first phase III trial investigating alirocumab. Alirocumab as monotherapy in patients not on other LLTs demonstrated significantly greater LDL-C-lowering compared to ezetimibe.
ODYSSEY OPTIONS I[20,21¶]	R, DB, AC 24 weeks	n=355 adult patients with non-FH or HeFH at high CV risk; inadequate LDL-C reduction with atorvastatin therapy with or without other LLT	Entry statin: atorvastatin 20 or 40 mg QD Alirocumab 75 mg q2w Ezetimibe 10 mg QD Doubling of entry atorvastatin dose Switching to rosuvastatin 40mg PB -7 total treatment groups	Atorvastatin 20 mg: Alirocumab: 44.1% Ezetimibe: 20.5% Double statin dose/day: 5.0% Atorvastatin 40 mg: Alirocumab: 54.0% Ezetimibe: 22.6%	When added to either atorvastatin 20 or 40 mg, alirocumab produced significantly greater LDL-C reductions compared to the addition of ezetimibe, doubling of daily, statin dose, or switching to rosuvastatin. Safety and tolerability of alirocumab treatment was comparable to the other treatment arms.

Study	Design/ Duration	Population	Intervention(s)*	Percent *reduction* in LDL-C from baseline at week 24	Conclusions
				Double statin dose/day: 3.8% Switching to rosuvastatin 40mg: 21.4% (p=not reported)	
ODYSSEY OPTIONS II[20,21¶]	R, DB, AC 24 weeks	n=305 adult patients with non-FH or HeFH at high CV risk; inadequate LDL-C reduction with rosuvastatin therapy with or without other LLT	Entry statin: rosuvastatin 10 or 20mg QD Alirocumab 75 mg q2w Ezetimibe 10 mg QD Doubling of entry rosuvastatin dose PB -6 total treatment groups	Rosuvastatin 10 mg: Alirocumab: 50.6% Ezetimibe: 14.4% Double statin dose/day: 16.3% Rosuvastatin 20 mg: Alirocumab: 36.3% Ezetimibe: 11.0% Double statin dose/day: 15.9% (p=not reported)	When added to rosuvastatin 10 or 20 mg, alirocumab produced significantly greater LDL-C reductions compared to the addition of ezetimibe or doubling of daily, statin dose. Safety and tolerability of alirocumab treatment was comparable to the other treatment arms.

*Up-titration from alirocumab 75 mg q2w to 150 mg q2w, or 150 mg q4w to 150 mg q2w at week 12 was allowed if LDL-C target values at week 8 were not met. All doses of evolocumab were administered subcutaneously; all doses of ezetimibe and statins were administered orally.
¶ trial results available through presentation slides
€ trial results available through meeting abstract
❖ trial results available through published article in medical journal
AC=active-controlled; ASCVD=atherosclerotic cardiovascular disease; CHD=coronary heart disease; CI=confidence interval; CV=cardiovascular; CVD=cardiovascular disease; DB=double-blind; DD=double-dummy; HC=hypercholesterolemia; HeFH=heterozygous familial hypercholesterolemia; LDL-C=low-density lipoprotein cholesterol; LLT=lipid-lowering therapy; PB=placebo; PC=placebo-controlled; PO=by mouth; QD=daily; q2w=every 2 weeks; q4w=every 4 weeks; R=randomized

As depicted in Table 2, the ODYSSEY LONG-TERM trial included patients with HeFH, established coronary heart disease (CHD), or a CHD risk equivalent, whereas those included in the ODYSSEY HIGH FH study strictly had HeFH.[15,37] A subgroup analysis of patients with HeFH and baseline LDL-C ≥160 mg/dL was conducted in the ODYSSEY LONG-TERM trial, which matches the inclusion criteria for patients in the ODYSSEY HIGH FH trial. For these patients, alirocumab reduced LDL-C by 45.7% to 52.4% after 24 weeks of therapy. The results of these 2 trials conclude that alirocumab has efficacy in the HeFH patient population through LDL-C reduction.

As stated previously, 4 ODYSSEY trials investigated the long-term efficacy of alirocumab after at least 52 weeks of therapy.[15,35-37] In these trials, persistent LDL-C reductions from baseline ranging from 43% to 52.4% were observed after 1 year of alirocumab therapy, suggesting that tolerance to the monoclonal antibody does not develop with continued use.

Safety and tolerability data for alirocumab are sparse in comparison to data available for evolocumab. According to the available data, the most commonly reported AEs to alirocumab therapy were general allergic reactions, local injection-site reactions, myalgia, arthralgia, upper respiratory infection, nasopharyngitis, urinary tract infections, and diarrhea.[15,20,21,33-38] These were similar to the AEs reported with evolocumab therapy. Neurocognitive disorders, injection-site reactions, and laboratory abnormalities occurred at either similar or lower rates than those reported in the comparator arms of all trials. The incidence of serious TEAEs in the alirocumab arms of these trials ranged from 2% to 18.8%. Data regarding adjudicated CV events while on alirocumab are conflicting. Some trials demonstrated a reduction in CV events, while others showed a higher incidence of CV events in comparison to placebo.

Pooled safety data from phase II and phase III alirocumab trials have been reported.[33,37] Of 2,476 patients on alirocumab therapy and 1,276 patients on placebo, 13.7% and 14.3% of patients experienced serious TEAEs, 0.5% and 0.9% experienced TEAEs leading to death, 5.3% and 5.1% experienced TEAEs leading to treatment discontinuation, and 0.4% and 0.5% experienced skeletal-muscle related TEAEs leading to treatment discontinuation, respectively. From these data, it can be concluded that alirocumab therapy is safe with comparable tolerability to placebo and may be used in high-risk patients with hypercholesterolemia.

Mortality Benefit

Aside from the post-hoc analysis within the ODYSSEY LONG-TERM trial, mortality benefit has yet to be established for the PCSK9 inhibitors in a single randomized controlled trial.[15] A meta-analysis of 24 clinical trials, published April 28, 2015, involving both evolocumab and alirocumab, suggests both mortality and safety benefits with these agents.[39] The meta-analysis encompasses all previously mentioned studies discussing these 2 PCSK9 inhibitors, as well as various other phase II and III studies.[13-15,19-21,23-28,33-38,40-48]

Cumulatively, 10,159 patients were included in the analysis of primary clinical outcomes; primary end points of this meta-analysis were all-cause mortality and CV mortality.[39] The Cochran Q test and I^2 statistic were used to detect heterogeneity.

The meta-analysis found a statistically significant reduction in all-cause mortality associated with PCSK9 inhibitor use compared to no PCSK9 inhibitor use.[39] Overall mortality rates were 0.31% (n=19) and 0.53% (n=21) in PCSK9 inhibitor-treated or non-treated patients, respectively (odds ratio [OR] 0.45, 95% confidence interval [CI]: 0.23 to 0.86; $I^2 = 0\%$). The review also found a small but statistically insignificant reduction in CV mortality (rates: 0.19% [n=12] vs. 0.33% [n=13], OR 0.50, 95% CI: 0.23 to 1.10).

The meta-analysis determined that PCSK9 inhibitors may have a muscle-sparing effect.[39] This was evident even in patients previously treated with statins. Patients treated with PCSK9 inhibitors experienced fewer incidences of CK elevation compared to those in the comparator arms of trials. With these mortality and safety data, a mechanism for improved survival through reduction in ASCVD risk can be proposed for these agents. Notably, no heterogeneity was observed among the trials used to assess the primary endpoints. The sensitivity analyses for each endpoint showed the positive effects of both PCSK9 inhibitors to be robust and consistent. Bias was not detected in reporting trial outcomes.

Study Limitations

The aforementioned studies are not without limitations. Despite successfully displaying efficacy in LDL-C reduction and favorable safety profiles, most of the evolocumab studies were of limited duration (12 weeks) and were not designed to evaluate long-term, clinical outcomes (e.g., ASCVD).[13,14,19,23-28] Although the OSLER-2 trial did demonstrate sustained efficacy and minimal safety concerns with evolocumab therapy after approximately 1 year, the patients recruited within the trial were from 4 prior trials.[13,49] The trials did not explicitly state that matching was conducted between patients of the various treatment arms. Prior statin therapy, the variable patient populations, and multiple dosing regimens within these trials might obscure the true benefit that patients of the OSLER trial-2 potentially gained from evolocumab treatment.

With the exception of ODYSSEY LONG-TERM,[15] adherence measures to treatment were not distinguished or included in the study design of the ODYSSEY trials investigating alirocumab.[15,20,21,33-38] This was likely due to an intention-to-treat approach to analysis. Consequently, the study endpoints from a majority of these trials were calculated without regard to treatment adherence. Nonadherence to treatment may actually underestimate the efficacy of alirocumab in these trials.

In contrast to evolocumab, there were no trials were identified investigating alirocumab in the HoFH patient population. In addition, it is difficult to obtain and investigate a true, statin-intolerant patient population.[23,33,38] Rather than a conclusive, biochemical diagnosis, statin intolerance is defined by a clinical diagnosis. The results extrapolated from the primary endpoints of these studies may not be completely applicable to statin-intolerant patients that are at high ASCVD risk. For these reasons, future studies must be designed and conducted to define the true effects these drugs have in statin-intolerant hypercholesterolemia and HoFH.

Additionally, at the time these trials were designed, the NCEP guidelines were used to stratify patients to ASCVD risk and to determine LDL-C goals for patients based on risk.[8] Since then, the ACC/AHA guidelines have been released which no longer support this approach to LLT.[4] There is a lack of consensus on how to apply the results of LDL-C reduction within these studies to ASCVD outcomes.

With regard to the meta-analyses, several limitations should be noted.[39] Though results from multiple trials were included, the studies were of short duration (2 to 24 months), and the overall incidence of mortality was quite low: among 10,159 patients, there were 40 deaths of any cause, and 25 deaths attributed to CVD. Also, not all data were obtained from published, peer-reviewed literature; data for several trials were derived from slide presentations or abstracts-alone. Navarese et al also indicated that the mechanisms of improved survival with PCSK9 inhibitors are unclear and the survival benefits may be attributed to the combined use of PCSK9 inhibitors and statins, especially in patients at high risk of ASCVD. They added that their findings on survival benefits may have been amplified due to higher baseline mortality rates among patients in these studies, in accordance with the theory that the benefit of treatment is greater among high-risk patients.

Conclusion

The available data from phase III clinical trials of evolocumab and alirocumab are promising. Regardless of background LLT, treatment with either PCSK9 inhibitor resulted in rapid and consistent reductions in LDL-C from baseline. For most patients with hypercholesterolemia, we can expect 50% to 60% reductions in LDL-C from baseline for those treated with either evolocumab dosing strategy, and 40% to 50% reductions in LDL-C from baseline for those treated with alirocumab 75 mg SC q2w. Reductions in LDL-C are dependent upon patient baseline characteristics. In those with HoFH, more data are needed to quantify the expected LDL-C reduction caused by these drugs, but the available data does support their use.

At this time, there is insufficient evidence to recommend preferential use of these agents over statins. Impending financial expenses also deem these treatment modalities infeasible for some patients. Due to the multitude of trials demonstrating a significant reduction in ASCVD events with their use, statins should still be used as first-line therapy for hypercholesterolemia. In the case of statin-intolerance, there are studies suggesting efficacy of these agents in LDL-C reduction;[23,33,38] however, these data are limited, and the safety of these agents remains unclear. Notably, neither alirocumab nor evolocumab has been approved by the FDA for LDL-C reduction in patients with statin intolerance or as monotherapy.[11,12] Rather than relying on reduction of absolute LDL-C levels, providers should now be diligent with following current guidelines by taking into consideration patient comorbidities, calculating an individual patient's ASCVD risk score, and optimizing statin therapy in the aspect of appropriate intensity with minimization of side effects.

As stated before, these drugs may help to meet the clinical needs of the following high-risk patient groups by reducing residual ASCVD risk: FH, refractory hypercholesterolemia, and statin-intolerant hypercholesterolemia. Although more long-term evidence is necessary to explore the effects of reduced LDL-C levels on the incidence of ASCVD events, it seems that these 2 agents should be used in patients at high risk for ASCVD on top of optimal statin therapy. In addition, these agents should be incorporated into hypercholesterolemia treatment guidelines for patients with HeFH or HoFH due to exposure to tremendously high LDL-C levels, and subsequent lifetime ASCVD risk in these patients. Targeting and inhibiting the enzyme PCSK9 is a novel treatment approach and more data must be collected prior to consideration in other types of hypercholesterolemia.

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