Efficacy and safety of PCSK9 monoclonal antibodies: an evidence-based review and update

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ABSTRACT
Objective: Treatment of dyslipidemia lowers cardiovascular (CV) risk. Although statin use is a cornerstone therapy, many patients are not achieving their risk-specific low-density lipoprotein cholesterol (LDL-C) goals. The proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies have been extensively studied as lipid-lowering therapy (LLT). Herein, we present an updated evidence-based review of the efficacy and safety of PCSK9 monoclonal antibodies in the treatment of familial and non-familial hypercholesterolemia.

Methods: PubMed database was searched to review Phase III studies on PCSK9 monoclonal antibodies. Then, the US National Institutes of Health Registry and the WHO International Clinical Trial Registry Platform were searched to identify and present the ongoing research.

Results: PCSK9 monoclonal antibodies were investigated for the treatment of dyslipidemia, as a single therapeutic agent or as an add-on therapy to the traditional LLT. They proved effective and safe in the treatment of familial and non-familial hypercholesterolemia, and in the prevention of adverse CV events.

Conclusions: The use of PCSK9 monoclonal antibodies in the treatment of dyslipidemia is currently recommended to achieve risk-specific LDL-C goal to reduce adverse CV events. Future results of the ongoing research might expand their clinical generalizability to broader patient populations.

Introduction
It has been well established that lipid-lowering therapy (LLT) targeting low-density lipoprotein cholesterol (LDL-C) lowers cardiovascular (CV) risk. This is largely based on significant benefits observed with statin therapy in the prevention of primary and secondary atherosclerotic cardiovascular disease (ASCVD)1,2. Although statins remain the cornerstone of LLT, yet patients on statin therapy may still experience CV events3, statin intolerance, or inability to achieve target LDL-C levels despite maximally-tolerated doses. Thus, alternative LLT to further decrease LDL-C levels and improve CV outcomes has been investigated1. Ezetimibe in combination with statin therapy has shown incremental lowering of LDL-C levels and improvement in CV outcomes. However, such improvements are modest and the overall outcome data on ezetimibe monotherapy are scarce1,2. Monoclonal antibodies are novel lipid-lowering agents that reduce LDL-C levels by inhibiting proprotein convertase subtilisin/kexin type 9 (PCSK9). The currently available antibodies, alirocumab and evolocumab, are fully human immunoglobulin-G (IgG) subtypes4 and are approved by the Food and Drug Administration (FDA) for heterozygous familial hypercholesterolemia (HeFH) and for the prevention of CV events in patients with established cardiovascular disease (CVD).

Evolocumab is also indicated for homozygous familial hypercholesterolemia (HoFH)5. International guidelines have been updated to include PCSK9 antibodies in their recommendations6-8. The development of a third PCSK9 antibody, bococizumab, in advanced phase III clinical trials was abandoned in 2016. After the completion of six bococizumab studies, an unexpected attenuation of effect on LDL-C over time was observed, in addition to high rates of injection-site reaction due to high immunogenicity9. However, the development of new investigational monoclonal antibodies to inhibit PCSK9 is well under way with promising initial results10-13. This review will discuss the efficacy and safety profile of PCSK9 monoclonal antibodies or inhibitors in the treatment of familial and non-familial hypercholesterolemia. For the purpose of this review, PCSK9 monoclonal antibodies or inhibitors will be used interchangeably.

Materials and methods
Search strategy for studies on PCSK9 monoclonal antibodies
PubMed literature search was carried out on 31 December 2019 for original trials, using broad MeSH terms in the
following search thread: ("alirocumab" [Supplementary Concept] OR "evolocumab" [Supplementary Concept] OR "bococizumab" [Supplementary Concept]). The search was limited to "Humans" and "Clinical Trial". The references' lists of the identified trials were manually searched to identify further potentially useful articles. Several meta-analyses, pre-specified, post hoc and pooled analyses of PSCK9 inhibitors trials have been included to emphasize their findings. The literature search was updated on March 1, 2020. Figure 1 presents the approximate publication period of time of Phase III clinical trials discussed in the review.

**Search strategy for registered clinical trials (ReCTs)**

Literature search on the ongoing active research on PCSK9 monoclonal antibodies was conducted on 15 March 2020. The search strategy included the individual agents separately: alirocumab and evolocumab. The United States (US) National Institutes of Health Registry (http://clinicaltrials.gov/) was searched for Phase III trials and recruitment status of "Active, not recruiting", "Recruiting" and "Not yet recruiting" and the World Health Organization (WHO) International Clinical Trial Registry Platform (ICTRP) (http://www.who.int/ictrp/network/en/) for Phase III trials.

**Mechanism of action of PCSK9 monoclonal antibodies**

The PCSK9 is a low-abundance circulating plasma protein that is synthetized and secreted by hepatocytes14. PCSK9 regulates LDL receptor (LDLR) on hepatocytes surfaces, which is the primary receptor that is responsible for clearing the circulating LDL particles by endocytosis. PCSK9 binds to LDLR, stabilizes the LDL/LDLR complex and prevents LDLR from being released from the endocytosed vesicle causing lysosomal destruction of the LDLR and thus preventing its recycling5,15. Subsequently, there is reduction in the LDLR density on the hepatocytes surfaces which affects the ability to eliminate the circulating LDL particles leading to an elevated plasma cholesterol level14. Preclinical trials have shown that PCSK9 has direct proinflammatory action on the vessel walls which could be explained by its effect on LDLR-related protein 1 (LRP1) which regulates plaque macrophages5. PCSK9 circulating in the plasma has also been postulated to flow through the arterial plaque adding up to the plaque PCSK9 concentration which controls LDLR expression in the atheroma and reduces levels of LRP15. Increased LDLR expression through the inhibition of PCSK9 will result in profound uptake of lipoprotein cholesterol into the atheroma theoretically while the reduction of LRP1 levels results in induction of inflammation4,5. Monoclonal antibodies such as alirocumab and evolocumab, self-administered subcutaneously every two or four weeks, bind to PCSK9 preventing its binding to LDLR. When PCSK9 is absent or its binding to LDLR is inhibited, LDL is degraded while the LDLR can be recycled then accumulate on the hepatocyte's membrane leading to an accelerated LDL clearance and reduced levels in blood5. Accordingly, PCSK9 inhibition have two counter-acting actions with a net effect of reduction of LDL-C levels and atheroma volume4. An injection of monoclonal antibodies can completely inactivate all the circulating PCSK9 within hours5,14, and all the newly secreted PCSK9 after several days5. Marked reduction in LDL-C levels starts one day after an injection14. Inhibition of PCSK9 can also be achieved by

![Figure 1. Timeline of phase III studies of alirocumab and evolocumab.](image-url)
targeting PCSK9 synthesis in hepatocytes. Inclisiran, a long-acting small interfering RNA (siRNA), that inhibits translation of PCSK9 mRNA leading to a reduced PCSK9 synthesis. Inclisiran is a valid alternative to PCSK9 inhibitors with an advantage of twice-a-year injection to produce an LDL-C reduction by 50% or more. Bempedoic acid is another promising agent that could be a potential alternative to statins. It is an oral once-daily molecule that acts as an inhibitor to adenosine triphosphate (ATP) citrate lyase. The latter is an enzyme that upstream from 3-hydroxy-3-methylglutaryl-coenzyme A. Thus, reducing cholesterol synthesis

Efficacy of PCSK9 monoclonal antibodies

The Phase I studies of evolocumab, alirocumab, and bococizumab have shown reduction in LDL-C levels in healthy volunteers and patients with familial and non-familial hypercholesterolemia. They were generally effective, safe and well-tolerated. Similar results have been obtained from Phase II studies, which are usually dose-finding, of alirocumab, bococizumab, and evolocumab. The PCSK9 monoclonal antibodies have been studied in Phase III clinical trials for lipid, cardiovascular, and safety outcomes. Data in HoFH are limited in general.

Lipid outcomes

For the purpose of Figure 2, when the monoclonal antibody was tested in several arms i.e. in different strengths and/or in combination with other LLT, the LDL-C values were averaged using the values of different arms of the Phase III trials presented in the review.

Primary hypercholesterolemia

Primary hypercholesterolemia is defined as blood cholesterol measurement >5.17 mmol/L (200 mg/dL) that could be attributed to genetics, obesity, or dietary intake. In patients with primary hypercholesterolemia in the absence or presence of various CV risk levels, who have not reached their CV risk-specific LDL-C goals, the effect of PCSK9 inhibitors on LDL-C levels has been extensively studied as monotherapy, in statin intolerance, or as an add-on to diet-alone or other LLT such as statins, ezetimibe, fenofibrate. Several studies have shown that alirocumab and evolocumab significantly reduce LDL-C levels at Weeks 12, 24, and 52, and 104 of therapy. In most trials, authors adopted the 2011 and 2012 European guidelines’ definitions of CV risk categories. Patients with very high CV risk are defined, as per studies, to have a documented coronary heart disease (CHD) or CHD risk equivalents such as type 1 (T1DM) or 2 (T2DM) diabetes mellitus (DM) with target organ damage, ischemic stroke, peripheral artery disease (PAD), or carotid artery occlusion >50% without symptoms, carotid endarterectomy or carotid artery stent procedure, or renal artery stenosis or renal artery stent procedure. High CV risk are defined as patients with no history of CVD or CHD but with other risk factors such as calculated 10-year risk of fatal CVD using the European Systematic Coronary Risk Evaluation (SCORE) score of ≥5% (although the guidelines specified >5% and <10%), T1DM or T2DM without target organ damage, moderate chronic kidney disease (CKD). Moderate CV risk is defined as SCORE score of ≥1 and <5%. On the other hand, the 2018 American guidelines defined very high-risk patients to have a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions such as age ≥65 years, HeFH, history of coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s), DM, hypertension, CKD (eGFR 15–59 mL/min/1.73 m²), current smoking persistently elevated LDL-C (LDL-C ≥2.6 mmol/L (100 mg/dL) despite maximally tolerated statin therapy and ezetimibe or history of congestive heart failure. It is worth nothing that the 2019 European guidelines re-defined very high risk CV category to include family history with ASCVD or with another major risk factor, and moderate risk CV category to include young patients (T1DM <35 years, T2DM <50 years) with DM duration of <10 years and without other risk factors.

Short-term trials (≤12 weeks)

The LAPLACE-2 study (n = 2067) enrolled patients with primary hypercholesterolemia and mixed dyslipidemia. Evolocumab 140 mg every 2 weeks (Q2W) or 420 mg monthly (QM), on top of moderate-intensity statins reduced LDL-C by 59–66% or by 62–65%, respectively. When added to

Figure 2. Approximate LDL-C reductions in phase III trials.
high-intensity statins, Q2W dose reduced LDL-C by 86–90%, while QM dose reduced the levels by 93–95%. Around 86–94% of the patients on evolocumab and 17–62% on ezetimibe achieved LDL-C level <1.8 mmol/L (70 mg/dL) regardless of the statin therapy used. In the large MENDEL-2 trial (n = 612), the biweekly and monthly evolocumab decreased LDL-C levels from baseline by an average of 57 and 56.1% compared to 17.8 and 18.6% for ezetimibe or to 0.1 and 1.3% for placebo (p < .001, all comparisons), respectively. There were higher rates in patients achieving LDL-C level <1.8 mmol/L (70 mg/dL) in the evolocumab groups (69%) than ezetimibe (1%) or placebo (1%) groups. Kiyosue et al.34 in the Japanese YUKAWA II study (n = 409), recruited high CV risk patients with hyperlipidemia and mixed dyslipidemia. Evolocumab 140 mg Q2W or 420 mg QM on top of atorvastatin 5 or 20 mg reduced LDL-C by an average of 67–76%. When studied in patients during hospitalization due to acute coronary syndrome (ACS) in the EVOPACS55 study (n = 308), evolocumab 420 mg QM for 2 doses added to high-dose statin resulted in a difference in mean percentage change from baseline of −40.7% (p < .001). In the evolocumab group, around 95.7% of patients achieved LDL-C levels <1.8 mmol/L (70 mg/dL) by Week 8 versus 37.6% in the placebo group. The BERSON56 trial (n = 981) evaluated the efficacy and safety of evolocumab (140 mg Q2W or 420 mg QM) combined with atorvastatin in T2DM patients with hyperlipidemia and mixed dyslipidemia. Evolocumab was well-tolerated and significantly decreased LDL-C levels by ≥70% in both dosing regimens (p < .0001). In a similar patient population in the BANTING57 trial (n = 421), evolocumab (420 mg QM) on top of statins reduced LDL-C by a mean of 54.3% compared to 1.1% in placebo group (p < .0001) with significantly more patients achieved LDL-C <1.8 mmol/L (70 mg/dL); 84.5 versus 15.4%, respectively. Evolocumab had no negative impact on glycemic parameters in both trials after 12 weeks of treatment56,57.

24-Week trials

In ODYSSEY EAST58 (n = 615), ODYSSEY KT59 (n = 199), ODYSSEY OPTIONS I51 (n = 355) and ODYSSEY OPTIONS II52 (n = 305) trials, alirocumab 75 mg Q2W (75Q2W), increased to 150 mg Q2W (150Q2W) at Week 12 if LDL-D was ≥1.8 mmol/L (70 mg/dL) at Week 8, was studied in patients with very high CV risk and LDL-C levels ≥1.8 mmol/L (70 mg/dL) or with high CV risk and LDL-C levels ≥2.6 mmol/L (100 mg/dL) despite maximally tolerated statin therapy. In ODYSSEY EAST58 trial that was conducted in three Asian countries (China, India, Thailand), there were reductions in LDL-C levels by 56 versus 20.3% with alirocumab versus ezetimibe (p < .0001). The ODYSSEY KT51 trial enrolled patients from South Korea and Taiwan who were on atorvastatin 40 to 80 mg, rosvastatin 20, or simvastatin 40 mg. The least-squares mean percentage change in LDL-C from baseline was −57.1% in alirocumab group and +6.3% in placebo group, with a difference between groups of −63.4% (p < .0001). In ODYSSEY OPTIONS I51 trial, alirocumab as an add-on to atorvastatin 20 mg and 40 mg reduced LDL-C levels by 44.1 and 54.0% compared to 20.5 and 22.6% with ezetimibe (p < .001, both comparisons), respectively. Switching atorvastatin 40 mg to rosvastatin 40 mg in a third arm resulted in 21.4% reduction, while doubling atorvastatin dose in the fourth arm yielded an average of 5% reduction in baseline LDL-C levels. In ODYSSEY OPTIONS II trial, alirocumab was added to either rosvastatin 10 mg or 20 mg. In rosvastatin 10 mg arm, alirocumab reduced LDL-C levels by 50.6% compared to 14.4% in ezetimibe group or 16.3% by doubling rosvastatin dose (p < .0001). In rosvastatin 20 mg arm, alirocumab reduced LDL-C levels by 36.3% compared to 11% in ezetimibe group (p = .0136) or to 15.9% in double-dose rosvastatin group (p = .0453). In the four aforementioned studies41,51,52,58, the reductions were observed at Week 4 and maintained through the study duration with an average of 80% or more of the patients on alirocumab achieving LDL-C <1.8 mmol/L (70 mg/dL). ODYSSEY DM-INSULIN39 trial (n = 517), in diabetics (types 1 and 2) with hypercholesterolemia and high CV risk on insulin and statins with or without other LLT, showed a least-squares mean percentage change in baseline LDL-C of −50.1% with alirocumab (75Q2W) versus −1.3% with placebo (p < .0001). The difference between the groups was −49.0% in T2DM and −47.8% in T1DM (p < .0001). The reductions were similar regardless of disease state or age. In ODYSSEY DM-DYSLIPIDEMIA40 trial (n = 413), patients with T2DM and mixed dyslipidemia with ASCVD or at least one additional CV risk factor were randomized to alirocumab (75Q2W) or usual care (maximally tolerated statins with other LLT; fenofibrate, ezetimibe, omega-3 fatty acid, nicotinic acid). The mean non-high-density lipoprotein cholesterol (non-HDL-C) reduction was −37.3% in alirocumab group versus −4.7% (difference of −32.5%, p < .0001) with >66% of patients achieving non-HDL-C level of 2.6 mmol/L (100 mg/dL). Airocumab also reduced LDL-C levels by 43%. In the trials that evaluated the every-4-week (Q4W) dose, alirocumab has shown similar outcomes. In ODYSSEY CHOICE II58 trial (n = 233), moderate, high, and very high CV risk patients with hypercholesterolemia receiving fenofibrate or ezetimibe or diet-alone, were randomized to alirocumab 150 mg Q4W (150Q4W) or 75Q2W increased to 150Q2W at Week 12, if target LDL-C was not achieved at Week 8 (75/150 mg). The least-squares mean LDL-C changes was −51.7% (150Q4W) and −53.5% (75Q2W) versus placebo +4.7% (p < .0001, both comparisons). The reductions were observed at Week 4 and maintained through the study duration with 63.9% (150Q4W) and 70.3% (75Q2W) of patients on alirocumab achieving LDL-C target versus 1.8% on placebo. ODYSSEY MONO59 trial (n = 103), the first study to test alirocumab in patients on no LLT, showed that patients on alirocumab (75Q2W) had a 47.2% reduction in LDL-C compared with a 15.6% with ezetimibe (p < .0001). A post-hoc pooled analysis60 from nine randomized, double-blind, placebo- or ezetimibe-controlled, 24- to 104-week ODYSSEY Phase III trials evaluated add-on alirocumab to statins in regimens of 150Q2W and 75/150 mg. The observed change in LDL-C level was −61.5% with alirocumab 150Q2W versus −1.0% with placebo, −46.4% with
alirocumab 75/150 mg versus +6.3% with placebo, and −48.7% with alirocumab 75/150 mg versus −20.6% with ezetimibe. Without statins, an LDL-C change of −54.9% was observed with alirocumab versus +4% with ezetimibe. Patients on alirocumab were more likely to achieve LDL-C < 1.8 mmol/L (70 mg/dL) and < 1.42 mmol/L (55 mg/dL). At Week 8, around 16.3% of patients on alirocumab 75Q2W and statins required dose increase to 150Q2W, while 34.8% alirocumab 75Q2W without statins required dose adjustment.

**Longer-term trials (≥48 weeks)**

Evolocumab 420 mg Q4W combined with diet-alone or with atorvastatin 10 mg or 80 mg (with or without ezetimibe), showed an average of 57% (p < .001) reduction in LDL-C at Week 12 maintained through Week 52 when studied in hyperlipidemic patients with CV risk in the DESCARTES44 trial (n = 900). Around 82.3% of patients on evolocumab achieved LDL-C level < 1.8 mmol/L (70 mg/dL) versus 6.4% on placebo. In the diet-alone group, the least-square mean reduction in LDL-C was 55.7%, in the atorvastatin 10 mg group was 61.6%, in the atorvastatin 80 mg group was 56.8% and in the atorvastatin 80 mg plus ezetimibe 10 mg group was 48.5% (p < .001, all comparisons). The ODYSSEY COMBO I63 trial (n = 316) in hypercholesterolemic patients at high CV risk, showed estimate mean difference in baseline LDL-C of −45.9% (p < .0001) with alirocumab 75Q2W at 24 weeks. Furthermore, 75% of patients achieved LDL-C < 1.8 mmol/L (70 mg/dL) in alirocumab group compared to 9% in the placebo group. The reductions were sustained till Week 52. In ODYSSEY CHOICE I66 trial (n = 803) in hypercholesterolemic patients at moderate-to-very-high CV risk, alirocumab 300 mg Q4W without statins showed mean LDL-C change from baseline by −52.7% compared to +0.3% with placebo (p < .0001) at Week 24. While those on statins showed a mean change of −58.8% compared to −0.1% with placebo (p < .0001). The results were maintained through Week 48 in both groups. When compared to ezetimibe in hypercholesterolemic patients at high CV risk in the ODYSSEY COMBO II50 trial (n = 720), alirocumab 75Q2W reduced LDL-C by a mean of 50.6% as compared to a mean of 20.7% with a difference of −29.8% (p < .0001) at Week 24. The reductions were sustained till Week 52 and the percentage of patients who achieved LDL-C < 1.8 mmol/L (70 mg/dL) was 77% on alirocumab versus 45.6% on ezetimibe (p < .0001).

**Familial hypercholesterolemia**

Alirocumab 150Q2W when added to statin therapy in ODYSSEY HIGH FH47 trial (n = 107) in patients with HeFH and LDL-C ≥ 4.14 mmol/L (160 mg/dL), resulted in a percent change in LDL-C from baseline of −45.7% compared to −6.6% by placebo with least-square mean difference between the groups of −39.1% (p < .0001). Forty one percent of the patients on alirocumab achieved LDL-C risk-specific goals versus 5.7% in the placebo group at Week 24. These reductions were maintained through the treatment phase of 78 weeks. At a dose of 75/150 mg in patients with HeFH in ODYSSEY FH I and FH II48, alirocumab on top of maximally tolerated statins led to 57.9 and 51.4% (p < .0001) reduction in LDL-C at Week 24, respectively, and were maintained up to week 78. After 78 weeks, the reductions were 51.8 and 52.1% from baseline LDL-C levels. The percentage of patients who achieved LDL-C levels < 1.8 mmol/L (70 mg/dL) was 59.8 and 68.2% versus 0.8 and 1.2% in placebo, respectively. Evolocumab 420 mg Q4W on top of stable LLT, reduced baseline LDL-C by 30.9% (p < .0001) in 50 patients with HoFH at 12 weeks in the TESLA-B trial35. In an open-label single-arm TAUSSIG61 trial (n = 300), evolocumab over 4 years was well-tolerated and effective in patients with HoFH (35%) and severe HeFH (65%) who completed Part A or B of the TESLA study. At Week 12 and 216, relative reductions in LDL-C were smaller in patients with HoFH (-21.2 and -24%, respectively) as compared with that in patients with severe HeFH (-54.9 and -47.2%, respectively). When studied in RUTHERFORD-236 trial (n = 331) which recruited patients with HeFH and LDL-C ≥ 2.6 mmol/L (100 mg/dL), evolocumab reduced baseline LDL-C by 61.3% with 420 mg QM and 59.2% with 140 mg Q2W (p < .0001, for both against placebo) at Week 12. In an analysis62 of patients with HeFH (n = 1257) in 4 double-blind, randomized, placebo-controlled, 78-week ODYSSEY studies (HIGH FH47, FH I and II48, and LONG TERM65) a mean percent change in baseline LDL-C of −43.6% was observed with alirocumab 75Q2W at Week 12, increased to −48.8% with alirocumab (75/150 mg) at Week 24. Mean changes of −57.1% at Week 12 and −55.0% at Week 24 were observed with 150Q2W (p < .0001). Around 75.3% (75/150 mg) or 64.5% (150 mg) of patients achieved their LDL-C goal of 1.8 or 2.6 mmol/L (70 or 100 mg/dL) based on CV risk by Week 24 and maintained it up to Week 78. In ODYSSEY OLE64 trial (n = 986), the mean LDL-C level reduction of 44.2% was observed in patients in alirocumab groups (75 mg or 150 mg Q2W) by Week 8 which increased to 47.9% by Week 96. Airocumab use for 18 weeks in apheresis-treated patients with HeFH was safe and effective in ODYSSEY ESCAPE64 trial (n = 62). Lipoprotein apheresis can decrease lipoproteins’ levels but is an invasive procedure. As compared to the placebo, there was a 75% additional reduction in the standardized rate of apheresis. A percentage of 63.4% of patients avoided all and 92.7% avoided at least half of the lipoprotein apheresis treatment. The open-label DE LAVAL study (n = 36) showed that evolocumab significantly reduced apheresis requirement as well. The patients were randomized to either discontinue pheresis and receive evolocumab (140 mg Q2W) or continue pheresis frequency. At Week 6, 84% versus 10% avoided apheresis (treatment difference, 74%, 95% confidence interval (CI) 45 – 87; p < .0001). Furthermore, in the recent TAUSSIG61 trial (n = 300), lipoprotein apheresis was used by 61 patients. Of the 34 patients with HoFH and the 27 with HeFH 9% and 48% were able to stop apheresis treatment when evolocumab was used, respectively.

**Mixed populations**

In Alirocumab expanded-use program42, an open-label single arm trial, in patients with HeFH and/or CHD and baseline
LDL-C of $\geq4.14$ mmol/L (160 mg/dL) on LLT, a reduction of 55% in LDL-C level was observed with alirocumab 150Q2W arm by Week 24. The single-arm ODYSSEY APPRISE study ($n = 955$) is the first study in a real life setting prior commercial availability of alirocumab in subjects (63% with HeFH; 68% with a history of CVD) inadequately controlled on their maximally-tolerated LLT. In the interim data of the first 843 patients, LDL-C level reduction from baseline was 56% at Week 12. The ODYSSEY JAPAN trial ($n = 216$) was a randomized double-blind trial in Japanese patients with HeFH or non-FH and at high CV risk who were on stable statins. Alirocumab (75/150 mg) at Week 24, showed a least-square mean change in baseline LDL-C of $-62.5\%$ versus $+1.6\%$ in placebo with 96.7% of patients achieving their LDL-C goals. An average reduction of 62.5% was maintained for 52 weeks. A post hoc analysis of the diabetic patients in ODYSSEY JAPAN showed a least-square mean change in baseline LDL-C of $-63.1\%$ in DM versus $-60.8\%$ in non-DM at Week 24, which was maintained for 52 weeks with similar percentage of patients attaining their LDL-C goals as in the parent trial. The ODYSSEY NIPPON trial ($n = 163$) was another one conducted in Japanese patients with either HeFH or non-HeFH with CHD who were on lowest-strengthatorvastatin (5 mg per day) or non-statin LLT. At Week 12, the least-square mean percent change in LDL-C from baseline was $-43.8\%$ with alirocumab 150Q4W, $-70.1\%$ with 150Q2W, and $-4.3\%$ with placebo. The study continued as 52-week open-label treatment period and the patients received 150Q4W with possible up-titration to 150Q2W at Week 24. The mean LDL-C change from baseline was $-45.1\%$ at Week 20, with a further reduction at Week 36, with achieved levels maintained to Week 64. In a pooled analysis of eight ODYSSEY Phase III trials ($n = 4629$) in patients with HeFH at high CV risk on maximally tolerated statin therapy, LDL-C reduction by 48.9% was observed in 75/150 mg arms versus 9.3% with ezetimibe and 60.4% in 150Q2W arms versus 0.5% increase with placebo ($p < .0001$, all comparisons) at Week 24. The LDL-C reductions appeared as early as Week 4 and maintained up to the studies’ durations. The percentage of patients who achieved risk-based LDL-C goals of 1.8 or 2.6 mmol/L (70 or 100 mg/dL) by Week 24 was 75–79% on alirocumab versus 52% on ezetimibe and 6–8% on placebo. In PROFICIO trial ($n = 3146$), a pooled analysis of four randomized Phase III evolocumab 12-week trials (LAPLACE-2$^{33}$, RUTHERFORD-2$^{36}$, MENDEL-2$^{37}$, GAUSS-2$^{71}$) that included patients with FH, primary hypercholesterolemia with different CV risks and prior statin intolerance, evolocumab as compared to placebo resulted in mean percent changes in LDL-C of $-65.7\%$ for the Q2W dose and $-65.0\%$ for the QM dose. Compared to ezetimibe, the mean percent changes in LDL-C was $-38.9\%$ for Q2W and $-40.3\%$ for QM. There were no differences between evolocumab and placebo or ezetimibe across the various subgroups i.e. age, gender, race, ethnicity, region, glucose tolerance status, or risk categories. In an analysis of the efficacy of biweekly and monthly evolocumab in hypercholesterolemic patients ($n = 1148$) from four Phase III randomized trials (LAPLACE-2, RUTHERFORD-2, MENDEL-2, GAUSS-2) who had fasting triglyceride (TG) levels of $\geq1.7$ mmol/L (150 mg/dL), a mean percentage change in LDL-C of $-67\%$ versus placebo and $-42\%$ versus ezetimibe was observed ($p < .001$, all comparisons), which was similar to the observed LDL-C reductions in patients without elevated TG levels.

Statin intolerance

It is estimated that about 10 of patients may be unable to tolerate any dose of statins (i.e. complete intolerance) or the dose that effectively reduces LDL-C (i.e. partial intolerance). More than half of the patients who experience statin-related adverse effects, discontinue their statin therapy. Thus, this precludes patients from achieving the target LDL-C level, and exposing high CV risk patients to increased risk of mortality or adverse CV events. Statin adverse muscle symptoms are considered the most predominant cause for statin discontinuation.

Therapy with PCSK9 inhibitors has been effective and well tolerated in statin-intolerant patients in the short-term (12–24 weeks) or longer-term (up to two years) pivotal trials. Statin-intolerance in such trials was defined as the inability to tolerate two or more statins at the lowest available dosage. Evolocumab therapy in three randomized double-blind trials, the 12-week Phase II (GAUSS; $n = 236$), the Japanese 12-week Phase III (GAUSS-4; $n = 61$) and the 24-week Phase III (GAUSS-2; $n = 307$), significantly reduced LDL-C levels and was associated with short-term tolerability. The efficacy and safety persisted over 24 weeks then up to two years, as shown in the two-stage GAUSS-3 trial ($n = 491$) trial and the subset analysis of the OSLEER open-label extension studies, respectively. In GAUSS-2 and GAUSS-3 trials, evolocumab reduced LDL-C by 53 to 56 and 52.8% ($p < .001$, both comparisons), respectively. Adverse muscle events occurred in 12 and 20.7% of patients on evolocumab as compared to 23 and 28.8% of patients on ezetimibe, respectively. In the GAUSS-4 trial, the percent change in mean LDL-C was $-40.1\%$ as compared to ezetimibe (adjusted $p < .0001$) with diarrhea (9.5%) and nasopharyngitis (12.5%) being the most common adverse events. Similarly, alirocumab in the ODYSSEY ALTERNATIVE trial ($n = 314$) was well-tolerated and produced significant reductions in LDL-C levels by 45% ($p < .0001$) at Week 24 in patients with statin intolerance due to muscle symptoms. Skeletal muscles adverse events were less frequent with alirocumab as compared to ezetimibe (hazard ratio (HR), 0.71, 95% CI 0.47 – 1.06, $p = .096$).

Cardiovascular outcomes

The use PCSK9 inhibitors has been associated with a benefit in CV outcomes. One interpretation of the potential mechanism is their ability to lower the atherogenic lipids levels (namely LDL-C, non-HDL-C, lipoprotein(a) (Lp(a))$^{39}$. A number of studies has shown that PCSK9 inhibitors had significant reduction in atherogenic lipid fractions i.e. LDL-C, non-HDL-C, apolipoprotein-B (apo-B), and Lp(a) levels. In a post hoc analysis of a Phase II trial, alirocumab reduced total LDL particle
(LDL-P) and very-low-density lipoprotein (VLDL), and increased HDL particles by 63.3, 36.4, and 11.2% (p < .01, all), respectively. Evolocumab in the BERSON trial, BANTING trial, and a post hoc analysis of the DESCARTES trial significantly decreased the serum levels and size of the lipoprotein particles. Both alirocumab and evolocumab caused significant reduction in LDL-apoB by 56.3% each and Lp(a) by 23.0–30.30% and 24.5–29.5%, respectively. In a recent pre-specified analysis of the ODYSSEY OUTCOMES trial, a reduction in Lp(a) was an independent factor of lowering the rate of major adverse CV events (MACE), and that a 1 mg/dL reduction in Lp(a) was associated with an HR of 0.994 (95% CI, 0.990–0.999, p = .0081). In addition, there has been a positive correlation between plasma levels of PCSK9 and the carotid intima media wall thickness, the platelet count in patients with coronary artery disease (CAD), and the necrotic core tissue fraction within the coronary plaques, suggesting that the PCSK9 protein may have a key modulating effect in atherosclerosis. The GLAGOV trial (n = 968) has confirmed that evolocumab in addition to statin therapy led to significant reduction in atheroma volume and induced plaque regression in higher percentage of patients. Alirocumab was evaluated in the Japanese Phase IV ODYSSEY J-IVUS study (n = 206) which enrolled hypercholesterolemic patients recently hospitalized with ACS. Using intravascular ultrasound imaging analysis, there was a numerically more percent reduction in normalized total atheroma volume which did not reach the statistical significance. It remains to be established whether PCSK9 inhibition has important clinical effects on arterial stiffness, endothelial function, and inflammatory responses. Circulating PCSK9 was significantly associated with arterial stiffness and a pro-inflammatory response on macrophage that stimulates cytokines. To date, two patient cases have reported with impressive results on the use of PCSK9 inhibitors through improvement in carotid-femoral pulse wave velocity. Two-month use of alirocumab has improved endothelial function as assessed by brachial artery vasoreactivity test.

Prior to the major clinical outcome trials, FOURIER, ODYSSEY OUTCOMES, and SPIRE, findings from the published evidence gave an important signal that the reduction of LDL-C using PCSK9 inhibitors lowered the adverse CV events. In the OSLER study (n = 4465), evolocumab as compared to the control group reduced LDL-C by 61% (p < .001) and adverse CV events rate by 53% (HR, 0.47, 95% CI 0.28–0.78; p = .003) after one year of treatment. Alirocumab in the ODYSSEY LONG TERM trial (n = 2341) over a period of 78 weeks, significantly reduced LDL-C by 62% (p < .001) and in a post hoc analysis of it, there was an evidence of a reduction in the rate of MACE (HR, 0.52, 95% CI 0.31–0.90; nominal p = .02). A post hoc analysis of ten ODYSSEY trials (n = 4974), showed that the incidence of MACE was reduced by 24% for every 39 mg/dL reduction in LDL-C (adjusted HR, 0.76, 95% CI 0.63–0.91; p = .0025) and by 29% for every additional 50% reduction in LDL-C from baseline (HR, 0.71, 95% CI 0.57–0.89; p = .003). A meta-analysis of 24 randomized control trials (RCTs) (n = 10,159) showed that the use of PCSK9 inhibitors was associated with reductions in LDL-C by 47.49% (p < .001), all-cause mortality (odds ratio (OR), 0.45, 95% CI 0.23–0.86; p = .015; heterogeneity p = .63; I² = 0%), MI (OR, 0.49, 95% CI, 0.26–0.93; p = .03; heterogeneity p = .45; I² = 0%), and CV mortality (OR, 0.50, 95% CI, 0.23–1.10; p = .084; heterogeneity p = .78; I² = 0%) compared with no PCSK9 inhibitors treatment. A study predicted the individual lifetime benefit of PCSK9 inhibition, expressed in terms of gain in life expectancy free of (recurrent) stroke or MI, in statin-treated patients with stable CAD based on competing two risk models developed in data from the Treating to New Targets (TNT) trial. The individual lifetime benefit varied substantially, ranging from <6 months free of stroke or MI in 61% of patients to ≥12 months in 10% of patients. The expected benefit was the highest in younger patients (aged 40–60 years) with risk factors, especially if LDL-C level is >1.8 mmol/L (70 mg/dL).

Three Phase III trials, FOURIER, ODYSSEY OUTCOMES, and SPIRE, investigated PCSK9 inhibitors in patients with a history of clinically evident CVD. The FOURIER trial (n = 27,564) randomized patients with stable ASCVD and fasting LDL-C level ≥ 1.8 mmol/L (70 mg/dL) or non-HDL ≥ 2.6 mmol/L (100 mg/dL) who were on statin therapy. At Week 48, evolocumab 140 mg Q2W or 420 mg QM, reduced LDL-C by 59% compared to placebo. The primary outcome of a composite of CV death, MI, stroke, hospitalization for unstable angina (UA), or coronary revascularization was significantly lower (HR, 0.85; 95% CI, 0.79–0.92; p < .001) at a median duration of follow-up of 2.2 years (Table 1). The reduction of the composite of CV events was greater in patients with high-risk features i.e. more recent MI (HR, 0.80, 95% CI, 0.71–0.9), multiple prior MI (HR, 0.82; 95% CI, 0.72–0.93), and residual multivessel CAD (HR, 0.79; 95% CI, 0.69–0.91) with absolute risk reductions that exceeded 3% (3.4, 3.7, and 3.6%, respectively) versus around 1% in the low-risk groups (0.8, 1.3, and 1.2%) 105. A Pre-specified secondary analysis of the FOURIER trial evaluated the effect of evolocumab on total CV events. The total CV events were reduced by 18% (incidence rate ratio (RR), 0.82; 95% CI, 0.75–0.90; p < .001) which was driven by decreases in MI, stroke, and coronary revascularization. In another secondary ad hoc analysis of the FOURIER trial, the reduction of adverse CV events was equally effective in patients with stable ASCVD regardless of the baseline LDL-C whether it was ≤1.8 mmol/L (70 mg/dL) or the background statins whether it was of a maximal or submaximal potency. Thirteen percent of patients in the FOURIER trial had PAD; evolocumab significantly lowered the primary end point in PAD patients (HR, 0.79; 95% CI 0.66–0.94; p = .0098) and the risk of major adverse limb events in all patients (HR, 0.58; 95% CI, 0.38–0.88; p = .0093). The reduction in LDL-C levels lowered the risk of major adverse limb events. Evolocumab induced a relative reduction in venous thromboembolism (VTE) events by 29% (HR, 0.71; 95% CI, 0.50–1.00; p = .05) in the first year and by 46% (HR, 0.54; 95% CI, 0.33–0.88; p = .014) thereafter, in a pre-specified analysis of the FOURIER trial. Moreover, evolocumab in the FOURIER trial reduced adverse CV events across the strata of baseline high-sensitivity C-reactive protein (hs-CRP) levels.
protein (hs-CRP) (< 1, 1 – 3, and >3 mg/dL) with more absolute risk reductions in the patients with higher-baseline hs-CRP110. A meta-analysis111 found that PCSK9 inhibitors do not impact the circulating hs-CRP levels in contrast to statins112 or bempedoic acid17,113. A recent post hoc analysis of the FOURIER trial found that after the first 12 months of evolocumab use, there was a 52% relative reduction (HR, 0.48; 95% CI, 0.25-0.93) in aortic stenosis (AS) events rates in evolocumab group, which was attributed to the reduction in Lp(a) levels114. A previous study has suggested that PCSK9 inhibitors may potentially have a role in reducing the risk of AS based on the finding that PCSK9 R46L loss-of-function mutation was associated with lower Lp(a) and LDL-C level as well as reduced risk of AS115. The ODYSSEY OUTCOMES116 trial (n = 18,924) randomized patients on statin therapy with inadequate LDL-C control who had a recent ACS event rather than the more stable ones enrolled in the FOURIER trial. Alirocumab 75 mg or 150 mg Q2W over a median follow up of 2.8 years, significantly reduced the four-point composite of CV death, nonfatal MI, fatal or nonfatal ischemic stroke, or UA requiring hospitalization (HR, 0.85, 95% CI, 0.78 – 0.93; p < 0.001) (Table 1). The absolute benefit was greater among patients who had a baseline LDL-C of ≥ 2.6 mmol/L (100 mg/dL) than among patients with lower baseline LDL-C level. In a pre-specified analysis116, alirocumab prevented total (first and recurrent) non-fatal CV events (HR, 0.87, 95% CI, 0.82 – 0.93) and all-cause mortality (HR, 0.83, 95% CI, 0.71 – 0.97) in the presence of a strong association between nonfatal and fatal event risk. In another pre-specified analysis117, alirocumab has also reduced the total (first and subsequent) hospitalizations (HR, 0.96 [95% CI, 0.92-1.00]; p = 0.04) and slightly increased days alive and out of hospital (RR, 1.003 [95% CI, 1.000-1.007]; p = 0.05) due to a decrease in days dead (RR, 0.847 [95% CI, 0.728-0.986]; p = 0.03), defined as the time from a patient’s death to the study end date. A third pre-specified analysis118 of the ODYSSEY OUTCOMES trial investigated the effect of alirocumab in ACS patients with a history of coronary artery bypass grafting. Alirocumab was associated with large absolute reductions in MACE and death. In a prespecified analysis of other vascular events in the ODYSSEY OUTCOMES trial, alirocumab lowered PAD events (HR, 0.69; 95% CI, 0.54–0.89; p = .004) significantly, but missed the statistical significance in reducing VTE events (HR, 0.67; 95% CI, 0.44–1.01; p = .06)119. When combined data from the FOURIER and ODYSSEY OUTCOMES trials (n = 46,488) were analyzed, it resulted in a 31% reduction in VTE events [HR, 0.69; 95% CI, 0.53–0.90; p = .007]109. Evidence also suggests the association with Lp(a) levels reduction109,119. The two parallel, SPIRE-1 and SPIRE-2, CV outcome trials (n = 27,438)104 were conducted in 2013 to assess the efficacy and safety of bococizumab, at a dose of 150 mg Q2W, in patients at high CV risk. However, the trials were terminated early by the sponsor after a median follow up of 10 months. The sponsor opted to stop the development of bococizumab due to the high rates of the anti-drug antibodies (ADAs), as detected in the data from other studies in the SPIRE program that consisted of a total of eight studies (i.e. six lipid-lowering and two CV outcome trials). In a combined analysis of SPIRE-1 and SPIRE-2 trials, bococizumab showed no benefit in term of MACE9,104 (Table 1).

### Safety of PCSK9 monoclonal antibodies

In general, the safety profile of both evolocumab and alirocumab is excellent. Nasopharyngitis and mild injection-site reactions are considered the most common adverse reactions5.

#### Adverse effects

In two meta-analyses1,79 of RCTs, treatment with PCSK9 inhibitors was not associated with the adverse effects commonly described with statin therapy such as myalgia and elevations in serum aminotransferases or creatine kinase, with overall serious adverse events that were comparable to the control group. The aforementioned meta-analyses did not report the injection site reactions which are the most frequent adverse events with the PCSK9 inhibitors use4. The allergic local injection-site reactions (e.g. itching, redness, swelling) rates were 3.8% in alirocumab group versus 2.1% in placebo (p < .001)99 and 5.9 versus 4.2% over a period of 78 weeks63. Injection-site reactions are usually mild and self-limited99. The reactions rates with evolocumab were 2.1% versus 1.6% in the placebo group98, and there was no increase in hypersensitivity with longer treatment120. Bococizumab caused higher injection-site reactions as compared to placebo (10.4 versus 1.3%, p < .001)104 and 12.7 per 100 person-years in six trials evaluating bococizumab. However, the rates did not increase with longer time121.

#### Anti-drug antibodies

Therapeutic molecules may have an immunogenicity potential that may generate ADAs. The ADAs can be generated in response to fully human (e.g. alirocumab and evolocumab).
or humanized (e.g. murine-derived bococizumab) monoclonal antibodies. High-titer ADAs have substantially developed in response to treatment with bococizumab (i.e. high degree of immunogenicity), while treatment with either alirocumab or evolocumab has not significantly been associated with ADAs generation\textsuperscript{104,121}. This immunologic difference explains the higher injection-site reactions rate reported with bococizumab\textsuperscript{104}. ADAs can be either neutralizing or binding\textsuperscript{122}. Binding ADAs bind to therapeutic proteins without affecting the molecules' function\textsuperscript{126}, while neutralizing ADAs can directly impair their function\textsuperscript{122}. In the ODYSSEY OUTCOMES\textsuperscript{99} trial, neutralizing ADAs were observed in 0.5% of patients on alirocumab versus 0.1% of those on placebo. Roth et al.\textsuperscript{123} reported data from 10 trials and found that ADAs against alirocumab were observed in 5.1% of patients as compared to 1.0% in the control group with persistent ADAs found in 1.4% versus 0.2% after 12 weeks or more, respectively. Neutralizing ADAs were reported in only 1.3% of the patients in alirocumab group. In the FOURIER\textsuperscript{98} trial, evolocumab generated binding ADAs in 0.3% of the patients and no neutralizing ADAs have been detected. These findings were consistent over a period of four years as observed in the OSLER-1\textsuperscript{120} study. In four RCTs that reported data regarding ADAs for evolocumab and alirocumab, the ADAs were transient and their titers decreased over time\textsuperscript{79}. Almost half of the patients who received bococizumab in the SPIRE studies had high-titer ADAs with neutralizing antibodies developed in 29% of the patients\textsuperscript{104}. Comparisons of ADAs incidence among the different PCSK9 inhibitors may be misleading because immunogenicity potential is dependent on various factors\textsuperscript{123}. Cross-reactivity between PCSK9 inhibitors is unlikely to occur due to the specificity of the binding domains\textsuperscript{121}. ADAs directed against PCSK9 inhibitors are one of the theoretical mechanisms for the PCSK9 inhibitors hypo-responsiveness (i.e. < 15% reduction in LDL-C level) due to the physiological impairment of monoclonal antibodies once absorbed into the circulation\textsuperscript{14}. The occurrence of ADAs with PCSK9 inhibitors has attracted widespread attention. Although autoantibodies were detected in some patients on alirocumab or evolocumab, reductions in LDL-C levels induced by either monoclonal antibody were not attenuated\textsuperscript{79}. ADAs did not appear to significantly attenuate the lipid-lowering effect of alirocumab\textsuperscript{99,123} or evolocumab\textsuperscript{98}, unlike that of bococizumab\textsuperscript{121}. The high immunogenicity rates and the wide variation in LDL-C response among patients on bococizumab led to the discontinuation of further clinical development of bococizumab\textsuperscript{9,121}.

**Neurocognitive events**

Low LDL-C levels in the clinical trials of PCSK9 inhibitors have raised a concern about the association of their use with cognitive impairment\textsuperscript{124}. Neurocognitive adverse events were reported as delirium, attention disorders, amnesia, dementia, disturbances in thinking and perception, or mental impairment disorders\textsuperscript{4,5}. Neurocognitive adverse events reported in the clinical trials of alirocumab and evolocumab were not significantly different from those reported in the control groups\textsuperscript{63,98,99}. Furthermore, similar findings were found in two meta-analyses of RCTs\textsuperscript{1,79} and in the EBBINGHAUS\textsuperscript{124} study (n = 1204), a sub-study of the FOURIER trial, that evaluated the cognitive deficits. The findings of the latter study were supported by a Mendelian randomization study which found no causal relationship between inhibition of PCSK9 function and neurodegenerative diseases\textsuperscript{125}.

**Diabetes**

It has been hypothesized that the significant LDL-C-lowering effect of the PCSK9 inhibitors may negatively affect the glycemic status, namely the new-onset diabetes, as suggested with statin therapy to be associated with an increase in diabetes incidence\textsuperscript{104,126}. It has been postulated that the genetic variations in the targets of statins and PCSK9 inhibitors i.e. 3-hydroxy-3-methylglutaryl-CoA reductase (HMGR) and PCSK9 respectively, have been associated with desirable protective effect against atherosclerosis but on the other hand with adverse effects in term of diabetes\textsuperscript{104}. The currently available evidence did not suggest significant increase in new-onset diabetes or worsening of preexisting diabetes on shorter or longer terms with either alirocumab\textsuperscript{139,63,99,127} or evolocumab\textsuperscript{56,57,98,120,128–130}. In the SPIRE\textsuperscript{104} studies, although bococizumab use was not associated with significant increase in new-diabetes, the early termination of the trials precluded the ability to assess adverse effect on glycemic control. The results of three recent meta-analyses\textsuperscript{1,79,126} are in line with the findings of the previous studies. However, one\textsuperscript{126} of the aforementioned meta-analyses has elaborated that the imbalance in the background LLT of the control arms may have masked the effect of PCSK9 inhibitors on diabetes.

**Fat-soluble vitamins and steroid hormones**

Fat-soluble vitamins and steroid hormones levels were measured as part of prespecified safety analyses in trials with PCSK9 inhibitors such as ODYSSEY LONG TERM\textsuperscript{135} and DESCARTES\textsuperscript{131}. In the alirocumab group, although the levels of vitamin E or vitamin K were below the lower limit of the normal range, there were no clinically important changes. Moreover, there was no clinically meaningful effect with regards to the changes in the levels of cortisol or other fat-soluble vitamins\textsuperscript{64}. Similarly, vitamin E levels were lower in evolocumab-treated subjects but the results were not statistically significant after the adjustment of LDL-C level, and there were no adverse effects reported for steroid or gonadal hormones\textsuperscript{31}.

**Cost-effectiveness of PCSK9 monoclonal antibodies**

Evaluation of cost effectiveness of PCSK9 inhibitors has been of interest to several trials. In 2015, they were not proven to be cost effective as their use increased annual prescription spending by $125 billion over ezetimibe in patients with HeFH or ASCVD\textsuperscript{132}. Another study\textsuperscript{133} recommended price reduction ($14,000–15,000) by 70% as they possessed...
### Table 2. Phase III registered clinical trials.

| Trial ID* | Agent | Trial brief title (acronym) | Target size | Primary outcome (time frame) | Start date | Status |
|-----------|-------|------------------------------|-------------|------------------------------|------------|--------|
| NCT02476006 | Alirocumab | Safety, tolerability, and effect of alirocumab in high cardiovascular risk patients with severe hypercholesterolemia not adequately controlled with conventional lipid-modifying therapies (ODYSSEY APPRISE) | 998 | Proportion of patients with adverse events and percent change in lipid levels (30 months) | June 2015 | Completed |
| NCT03433755 | Evolocumab | Safety and efficacy of evolocumab in addition to optimal stable background statin therapy in Chinese subjects with primary hypercholesterolemia and mixed dyslipidemia | 450 | Mean percent change in LDL-C from baseline (10 and 12 weeks) | May 2019 | Recruiting |
| NCT03156621 | Alirocumab | Study in participants HoFH (ODYSSEY HoFH) | 69 | Percent change in LDL-C from baseline (12 weeks) | October 2017 | Active, not recruiting |
| NCT03672401 | Evolocumab | Effect of evolocumab in patients at high cardiovascular risk without prior MI or stroke (VESALIUS-CV) | 13,000 | Time to coronary heart disease death, MI, or ischemic stroke (4.5 years) | June 2019 | Recruiting |
| NCT03080935 | Evolocumab | Further cardiovascular outcomes research with PCSK9 inhibition in subjects with elevated risk open-label extension (FOURIER OLE) | 5,037 | Subject incidence of adverse events (5 years) | September 2016 | Active, not recruiting |
| NCT03570697 | Evolocumab | Imaging of coronary plaques in subjects treated with evolocumab (HUYGENS) | 164 | Absolute change in minimum FCT (50 weeks) | November 2018 | Active, not recruiting |
| NCT03689946 | Evolocumab | Effect of evolocumab on coronary artery plaque volume and composition by CCTA and microrcalciﬁcation by F18-NaF PET | 55 | Change in NCPV from baseline (18 months) | March 2019 | Recruiting |
| NCT02729025 | Evolocumab | Effects of proprotein convertase subtilisin/Kexin Type 9 (PCSK9) inhibition on arterial wall inﬂammation in patients with elevated Lp(a) (ANITSCHKOW) | 129 | Percent change in Lp(a) in target-to-background ratio of an index vessel by FDG-PET/CT (16 weeks) | April 2016 | Completed |
| JPRN-jRCT1051180064 | Alirocumab | Effect of alirocumab and rosuvastatin or rosuvastatin alone on lipid core plaques in coronary artery disease evaluated by near-infrared spectroscopy intravascular ultrasound (ANTARES) | 30 | Absolute change of maxLCBI (4mm) from baseline (36 weeks) | April 2018 | Recruiting |
| JPRN-jRCT1051180063 | Alirocumab | Efficacy of Alirocumab for thin-cap ﬁbroatheroma in patients with coronary artery disease estimated by optical coherence tomography trial (ALTAR) | 24 | Change in minimum FCT between baseline (36 weeks) | September 2017 | Completed |
| NCT03067844 | Alirocumab | Vascular effects of alirocumab in acute MI-patients (PACMAN-AMI) | 294 | Change in PAV from baseline (52 weeks) | April 2017 | Recruiting |

#### Special patient populations

| Trial ID* | Agent | Trial brief title (acronym) | Target size | Primary outcome (time frame) | Start date | Status |
|-----------|-------|------------------------------|-------------|------------------------------|------------|--------|
| NCT03510884 | Alirocumab | An efficacy and safety study of alirocumab in children and adolescents with HeFH | 150 | Percent change in LDL-C from baseline (24 weeks) | May 2018 | Recruiting |
| NCT03510715 | Alirocumab | An efficacy and safety study of alirocumab in children and adolescents with HoFH | 18 | Percent change in LDL-C from baseline (12 weeks) | August 2018 | Completed |
| NCT02392539 | Evolocumab | Trial assessing efﬁcacy, safety and tolerability of PCSK9 inhibition in pediatric subjects with genetic LDL disorders (HAUSER-RCT) | 159 | Percentage change LDL-C levels from baseline (24 weeks) | February 2016 | Completed |
| NCT02624869 | Evolocumab | Open label study to evaluate safety, tolerability and efﬁcacy of evolocumab (AMG 145) in pediatric subjects (10–17 years of age) with HeFH or HoFH (HAUSER-OLE) | 163 | Number of participants with treatment-related adverse events as assessed by CTCAE V4.0 (80 weeks) | September 2016 | Active, not recruiting |
Table 2. Continued.

| Trial ID | Target size | Primary outcome (time frame) | Start date | Status |
|----------|-------------|------------------------------|------------|--------|
| NCT03207945 | HIV subjects | Alirocumab Effect of PCSK9 inhibition on cardiovascular risk in subjects with HIV & hyperlipidemia/mixed dyslipidemia | February 2018 | Recruiting |
| NCT02833844 | HIV subjects | Evolocumab Safety, tolerability & efficacy on LDL-C of evolocumab in subjects with HIV & hyperlipidemia/mixed dyslipidemia | May 2017 | Completed |
| NCT03734211 | Heart transplant recipients | Evolocumab Cholesterol lowering with evolocumab to prevent cardiac allograft vasculopathy in de-novo heart transplant recipients (EVOLVD) | February 2019 | Recruiting |
| NCT03480568 | Dialysis patients | Alirocumab Alirocumab in patients on a stable dialysis regimen | May 2018 | Recruiting |
| NCT03344692 | Diabetics | Alirocumab Effect of alirocumab on postprandial hyperlipemia in patients with type 2 diabetes (EUTERPE) | February 2019 | Recruiting |

Registered clinical trials

The documented significant benefit of the PCSK9 monoclonal antibodies in decreasing lipid parameters and adverse CV events encouraged further investigations on their efficacy and safety. Research is ongoing in patients with familial and non-familial hypercholesterolemia. New research is targeting special patient populations such as pediatrics and human immunodeficiency virus (HIV) subjects. Relevant ongoing Phase III trials are listed in Table 2.

Conclusions

The currently-available PCSK9 monoclonal antibodies, alirocumab and evolocumab, are safe and effective when used as an add-on or as monotherapy. They are effective in lowering LDL-C levels by more than 50% in pooled populations. The outcome studies have confirmed that the significant LDL-C-lowering capacity was translated into a reduction in CV events without causing excessive adverse effects. The benefit in CV outcomes was attributed to the ability of PCSK9 inhibitors to lower atherogenic lipid fractions such as LDL-C, non-HDL-C, apo-B, and Lp(a) levels and atheroma volume. The ability to lower Lp(a) levels could potentially reduce PAD, VTE, and AS events as well.

Transparency

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