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PCSK9 Inhibitor Monoclonal Antibodies for the Treatment of Hypercholesterolemia

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Summary

- Monoclonal antibodies targeted against the proprotein convertase subtilisin kexin type 9 (PCSK9) protein increase the liver's ability to remove low-density lipoprotein cholesterol (LDL-C) from the blood, which may reduce the development of atherosclerosis. Three PCSK9 inhibitor monoclonal antibodies — evolocumab (Repatha, Amgen Inc.), alirocumab (Praluent, Sanofi/ Regeneron Pharmaceuticals Inc.), and bococizumab (RN316, Pfizer Inc.) — are currently being evaluated in phase 3 clinical outcome trials for patients who cannot achieve sufficient lowering of LDL-C with standard lipid-lowering therapy. A phase 2 trial was recently completed for a fourth drug, LY3015014 (Eli Lilly). Evolocumab was approved in September 2015 for sale in Canada; the annual price is C$7,263.36 per patient. Alirocumab is currently being reviewed by Health Canada.

- Results from 19 phase 3 trials evaluating the effect of evolocumab (seven trials; n = 4,500) and alirocumab (12 trials; n = 4,205) with or without background lipid-lowering therapy on LDL-C levels (a surrogate measure of the effect on cardiovascular outcomes) in different patient populations with hypercholesterolemia have been reported. Mean reductions in LDL-C from baseline between 55% and 76% versus placebo and between 38% and 47% versus ezetimibe were reported with evolocumab at 12 weeks. One trial showed a mean reduction in LDL-C of 57% versus placebo at 52 weeks when evolocumab was added to diet with or without other lipid-lowering therapy. Alirocumab produced reductions in LDL-C between 20% and 64% versus placebo and between 24% and 36% versus ezetimibe at 24 weeks.

- Longer-term phase 3 trials of evolocumab (two trials; n = 4,465) and alirocumab (one trial; n = 2,341) report sustained reductions in LDL-C of 52% with evolocumab versus placebo at week 124 and 56% with alirocumab versus placebo at week 78. Pre-specified exploratory and post hoc analyses from these trials suggest there may be a reduction in cardiovascular events with evolocumab and alirocumab at 12 to 18 months compared with standard therapy alone, although these trials were not designed as cardiovascular outcome trials.

- The most common adverse effects of evolocumab and alirocumab were nasopharyngitis, upper respiratory tract infections, and injection site reactions. A higher frequency of neurocognitive adverse events has been observed with both evolocumab (0.9% versus 0.3% for placebo) and alirocumab (1.2% versus 0.5% for placebo). The FDA has directed developers of PCSK9 inhibitor monoclonal antibodies to monitor for neurocognitive adverse effects in ongoing clinical outcome trials.

- None of the completed phase 3 trials were of sufficient duration to assess long-term efficacy or safety. The trials also lacked the sample size required to detect rare adverse events or differences in cardiovascular outcomes.
- Four large-scale clinical outcome trials are evaluating the effectiveness and safety of evolocumab, alirocumab, and bococizumab when added to standard lipid-lowering therapy for the primary prevention of cardiovascular events in high-risk patients or secondary prevention in patients who have a history of atherosclerotic cardiovascular disease. Results are anticipated in late 2017 or early 2018.
- The long-term safety, efficacy, and cost-effectiveness of PCSK9 inhibitor monoclonal antibodies for the primary or secondary prevention of cardiovascular morbidity and mortality need to be assessed in various patient populations with hypercholesterolemia to determine the impact on clinical practice.

Background

Cardiovascular disease is one of the leading causes of morbidity and mortality in Canada.[1,2] In 2011, almost 30% of all deaths in Canada were the result of cardiovascular disease.[3] The economic burden of cardiovascular disease in Canada is substantial. The total cost for the use of health care resources and lost productivity was estimated to be C$20.9 billion in 2005.[1] This figure is expected to increase to C$28.3 billion in 2020.[1]

Low-density lipoprotein cholesterol (LDL-C) is a major modifiable risk factor for myocardial infarction, peripheral vascular disease, stroke, and death from atherosclerotic cardiovascular disease.[2] Statin therapy has been shown to decrease LDL-C by approximately 25% to 50%, with a corresponding 24% to 45% risk reduction in cardiovascular events.[4,5] However, many patients remain at risk for future cardiovascular events despite receiving maximally tolerated statin therapy.[6-9] In addition, some individuals are unable to tolerate statin therapy, primarily due to muscle-related adverse effects.[10] Patients with familial hypercholesterolemia, a genetic disorder characterized by very high plasma levels of LDL-C at an early age, are often not able to achieve targeted LDL-C levels with statins alone or in combination with other lipid-lowering therapies.[11] Treatment options for these patients are limited, particularly for those with the more serious homozygous form of the genetic disorder. For example, lomitapide (Juxtapid, Aegerion Pharmaceuticals Ltd., Toronto, Ontario), a novel microsomal triglyceride transfer protein inhibitor, was approved by Health Canada for the treatment of homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering therapy in February 2014.[12] However, lomitapide has been associated with liver toxicity and there are currently no data available for cardiovascular outcomes.[13] Additional approaches are needed for difficult-to-treat patient populations who do not achieve sufficient lowering of LDL-C with conventional statin therapy.

The Technology

A monoclonal antibody is a type of protein that is synthesized in laboratory to bind to substances in the body; it can be used as a biological therapy.[14,15] Phase 3 data have been reported for two proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor monoclonal antibodies: evolocumab (Repatha, Amgen Inc., Thousand Oaks, California) and alirocumab (Praluent, Sanofi, New York, New York/Regeneron Pharmaceuticals Inc., Tarrytown, New York).[16] Both are fully human monoclonal antibodies targeted against PCSK9, a protein that binds to low-density lipoprotein (LDL) receptors and facilitates their degradation.[17,18] This reduces the liver's ability to remove LDL-C from the blood. Inhibiting PCSK9 increases the number of LDL receptors on the surface of the liver for removing LDL-C from the blood, which

may reduce the development of atherosclerosis (a narrowing of arteries due to an accumulation of fatty deposits or plaques in the arterial wall) and coronary artery disease. These new drugs are administered subcutaneously by self-injection using a single-dose, pre-filled auto-injector pen or pre-filled syringe every two weeks.[17,18] Of note, pre-filled syringes of evolocumab are currently not available in Canada.[19] A monthly dose of evolocumab can be administered by using three pre-filled auto-injector pens or pre-filled syringes consecutively.[19] Amgen plans to release a single injection option for the monthly administration of evolocumab in 2016.[17] Bococizumab (RN316, Pfizer Inc., New York, New York) is a humanized PCSK9 inhibitor monoclonal antibody that is also undergoing phase 3 testing in patients with uncontrolled LDL-C levels despite the use of optimal statin therapy or documented statin intolerance. The drug is administered every two weeks.[16] Phase 3 results for bococizumab are currently not available.

LY3015014 (Eli Lilly, Indianapolis, Indiana) is a humanized PCSK9 inhibitor monoclonal antibody with a proposed longer duration of action.[20] Phase 2 results of LY3015014 when given every four or eight weeks in patients with hypercholesterolemia have been released,[20] but there are currently no ongoing phase 3 trials.

Regulatory Status

Amgen Canada Inc. received Health Canada approval for evolocumab in September 2015; it will be commercialized under the trade name Repatha.[21] It is indicated as an adjunct to diet and maximally tolerated statin therapy in adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease who require additional lowering of LDL-C.[19] It is also indicated as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in adults and adolescent patients aged 12 years and over with homozygous familial hypercholesterolemia who require additional lowering of LDL-C.[19] Health Canada is currently reviewing alirocumab for regulatory approval.[22]

In July 2015, the US Food and Drug Administration (FDA) approved alirocumab as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease who require additional lowering of LDL-C.[23] In August 2015, the FDA approved evolocumab for the same indications as alirocumab with the addition of use in adults with homozygous familial hypercholesterolemia.[24] Amgen is currently seeking FDA approval for a new delivery option of evolocumab by single-dose, once-monthly injection.[25]

In September 2015, the European Commission (EC) granted marketing authorization for alirocumab to be used in adults with primary hypercholesterolemia (including heterozygous familial and non-familial hypercholesterolemia) or mixed dyslipidemia in combination with statins and other lipid-lowering therapies or as monotherapy in patients who are statin intolerant, or for whom a statin is contraindicated.[26] The EC approved evolocumab in July 2015 for the same indications as alirocumab with the addition of use in combination with statins and other lipid-lowering therapies in adults and adolescents 12 years and over with homozygous familial hypercholesterolemia.[27]

Patient Group

Dyslipidemia (an abnormal level of lipids and lipoproteins in the blood) is a major risk factor for developing atherosclerosis.[2] Progression of atherosclerosis may lead to coronary artery disease, myocardial infarction, heart failure, peripheral artery disease, and stroke. Results from the 2012 to 2013 Canadian Health Measures Survey estimate that 38% of adults aged 18 to 79 years have dyslipidemia (defined as having LDL-C of 3.5 mmol/L or greater, or a total cholesterol to high-density lipoprotein cholesterol [HDL-C] of 5.0 mmol/L or greater, or self-reported use of a lipid-modifying medication).[28] Of these, 19% had elevated levels of LDL-C consistent with hypercholesterolemia. Extrapolating to current estimates of population by age group,[29] an estimated 5.2 million adult Canadians have hypercholesterolemia. Approximately 83,500 Canadians are estimated to have familial hypercholesterolemia.[11] Although clinical trials typically report statin intolerance in up to 5% of patients with hypercholesterolemia, the frequency of statin intolerance in clinical practice has been described to be as high as 20%.[30,31] However, the prevalence of true statin intolerance is likely much less. In a recent large retrospective database study, 10% of patients prescribed a statin discontinued treatment because of a perceived statin-related adverse effect.[31] However, 90% of those who were re-challenged were subsequently able to tolerate the same or a different statin.[31]

Current Practice

Guidelines released from the Canadian Cardiovascular Society (CCS) in 2012 recommend that the initiation of treatment for dyslipidemia be based on the risk of coronary artery disease and lipid levels.[2] An LDL-C of 5.0 mmol/L or greater is considered high for patients at low risk of cardiovascular disease. An LDL-C of 3.5 mmol/L or greater is considered high for patients at moderate risk of cardiovascular disease. Cardiovascular risk is generally estimated using the Framingham risk score based on the patient's age, sex, total cholesterol, HDL-C, blood pressure (treated or untreated), and smoking status, with further adjustment based on the presence of comorbidities including diabetes, chronic kidney disease, clinical evidence of atherosclerotic cardiovascular disease, and a family history of premature cardiovascular disease. All patients with familial hypercholesterolemia are considered high-risk.[11] Treatment is considered in all high-risk patients even if cholesterol levels are normal. Treatment is also considered in moderate-risk or low-risk patients depending on the levels of LDL-C, apolipoprotein B, and non-HDL-C. The guidelines recommend LDL-C reduction with statins as the primary target of therapy. The goal of treatment is an LDL-C level of 2.0 mmol/L or less, or a 50% or greater reduction in LDL-C level.[2,11] When goal LDL-C levels cannot be achieved with statins alone, the addition of adjunctive drugs such as ezetimibe or bile acid sequestrants is recommended on an individualized basis.[2,11]

The 2013 publication of the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines present a different perspective on risk stratification and treatment goals. The Expert Panel was unable to find evidence to support titrating lipid-lowering therapy to achieve target LDL-C or non-HDL-C levels, and therefore did not support the use of LDL-C level alone as a target for treatment.[32] Instead, the guidelines recommend using a new method for cardiovascular risk assessment, the heart risk calculator, to determine the appropriate intensity of statin therapy in those who would most likely benefit.[33] However, despite these ACC/AHA guidelines, the CCS continues to stand by its recommendations for cardiovascular risk stratification and supports using LDL-C level as a target of therapy.[34]

Methods

A peer-reviewed literature search was conducted using the following bibliographic databases: MEDLINE, PubMed, Embase, and The Cochrane Library. Grey literature was identified by searching relevant sections of the CADTH Grey Matters checklist (https://www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine). Methodological filters were applied to limit the search to health technology assessments, systematic reviews, meta-analyses, and randomized controlled trials. No language or date limits were applied. Regular alerts were established to update the search until November 23, 2015. Phase 3 randomized controlled trials published in full or presented as unpublished data from industry communications and conference abstracts reporting the clinical efficacy and safety of PCSK9 inhibitor monoclonal antibodies for the treatment of hypercholesterolemia were selected for inclusion in "The Evidence" section of this bulletin. Open-label extension trials of phase 2 and 3 trials evaluating cardiovascular outcomes were also included. Longer-term phase 3 data from randomized controlled trials and open-label extension trials of phase 2 and 3 trials evaluating the safety of evolocumab and alirocumab in a larger patient population (n > 500) were included in the "Adverse Event" section. Phase 2 safety data for bococizumab and LY3015014 were also included. Meta-analyses, case reports, editorials, letters, and narrative literature reviews were excluded.

The Evidence

Nineteen phase 3 clinical trials evaluating evolocumab and alirocumab in various patient populations for the reduction of LDL-C levels (a surrogate measure of the beneficial effect on cardiovascular outcomes) are summarized in Appendix A (Table A-1), including study design, inclusion criteria, background therapy, treatment regimens, and primary outcome results. All trials reported statistically significant reductions in LDL-C levels from baseline relative to the comparators (with the exception of ODYSSEY OPTIONS II). Results from the longer-term trials suggest a sustained reduction in LDL-C. Pre-specified exploratory and post hoc analyses from the OSLER and ODYSSEY LONG-TERM studies also suggest a beneficial effect on cardiovascular outcomes with both evolocumab and alirocumab (Table 1). However, these trials were not designed as cardiovascular outcome trials. Hence, these findings will need to be confirmed in ongoing large-scale cardiovascular outcome trials (Table 2).

None of these surrogate-based phase 3 trials were of sufficient duration to assess long-term efficacy or safety. The trials also lacked the sample size required to detect rare adverse events or differences in cardiovascular outcomes.

Evolocumab Surrogate Outcome Trials

Results from seven multi-centre, double-blind, placebo- and/or active (ezetimibe)-controlled, randomized phase 3 trials evaluating evolocumab in more than 4,500 patients have been reported.[35-41] The co-primary outcomes of five trials were the per cent change from baseline in LDL-C at 12 weeks and averaged between weeks 10 and 12 (to more accurately reflect average LDL-C reduction over the entire dosing interval).[35-37,39,40] This bulletin reports data for the treatment difference at 12 weeks. The primary outcomes for the other two trials were per cent change from baseline in LDL-C at 12 weeks[41] or at 52 weeks.[38]

Five of the trials evaluated evolocumab administered at a dose of 140 mg every two weeks or 420 mg every month in patients with primary hypercholesterolemia (non-familial and heterozygous familial hypercholesterolemia) and mixed dyslipidemia.[35-37,39,40] A heterogeneous population was assessed in these trials, in which approximately 20% had a history of coronary heart disease and fewer than 50% of participants were considered to be at moderate to high cardiovascular risk at baseline. One trial evaluated evolocumab administered at a dose of 420 mg every month in patients with homozygous familial hypercholesterolemia.[41] Approximately 43% of these patients had established coronary artery disease. One trial evaluated evolocumab at a dose of 420 mg every month in patients with a range of cardiovascular risks.[38] The majority (64%) of participants in this trial were at low or moderate cardiovascular risk. Patients enrolled in the evolocumab phase 3 clinical program (who were not considered statin intolerant) were not all required to be taking maximally tolerated statin background therapy prior to the addition of evolocumab, which may not be well aligned with the proposed future use of evolocumab in clinical practice.

The MENDEL-2 study (n = 614) reported a 55% to 57% reduction in LDL-C (depending on the dose of evolocumab) versus placebo in patients not receiving any background lipid-lowering therapy.[35] Evolocumab also reduced LDL-C by 38% to 39% (depending on the dose of evolocumab) compared with ezetimibe. However, this trial enrolled low-risk patients who may not be the target population for therapy with evolocumab.

LAPLACE-2 (n = 1,896) assessed the addition of evolocumab to moderate- or high-intensity background statin therapy.[36] Reductions in LDL-C for the different doses of evolocumab ranged from 55% to 76% versus placebo and 39% to 47% versus ezetimibe. The YUKAWA-2 study (n = 404) reported that adding evolocumab to background statin therapy in Japanese patients with high cardiovascular risk produced reductions in LDL-C ranging from 67% to 76% (depending on the dose of evolocumab) compared with placebo.[37]

GAUSS-2 (n = 307) evaluated evolocumab in patients with statin intolerance.[39] Results showed a similar reduction in LDL-C for both doses of evolocumab versus ezetimibe (38%; 95% confidence interval [CI], 44% to 32% for 140 mg every two weeks; and 38%; 95% CI, 42% to 33% for 420 mg every month). Although participants were required to have previous documented intolerance to two or more statins, the study design did not include a blinded placebo run-in period or statin re-challenge group to validate the definition of statin intolerance used for eligibility. Of note, a placebo-controlled statin re-challenge has been included in the ongoing GAUSS-3 study.[42]

In RUTHERFORD-2 (n = 329), patients with heterozygous familial hypercholesterolemia receiving background treatment with stable, maximally tolerated statins with or without other lipid-lowering therapy showed a reduction in LDL-C of 59% to 61% (depending on the dose of evolocumab) compared with placebo.[40] The TESLA Part B study (n = 49) is currently the only study that has evaluated the use of a PCSK9 inhibitor monoclonal antibody exclusively in patients with homozygous familial hypercholesterolemia.[41] Results showed a reduction in LDL-C in patients receiving evolocumab in addition to background lipid-lowering therapy of 31% (95% CI, 44% to 18%) versus placebo. Patients who did not have any functioning LDL receptors due to genetic mutations did not respond to therapy with evolocumab.

DESCARTES (n = 901) was designed to evaluate the long-term efficacy of evolocumab in patients with a range of cardiovascular risks.[38] Patients in each treatment group received background therapy with diet alone, atorvastatin, or atorvastatin with or without ezetimibe based on baseline LDL-C levels and cardiovascular risk. The mean reduction in LDL-C at 52 weeks versus placebo was 57% (range 49% to 62% based on background therapy; $P < 0.001$ for all comparisons). The majority (64%) of participants in this trial were at low or moderate cardiovascular risk, and thus results may not be entirely applicable to the target population for therapy with evolocumab.

Alirocumab Surrogate Outcome Trials

Results from 12 multi-centre, double-blind, placebo- and/or active (ezetimibe)-controlled, randomized phase 3 trials evaluating alirocumab in 4,200 participants have been reported.[43-52] The majority of the trials enrolled patients with heterozygous familial hypercholesterolemia, established cardiovascular disease, or at high risk for cardiovascular disease and who were already taking a maximally tolerated dose of statin with or without other lipid-lowering therapies. The alirocumab dosing regimens evaluated were 75 mg every two weeks, 150 mg every month, or 300 mg every month (all with titration at week 12 to 150 mg every two weeks if LDL-C lowering goals were not met). An initial dose of 150 mg every two weeks was also tested. The primary outcome in all of the trials was the mean per cent reduction in LDL-C from baseline to week 24.

ODYSSEY MONO (n = 103) showed a 32% (95% CI, 40% to 23%) reduction in LDL-C compared with ezetimibe in moderate-risk patients without background lipid-modifying therapy.[43] However, given the availability of effective and lower-cost therapies with statins and ezetimibe, it is unlikely that alirocumab will be used in clinical practice as first-line monotherapy in a moderate-risk population.

> **"Approximately 75% of patients who met the clinical definition of statin intolerance completed the 24-week trial when randomly assigned to receive atorvastatin."**

ODYSSEY COMBO I (n = 316) and COMBO II (n = 720) studied the effect of alirocumab on LDL-C in patients with established cardiovascular disease or at high risk for cardiovascular events receiving background therapy with a maximally tolerated statin therapy.[44,45] COMBO I showed a 46% (95% CI, 53% to 39%) reduction in LDL-C compared with placebo, and COMBO II reported a 30% (95% CI, 34% to 25%) reduction in LDL-C relative to ezetimibe. ODYSSEY JAPAN (n = 216) reported a 64% (95% CI, not reported) reduction in LDL-C versus placebo in Japanese patients with heterozygous familial hypercholesterolemia or at high cardiovascular risk.[46]

The ODYSSEY OPTIONS I (n = 355) and OPTIONS II (n = 305) trials were block randomized based on background moderate doses of atorvastatin and rosuvastatin, respectively.[47,48] Patients were randomized to addition of alirocumab or ezetimibe, doubling of the statin dose, or a switch from atorvastatin to rosuvastatin (OPTIONS I trial). Results showed that adding alirocumab to atorvastatin statistically significantly reduced LDL-C more than adding ezetimibe, doubling the atorvastatin dose, or switching atorvastatin to rosuvastatin.

ODYSSEY ALTERNATIVE (n = 314) evaluated alirocumab in patients with well-documented statin intolerance and moderate to very high cardiovascular risk.[50] All participants initially received single-blind placebo during a run-in period of four weeks. Patients were excluded from the trial if muscle-related adverse events were reported with placebo. The trial included an atorvastatin re-challenge group, but formal statistical analyses evaluating the effect of atorvastatin versus other comparators were not conducted. There was a 30% (95% CI, 37% to 24%) reduction in LDL-C versus ezetimibe. However, some participants were shown to not be truly statin intolerant. Approximately 75% of patients who met the clinical definition of statin intolerance completed the 24-week trial when randomly assigned to receive atorvastatin. Furthermore, 49% of discontinuations during a single-blind, placebo run-in period were due to muscle-related adverse events.

ODYSSEY CHOICE I (n = 803) and CHOICE II (n = 231) evaluated the efficacy of alirocumab at different doses and dosing frequencies (150 mg or 300 mg every month) than the other ODYSSEY trials.[49] Results showed similar reductions in LDL-C versus placebo with or without concomitant statin therapy (range 52% to 59%), suggesting that the dosing regimen of alirocumab may be individualized based on patient characteristics such as background lipid-lowering therapy, baseline LDL-C level, and cardiovascular risk.

The ODYSSEY FH I (n = 486), FH II (n = 249), and HIGH FH (n = 107) trials evaluated alirocumab in patients with heterozygous familial hypercholesterolemia not adequately controlled on stable maximally tolerated statin therapy with or without other lipid-lowering therapy.[51,52] Results showed larger reductions in LDL-C versus placebo in patients receiving an initial dose of 75 mg every two weeks in ODYSSEY FH I (58%; 95% CI, 63% to 53%) and FH II (51%; 95% CI, 58% to 45%) than in patients receiving an initial dose of 150 mg every two weeks in

HIGH FH (39%; 95% CI, 51% to 27%). Longer-term results from ODYSSEY FH I and FH II show a sustained reduction in LDL-C at 78 weeks (52% for each trial versus placebo).[53]

Evolocumab and Alirocumab Exploratory Cardiovascular Outcome Trials

OSLER-1 and OSLER-2 were open-label, multi-centre, randomized extension trials designed to assess the long-term efficacy and safety of evolocumab.[54] The OSLER-1 study recruited patients who had completed one of the five phase 2 trials. The OSLER-2 study recruited patients who participated in one of the seven phase 3 trials. Regardless of the assignment in the original trial, a total of 4,465 eligible patients (1,324 patients in OSLER-1 and 3,141 patients in OSLER-2) were randomly assigned to receive either evolocumab 140 mg every two weeks or 420 mg monthly (n = 2,976) in addition to their standard therapy, or standard therapy alone (n = 1,489). Data from the OSLER-1 and OSLER-2 studies were combined into a single analysis set. The primary outcome was the incidence of adverse events. Although not powered or designed as outcomes trials, a pre-specified exploratory outcome was the incidence of adjudicated cardiovascular events, ascertained over the course of the study, including death, myocardial infarction, unstable angina, coronary revascularization, stroke, transient ischemic attack, and heart failure requiring hospitalization. All cardiovascular events were combined in an exploratory composite analysis that was based on the events that were pre-specified in the trial protocols. In addition, all cardiovascular outcomes excluding heart failure requiring hospitalization were combined into a post hoc composite of major adverse cardiovascular events (MACE). The secondary outcome was the per cent change from baseline in the LDL-C level. Patients were followed for a median of 11.1 months.

The mean age of patients enrolled in the OSLER studies was 58 years and 80.4% had at least one cardiovascular risk factor. A total of 3,128 (70.1%) patients were receiving statin therapy at the initiation of the extension trials. A composite of all cardiovascular events results showed that patients in the evolocumab group had a lower event rate than the standard statin therapy group (0.95% versus 2.18%, respectively; hazard ratio 0.47; 95% CI, 0.28 to 0.78; $P = 0.003$) (Table 1). Similar results were obtained for MACE (0.95% for evolocumab versus 2.11% for standard therapy; hazard ratio 0.47; 95% CI, 0.28 to 0.78). Patients receiving evolocumab achieved a 61% reduction in LDL-C level at week 12 (95% CI, 59% to 63%; $P < 0.001$) compared with standard therapy. This effect was sustained over time with a 58% reduction in LDL-C at 48 weeks. An analysis from OSLER-1 also shows a sustained reduction in LDL-C of 54% at week 52 and 52% at week 124.[55]

The OSLER studies enrolled a heterogeneous group of participants with varying degrees of cardiovascular risk and intensity of statin therapy. Although this diversity allows for generalizability of the findings, not all study patients would represent the target population for therapy with evolocumab. The open-label design of the trials and more frequent visits for patients assigned to evolocumab may have influenced reporting of events, both cardiovascular and safety. This issue may particularly limit the finding that coronary revascularization was the single most frequently reported cardiovascular event, since the decision to perform this procedure could have been influenced by knowledge of treatment assignment.

"Although these results suggest that evolocumab and alirocumab may have a beneficial effect on cardiovascular outcomes, the number of cardiovascular events reported in the studies were relatively low…"

ODYSSEY LONG TERM was a multi-centre, randomized, double-blind, placebo-controlled trial designed to assess long-term outcomes with alirocumab.[56] A total of 2,341 patients with heterozygous familial hypercholesterolemia, established coronary heart disease, or risk equivalents for coronary heart disease (such as peripheral artery disease, ischemic stroke, moderate chronic kidney disease, or diabetes mellitus) were included if they had an LDL-C level of 1.8 mmol/L or greater despite receiving maximally tolerated dose of statin therapy with or without other lipid-lowering therapy. Eligible patients were randomly assigned to receive subcutaneous alirocumab 150 mg (n = 1,553) or placebo (n = 788) every two weeks for 78 weeks. The primary efficacy outcome was the percentage change from baseline in LDL-C level at week 24. A post hoc analysis was

Table 1: Cardiovascular Outcomes from Phase 3 Trials — Pre-Specified Exploratory and Post Hoc Analyses

OSLER-1 and OSLER-254			
Cardiovascular Event	Evolocumab (N = 2,976) n (%)	Placebo (N = 1,489) n (%)	Hazard Ratio (95% CI)
All cardiovascular events	29 (0.95)	31 (2.18)	0.47 (0.28 to 0.78)
MACE[a]	28 (0.95)	30 (2.11)	0.47 (0.28 to 0.78)
Cardiovascular death, including death from unknown cause	4 (0.14)	3 (0.2)	NR
Non-cardiovascular death	0	3 (0.2)	
Myocardial infarction	9 (0.3)	5 (0.3)	
Hospitalization for unstable angina	3 (0.1)	3 (0.2)	
Coronary revascularization	15 (0.5)	17 (1.1)	
Stroke	3 (0.1)	2 (0.1)	
Transient ischemic attack	1 (0.0)	5 (0.3)	
Heart failure requiring hospitalization	1 (0.3)	1 (0.07)	
ODYSSEY LONG TERM[56]			
Cardiovascular Event	Alirocumab (N = 1,150) n (%)	Placebo (N = 788) n (%)	*P* value
Positively adjudicated cardiovascular event	72 (4.6)	40 (5.1)	0.68
Adjudicated major cardiovascular events in post hoc analysis[b]	27 (1.7)	26 (3.3)	0.02 Hazard ratio 0.52 95% CI, 0.31 to 0.90
Death from coronary heart disease, including death from unknown cause	4 (0.3)	7 (0.9)	0.26
Non-fatal myocardial infarction	14 (0.9)	18 (2.3)	0.01
Fatal or non-fatal ischemic stroke	9 (0.6)	2 (0.3)	0.35
Unstable angina requiring hospitalization	0	1 (0.1)	0.34
Congestive heart failure requiring hospitalization	9 (0.6)	3 (0.4)	0.76
Ischemia-driven revascularization procedure	48 (3.1)	24 (0.3)	1

CI = confidence interval; MACE = major adverse cardiac events; NR = not reported.

[a] MACE is a post hoc composite that includes death, major coronary events, and major cerebrovascular events (excludes heart failure requiring hospitalization).

[b] The post hoc analysis included a composite of death from coronary heart disease, non-fatal myocardial infarction, fatal or non-fatal ischemic stroke, and unstable angina requiring hospitalization (excluded heart failure requiring hospitalization and ischemia-driven revascularization procedure).

Table 2: Phase 3 Ongoing Cardiovascular Outcome Trials

Study Details	FOURIER[58]	ODYSSEY OUTCOMES[57,59]	SPIRE-1[60]	SPIRE-2[61]
Estimated enrolment	27,500	18,000	17,000	9,000
Patient population	Adults 40 to 85 years of age receiving statin therapy with a history of MI, ischemic stroke, or peripheral arterial disease at high risk for a recurrent event with LDL-C ≥ 1.8 mmol/L or non-HDL-C ≥ 2.6 mmol/L, and fasting triglycerides ≤ 4.5 mmol/L	Patients 40 years of age or older who have experienced an acute coronary syndrome event 4 to 52 weeks prior to randomization with LDL-C ≥ 1.8 mmol/L, non-HDL-C ≥ 2.6 mmol/L, or apolipoprotein B ≥ 0.8 mmol/L despite maximally tolerated doses of atorvastatin or rosuvastatin	High-risk patients 18 years of age or older with or without a history of cardiovascular events receiving background lipid-lowering therapy with LDL-C ≥ 1.8 mmol/L and < 2.6 mmol/L or non-HDL-C ≥ 2.6 mmol/L and < 3.4 mmol/L	High-risk patients 18 years of age or older with or without a history of cardiovascular events receiving background lipid-lowering therapy with LDL-C ≥ 2.6 mmol/L or non-HDL-C ≥ 3.4 mmol/L
Intervention	Evolocumab 140 mg SC Q2W or Evolocumab 420 mg SC QM[a]	Alirocumab 75 mg[b] SC Q2W	Bococizumab 150 mg SC Q2W	
Comparator	Placebo SC Q2W or QM	Placebo SC Q2W	Placebo SC Q2W	
Primary outcome	Time from randomization to occurrence of CV event (composite of CV death, MI, hospitalization for unstable angina, stroke, or coronary revascularization)	Time from randomization to occurrence of CV event (composite of CHD death, non-fatal MI, fatal and non-fatal ischemic stroke, and hospitalization for unstable angina)	Time from randomization to occurrence of CV event (composite of CV death, non-fatal MI, non-fatal stroke, and hospitalization for unstable angina needing urgent revascularization)	
Follow-up	60 months	64 months	60 months	
Expected primary completion	October 2017	December 2017	April 2018	January 2018

CHD = coronary heart disease; CV = cardiovascular; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; Q2W = once every 2 weeks; QM = once every month; SC = subcutaneously.

[a] Based on investigator and/or patient preference for biweekly or monthly regimen. No adjustment is permitted based on LDL-C values.

[b] The initial dose of alirocumab is 75 mg Q2W, with drug discontinuation for LDL-C < 0.4 mmol/L on repeated measurements, and up-titration to 150 mg Q2W for LDL-C ≥ 1.3 mmol/L after 2 doses of 75 mg.

performed to compare the frequency of major cardiovascular events (a composite of death from coronary heart disease, non-fatal myocardial infarction, fatal or non-fatal ischemic stroke, or unstable angina requiring hospitalization) between the study groups. This composite is being used as the pre-specified primary outcome in the ongoing ODYSSEY OUTCOMES study.[57]

The mean age of patients enrolled in the ODYSSEY LONG TERM study was 60 years. All but two patients were receiving a statin, and 46.8% were receiving high-dose statin therapy; 28.1% were also receiving other lipid-lowering therapy. A total of 68.9% of patients had a history of coronary heart disease, and 17.7% had heterozygous familial hypercholesterolemia. At week 24, the difference between the alirocumab and placebo groups in change from baseline LDL-C was –61.9% (95% CI, 64% to 59%; $P < 0.001$). This effect was sustained with a 56% reduction in LDL-C from baseline versus placebo at 78 weeks. The frequency of major cardiovascular events was lower with alirocumab than with standard statin therapy alone (1.7% versus 3.3%, respectively; hazard ratio 0.52; 95% CI, 0.31 to 0.90; $P = 0.02$). When all adjudicated cardiovascular events were included (with the addition of congestive heart failure requiring hospitalization and ischemia-driven coronary revascularization), the difference between groups was not significant.[56]

Although these results suggest that evolocumab and alirocumab may have a beneficial effect on cardiovascular outcomes, the number of cardiovascular events reported in the studies were relatively low, which limits the robustness of these data. In addition, although only patients at high risk for cardiovascular events were included in the ODYSSEY LONG TERM trial, the minority (47%) were receiving high-dose statin therapy, which may have resulted in an overestimation of the potential beneficial effect of alirocumab on cardiovascular outcomes. Consequently, these findings require confirmation in prospectively designed cardiovascular outcome trials; such studies are currently ongoing for evolocumab, alirocumab, and bococizumab in the form of four multi-centre, double-blind, randomized, placebo-controlled trials evaluating their long-term safety and cardiovascular effects (Table 2). [57-61]

Adverse Events

Both evolocumab and alirocumab were generally well tolerated in short-term phase 3 trials with no notable disparities relative to comparators in deaths, serious adverse events, or adverse events leading to discontinuation. There is concern that prolonged low levels of LDL-C may have negative effects such as increasing the risk of hemorrhagic stroke or neurocognitive adverse events.[62] Although there is currently no evidence of adverse effects from low LDL-C from any of the short-term phase 3 trials, long-term clinical outcome trials are continuing to monitor for this effect.

"The multi-centre, double-blind, placebo-controlled, randomized trial will evaluate cognitive function over four years using formal neurocognitive testing with validated instruments."

The DESCARTES trial reported a similar overall frequency of adverse events occurring during treatment in the evolocumab and placebo groups.[38] The most common adverse events reported with evolocumab were nasopharyngitis (10.5% versus 9.6% with placebo), upper respiratory tract infection (9.3% versus 6.3% with placebo), influenza (7.5% versus 6.3% with placebo), and back pain (6.2% versus 5.6% with placebo). More patients in the evolocumab group were reported to have serious adverse events (5.5% versus 4.3%) during treatment and to have adverse events leading to discontinuation (2.2% versus 1.0%) than the placebo group. A review of the individual adverse events did not reflect any specific treatment-related safety risks with evolocumab. There were more reports of myalgia (4.0% versus 3.0%) and elevated creatinine kinase levels (1.2% versus 0.3%) among patients receiving evolocumab than placebo.

The most common adverse events occurring in patients treated with evolocumab as reported in the OSLER studies were nasopharyngitis (9.4% versus 9.4% with placebo), upper respiratory tract infection (5.4% versus 4.8% with placebo), arthralgia (4.6% versus 3.2% with placebo), and back pain (4.2%

versus 3.7% with placebo).[54] The frequency of neurocognitive adverse events was higher in the evolocumab group than in the placebo group (0.9% versus 0.3%, respectively). Some non-specific adverse events (arthralgia, headache, limb pain, and fatigue) were also reported more frequently in the evolocumab group. Injection site reactions were reported in 129 (4.3%) patients in the evolocumab group (the only group in which such events were analyzed), leading to discontinuation of evolocumab in six (0.2%) patients. No neutralizing antibodies against evolocumab were detected. It should be noted that participants in the OSLER studies had already completed a previous trial and patients who had experienced an adverse effect leading to discontinuation of evolocumab in the parent short-term trials were not included, which may have skewed the true number of potential adverse events.

The most common adverse effects of alirocumab reported in ODYSSEY LONG TERM included nasopharyngitis (13.5% versus 13.1% with placebo), upper respiratory tract infections (7.4% versus 8.6% with placebo), and injection site reactions (5.9% versus 4.2% with placebo).[56] Patients receiving alirocumab had a higher frequency of injection site reactions (5.9% versus 4.2%), myalgia (5.4% versus 2.9%), neurocognitive events (1.2% versus 0.5%), and ophthalmologic events (2.9% versus 1.9%) compared with those who received placebo. The neurocognitive events (including amnesia, memory impairment, and confusional state) were self-reported by patients. Rare and sometimes serious cases of neurologic (one case each of ataxia, demyelination, dysarthria, Miller Fischer Syndrome, and optic neuritis) and general allergic events (three cases of asthma; one case each of angioedema, allergic dermatitis, drug hypersensitivity, hypersensitivity, hypersensitivity vasculitis, laryngeal edema, and rash) were reported in patients receiving alirocumab.

No formal neurocognitive testing was used for the detection of neurocognitive events in the OSLER or ODYSSEY LONG TERM studies. In 2014, the FDA directed developers of PCSK9 inhibitor monoclonal antibodies to monitor for neurocognitive adverse effects and to consider formal neurocognitive testing in at least a subset of participants in ongoing clinical outcome trials.[63] The EBBINGHAUS study is investigating evolocumab for neurocognitive adverse effects in a subset of patients (n = 4,000) enrolled in the FOURIER cardiovascular outcome trial (Table 2).[64] The multi-centre, double-blind, placebo-controlled, randomized trial will evaluate cognitive function over four years using formal neurocognitive testing with validated instruments. Neurocognitive testing will also be performed in a subset of patients enrolled in the SPIRE-1 and SPIRE-2 cardiovascular outcome trials of bococizumab.[60,61] The ODYSSEY OUTCOMES trial will monitor for neurocognitive adverse effects associated with alirocumab but will not conduct formal neurocognitive testing.[57]

Results from the phase 2b trial evaluating bococizumab showed that the percentage of patients reporting adverse events or serious adverse events were similar across placebo and bococizumab groups.[65] Nasopharyngitis and upper respiratory tract infections were the most reported adverse events, occurring with a similar frequency in the placebo and bococizumab groups. One patient experienced two concurrent serious adverse events (viral upper respiratory tract infection and severe dyspnea) that were considered to be related to treatment with bococizumab. The most frequently reported treatment-related adverse events were injection site reactions.

There were no treatment-related serious adverse events in the phase 2 trial evaluating LY3015014.[20] The most common adverse events were nasopharyngitis, injection site pain, headache, injection site erythema, and back pain.

Cost

In Canada, the annual price for evolocumab is C$7,263.36 for the 140 mg dose administered every two weeks (Geoff Sprang, Executive Director – Value, Access, and Policy, Amgen Canada, Mississauga, ON: personal communication, 2015 July 15). In June 2015, Amgen Canada Inc. filed a submission to the CADTH Common Drug Review (CDR) for public drug plan formulary listing of evolocumab to treat primary hyperlipidemia and mixed dyslipidemia.[66,67] The manufacturer's price for alirocumab is currently unavailable in Canada. No Canadian economic evaluations were retrieved for PCSK9 inhibitor monoclonal antibodies during the course of this project.

In the US, the wholesale acquisition cost of alirocumab has been set at US$14,600 per year for both the 75 mg and 150 mg doses administered every two weeks.[18] The yearly cost of evolocumab is US$14,100 for the 140 mg dose administered every two weeks.[17] A recent report issued by the Institute for Clinical and Economic Review (ICER) provides the potential budget impact of using PCSK9 inhibitor monoclonal antibodies on the US health care system.[68] Based on estimations for the magnitude of improvement in patient outcomes and a threshold

cost required to avoid excessive cost burdens to the US health care system, the ICER report states that the annual price of the PCSK9 inhibitor monoclonal antibodies would need to be US$2,177 (representing an 85% reduction from the list price) to enable use without limitation in the eligible populations, i.e., adults with familial hypercholesterolemia or established atherosclerotic cardiovascular disease who cannot achieve a sufficient reduction in LDL-C on high-intensity statin therapy or who are statin intolerant.[68] Current estimated yearly costs for evolocumab in the European Union range from US$6,780 in the United Kingdom to US$8,820 in Finland.[69]

Concurrent Developments

Other PCSK9 Inhibitor Monoclonal Antibodies

A phase 2b trial evaluating the effect of treatment with bococizumab in patients with hypercholesterolemia on background statin therapy showed a dose-dependent reduction in LDL-C at week 12 of up to 53.1% compared with placebo.[65] Bococizumab is currently undergoing phase 3 testing for efficacy of LDL-C lowering in patients with hypercholesterolemia who are unable to reach target LDL-C goals despite therapy with a maximally tolerated statin or are statin intolerant (Table A-2, Appendix A). Two trials[60,61] are also assessing bococizumab in addition to lipid-lowering therapy for the primary or secondary prevention of cardiovascular events in high-risk patients. These are described in the next section. Phase 2 results for LY3015014 show dose-dependent reductions in LDL-C of up to 50.5% compared with placebo when added to standard of care lipid-lowering therapy in patients with primary hypercholesterolemia.[20] There are currently no phase 3 trials evaluating LY3015014.

Cholesteryl Ester Transfer Protein Inhibitors

Cholesteryl ester transfer protein (CETP) inhibitors block the transfer of cholesterol from HDL to other lipoproteins, resulting in an increase in HDL-C and a reduction in LDL-C.[70] The development of one of the first CETP inhibitors, torcetrapib (Pfizer Inc., New York, New York), was stopped in 2006 following results that despite a 72% increase in HDL-C and a 25% decrease in LDL-C, torcetrapib was associated with an increased risk of cardiovascular events and mortality.[71] These adverse events may have been the result of "off target" effects on blood pressure and serum aldosterone levels that were unrelated to CETP inhibition.[72] Development of a second CETP inhibitor, dalcetrapib (Roche, Basel, Switzerland) was terminated in 2012 when phase 3 data in patients with coronary artery disease failed to show clinically meaningful efficacy when added to a statin for a reduction in cardiovascular events.[72] The development of another CETP inhibitor, evacetrapib (Eli Lilly & Co., Indianapolis, Indiana), was discontinued in October 2015 after results from the ACCELERATE study showed a lack of efficacy of adding evacetrapib to statin therapy for the prevention of cardiovascular events in patients with high-risk cardiovascular disease.[73] Anacetrapib (Merck & Co. Inc, Whitehouse Station, New Jersey) is currently the only CETP inhibitor undergoing phase 3 investigation with three trials: DEFINE, REVEAL, and REALIZE.[74-76] The DEFINE study showed that, when used in combination with a statin in patients with known coronary artery disease, anacetrapib produced a 40% reduction in LDL-C and a 138% increase in HDL-C at 24 weeks compared with placebo.[76] Anacetrapib does not appear to affect serum levels of aldosterone or increase blood pressure.[72] The REVEAL study is evaluating the long-term safety and efficacy of anacetrapib with a statin for the secondary prevention of major coronary events in patients who have a history of cardiovascular disease. The trial is expected to enroll more than 30,000 patients, who will be followed for up to four years. Results are anticipated in January 2017.[74] The REALIZE trial is evaluating the efficacy and tolerability of anacetrapib when added to statin therapy in patients with heterozygous familial hypercholesterolemia. The primary outcome is the per cent change from baseline in LDL-C at week 52. It is expected to enroll approximately 300 patients and be completed in October 2018.[75] A fifth CETP inhibitor, TA-8995 (Dezima Pharma B.V., Naarden, The Netherlands), is in early clinical development.[77] Results from a phase 2b study showed that TA-8995 reduced LDL-C by 27% to 68% and increased HDL-C by 76% to 179% at 12 weeks, depending on the TA-8995 dose and statin co-administration regimen selected, in patients with mild dyslipidemia.[78] The manufacturer plans to initiate a phase 3 cardiovascular outcomes trial in 2016.[77]

Other Investigational Lipid-Lowering Therapies

Mipomersen (Kynamro, Genzyme Corporation, Cambridge, Massachusetts), an inhibitor of apolipoprotein B synthesis that lowers LDL, was approved by the FDA in January 2013 for use in addition to lipid-lowering medications and diet to treat patients with homozygous familial hypercholesteromia.[79] Of note, the mechanism of action used by mipomersen is also referred to as antisense therapy.[80] Mipomersen has not yet been approved in Canada; it is anticipated that the

manufacturer may pursue the Canadian market in the future.[81] Mipomersen has been associated with adverse effects on the liver and has not been evaluated for a beneficial effect on cardiovascular outcomes.[79] ETC-1002 (Esperion Therapeutics Inc., Ann Arbor, Michigan), a novel small molecule regulator of lipid and carbohydrate metabolism designed to lower LDL-C via oral administration, is currently undergoing phase 2 testing in patients with hypercholesterolemia.[82]

Rate of Technology Diffusion

Four multi-centre, double-blind, randomized, placebo-controlled trials are currently evaluating evolocumab, alirocumab, and bococizumab for long-term safety and effects on cardiovascular outcomes (Table 2).[57-61] Results from these large-scale long-term trials will help determine whether the lipid modifications observed with PCSK9 inhibitor monoclonal antibodies, in addition to statin therapy, are effective for the primary prevention of cardiovascular events in high-risk patients or secondary prevention in patients who have a history of atherosclerotic cardiovascular disease. Several other phase 3 trials evaluating evolocumab, alirocumab, and bococizumab in various patient populations for LDL-C reduction and safety outcomes are also currently underway. Details of these trials are presented in Appendix A (Table A-2).

The rate of technology diffusion of PCSK9 inhibitor monoclonal antibodies will be influenced by findings from the above studies when they are available, especially the cardiovascular studies. Given there are still considerable unmet needs in the prevention of initial or recurrent cardiovascular events, and based on their demonstrated effect on LDL-C level, it may be anticipated that there will be a significant demand for PCSK9 inhibiting therapy. This demand may further increase, should morbidity or mortality benefits be confirmed with ongoing studies.

Implementation Issues

PCSK9 inhibitor monoclonal antibodies have the potential to fill an important treatment gap in patients with harder-to-treat hypercholesterolemia. Results from trials, which mainly focus on surrogate markers of cardiovascular outcomes, showed that PCSK9 inhibitor monoclonal antibodies produce statistically significant reductions in LDL-C regardless of background lipid-lowering therapy. Based on the relatively short-term evidence that is currently available, these drugs appear to be safe, although the FDA has identified a potential signal for neurocognitive adverse effects. Given that cardiovascular disease is still one of the most important causes of death in Canada, despite the availability of statins for 25 years, PCSK9 inhibitor monoclonal antibodies are expected to be rapidly adopted if approved, particularly for patients with harder-to-treat hypercholesterolemia. However, long-term safety and the effect on cardiovascular outcomes remain to be established. Findings from long-term outcomes trials will not be available until 2017 or 2018.

Given the potential broad clinical use of this new drug class, the high price, and the long time frame required for the introduction of less expensive subsequent entry biologics, the introduction of PCSK9 inhibitor monoclonal antibodies may potentially have a substantial budgetary impact on the Canadian health care system. Careful patient selection will be necessary. The requirement to self-administer the drug subcutaneously may also impact long-term patient acceptability and adherence. In order to determine the clinical impact and value of this new drug class on the potentially broad and diverse population of patients with difficult-to-treat hypercholesterolemia, the long-term safety, efficacy, and cost-effectiveness of PCSK9 inhibitor monoclonal antibodies need to be clarified.

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APPENDIX A

Table A-1: Summary of Phase 3 Short-Term Surrogate Outcome Trials

Trial Name	N	Study Details	Study Groups	Mean Treatment Difference[a] in LDL-C (95% CI or SE)
Monotherapy				
MENDEL-2[35]	614	**Design** Multi-centre, double-blind, double-dummy, randomized, placebo- and active-controlled **Patient population** Age 18 to 80 years, Framingham risk score ≤ 10%, with LDL-C between 2.6 mmol/L and 4.9 mmol/L, no lipid-lowering drugs 3 months prior **Background therapy** None	**Evolocumab dose(s)** 140 mg SC Q2W 420 mg SC QM **Active control** Ezetimibe 10 mg PO QD **Placebo controls** Placebo SC (Q2W or QM) Placebo PO QD	**Evolocumab 140 mg Q2W at 12 weeks** −57.1 (−61.1 to −53.1) vs. placebo[b] −39.3 (−43.3 to −35.3) vs. ezetimibe[b] **Evolocumab 420 mg QM at 12 weeks** −54.8 (−58.5 to −51.1) vs. placebo[b] −37.6 (−41.2 to −33.9) vs. ezetimibe[b]
ODYSSEY MONO[43]	103	**Design** Multi-centre, double-blind, double-dummy, randomized, active-controlled **Patient population** Patients aged over 18 years with LDL-C between 2.6 mmol/L to 4.9 mmol/L with moderate CVD risk (10-yr risk of fatal CVD ≥ 1% and < 5% using European Systemic Coronary Risk Estimation ([SCORE]) not receiving statin or any other lipid-lowering therapy at least 4 weeks prior to screening **Background therapy** None	**Alirocumab dose(s)** 75 mg SC Q2W[c] **Active control** Ezetimibe 10 mg PO QD	**Alirocumab 75/150 mg Q2W at 24 weeks** −31.6 (−40.2 to −23.0) vs. ezetimibe[b]

Table A-1: Summary of Phase 3 Short-Term Surrogate Outcome Trials

Trial Name	N	Study Details	Study Groups	Mean Treatment Difference[a] in LDL-C (95% CI or SE)
In combination with statin ± ezetimibe				
LAPLACE-2[36]	1,896	**Design** Multi-centre, double-blind, double-dummy, randomized, placebo- and active-controlled **Patient population** Patients aged 18 to 80 years with primary hypercholesterolemia or mixed dyslipidemia with LDL-C ≥ 4.0 mmol/L; (no statin at screening), LDL-C ≥ 2.6 mmol/L (less than maximally tolerated statin dose at screening), or LDL-C ≥ 2.1 mmol/L (maximally tolerated statin at screening) **Background therapy** Statin[d]	**Evolocumab dose(s)** 140 mg SC Q2W 420 mg SC QM **Active control** Ezetimibe 10 mg PO QD (only used for patients assigned to atorvastatin 10 mg or 80 mg) **Placebo controls** Placebo SC (Q2W or QM) Placebo PO QD	**Evolocumab 140 mg Q2W at 12 weeks** −68.2 (−74.7 to −61.7) + rosuvastatin 5 mg vs. placebo[b] to −76.3 (−86.9 to −65.7) + atorvastatin 80 mg vs. placebo[b] −39.6 (−45.8 to −33.4) + atorvastatin 10 mg vs. ezetimibe[b] to −47.2 (−57.5 to −36.9) + atorvastatin 80 mg vs. ezetimibe[b] **Evolocumab 420 mg QM at 12 weeks** −55.0 (−65.3 to −44.7) + rosuvastatin 40 mg vs. placebo[b] to −70.5 (−79.8 to −61.2) + atorvastatin 80 mg vs. placebo[b] −38.9 (−48.2 to −29.6) + atorvastatin 10 mg vs. ezetimibe[b] to −41.1 (−47.8 to −34.4) + atorvastatin 80 mg vs. ezetimibe[b]

Table A-1: Summary of Phase 3 Short-Term Surrogate Outcome Trials

Trial Name	N	Study Details	Study Groups	Mean Treatment Difference[a] in LDL-C (95% CI or SE)
YUKAWA-2[37]	404	**Design** Multi-centre, double-blind, randomized, placebo-controlled **Patient population** Japanese patients aged 20 to 80 years who met the Japan Atherosclerosis Society guidelines definition of high CV risk with fasting LDL-C ≥ 2.6 mmol/L on stable statin therapy for at least 4 weeks **Background therapy** Atorvastatin 5 mg or 20 mg PO QD	**Evolocumab dose(s)** 140 mg SC Q2W 420 mg SC QM **Placebo control** Placebo SC (Q2W or QM)	**Evolocumab 140 mg Q2W at 12 weeks** −74.9 (2.7) + atorvastatin 5 mg vs. placebo[b] −75.9 (3.9) + atorvastatin 20 mg vs. placebo[b] **Evolocumab 420 mg QM at 12 weeks** −69.9 (2.4) + atorvastatin 5 mg vs. placebo[b] −66.9 (3.0) + atorvastatin 20 mg vs. placebo[b]
ODYSSEY COMBO I[44]	316	**Design** Multi-centre, double-blind, randomized, placebo-controlled **Patient population** Patients 18 years and older with established CVD and LDL-C ≥ 1.8 mmol/L, or CHD risk equivalents (e.g., CKD or diabetes with additional risk factors) and LDL-C ≥ 2.6 mmol/L on stable maximally tolerated statin for at least 4 weeks with or without other lipid-modifying therapy **Background therapy** Statin ± lipid-lowering therapies[e]	**Alirocumab dose(s)** 75 mg SC Q2W[c] **Placebo control** Placebo SC Q2W	**Alirocumab 75/150 mg Q2W at 24 weeks** −45.9 (−52.5 to −39.3) vs. placebo[b]

Table A-1: Summary of Phase 3 Short-Term Surrogate Outcome Trials

Trial Name	N	Study Details	Study Groups	Mean Treatment Difference[a] in LDL-C (95% CI or SE)
ODYSSEY COMBO II[45]	720	**Design** Multi-centre, double-blind, double-dummy, randomized, active-controlled **Patient population** Patients 18 years and older with established CVD and LDL-C ≥ 1.8 mmol/L, or CHD risk equivalents (e.g., CKD or diabetes with additional risk factors) and LDL-C ≥ 2.6 mmol/L on stable maximally tolerated statin for at least 4 weeks with or without other lipid-modifying therapy **Background therapy** Atorvastatin 40 to 80 mg, rosuvastatin 20 to 40 mg, or simvastatin 80 mg PO QD	**Alirocumab dose(s)** 75 mg SC Q2W[c] **Active control** Ezetimibe 10 mg PO QD	**Alirocumab 75/150 mg Q2W at 24 weeks** −29.8 (−34.4 to −25.3) vs. ezetimibe[b]
ODYSSEY JAPAN[46]	216	**Design** Multi-centre, double-blind, randomized, placebo-controlled **Patient population** Japanese patients with hypercholesterolemia and high CV risk or heterozygous familial hypercholesterolemia **Background therapy** Statin ± lipid-lowering therapies[e]	**Alirocumab dose(s)** 75 mg SC Q2W[c] **Placebo control** Placebo SC Q2W	**Alirocumab 75/150 Q2W at 24 weeks** −64 vs. placebo[b]
ODYSSEY OPTIONS I[47]	355	**Design** Multi-centre, double-blind, double-dummy, randomized, active-controlled **Patient population** Patients 18 years and older with established CVD and LDL-C ≥ 1.8 mmol/L, or CHD risk equivalents (e.g., CKD or diabetes with additional risk factors) and LDL-C ≥ 2.6 mmol/L not adequately controlled with atorvastatin 20 mg or 40 mg ± other lipid-modifying therapy (excluding ezetimibe) **Background therapy** Atorvastatin (20 mg or 40 mg) PO QD ± lipid-lowering therapies	**Alirocumab dose(s)** 75 mg SC Q2W[f] **Active controls** Ezetimibe 10 mg PO QD Atorvastatin 40 mg PO QD Atorvastatin 80 mg PO QD Rosuvastatin 40 mg PO QD	**Alirocumab 75/150 mg Q2W at 24 weeks** −23.6 (−40.7 to −6.5) + atorvastatin 20 mg vs. ezetimibe[b] −39.1 (−55.9 to −22.2) + atorvastatin 20 mg vs. atorvastatin 40 mg[b] −31.4 (−47.4 to −15.4) + atorvastatin 40 mg vs. ezetimibe[b] −32.6 (−48.4 to −16.9) + atorvastatin 40 mg vs. rosuvastatin 40 mg[b] −49.2 (−65.0 to −33.5) + atorvastatin 40 mg vs. atorvastatin 80 mg[b]

Table A-1: Summary of Phase 3 Short-Term Surrogate Outcome Trials

Trial Name	N	Study Details	Study Groups	Mean Treatment Difference[a] in LDL-C (95% CI or SE)
ODYSSEY OPTIONS II[48,83]	305	**Design** Multi-centre, double-blind, double-dummy, randomized, active-controlled **Patient population** High or very high CV risk with familial or non-familial hypercholesterolemia not adequately controlled with rosuvastatin 10 mg or 20 mg ± other lipid-modifying therapy (excluding ezetimibe) **Background Therapy** Rosuvastatin (10 mg or 20 mg) PO QD ± lipid-lowering therapies	**Alirocumab dose(s)** 75 mg SC Q2W[f] **Active controls** Ezetimibe 10 mg PO QD Rosuvastatin 20 mg PO QD Rosuvastatin 40 mg PO QD	**Alirocumab 75/150 mg Q2W at 24 weeks** −36.1 (−51.5 to −20.7) + rosuvastatin 10 mg vs. ezetimibe[b] −34.2 (−49.2 to −19.3) + rosuvastatin 10 mg vs. rosuvastatin 20 mg[b] −25.3 (−50.9 to 0.3) + rosuvastatin 20 mg vs. ezetimibe (*P* = 0.0136) −20.3 (−45.8 to −5.1) + rosuvastatin 20 mg vs. rosuvastatin 40 mg (*P* = 0.0453)
In addition to diet alone or statin ± ezetimibe				
DESCARTES[38]	901	**Design** Multi-centre, double-blind, randomized, placebo-controlled **Patient population** Patients aged 18 to 75 years with hypercholesterolemia and LDL-C ≥ 1.94 mmol/L on background lipid-lowering therapy **Background therapy** Diet ± atorvastatin ± ezetimibe[g]	**Evolocumab dose(s)** 420 mg SC QM **Placebo control** Placebo SC QM	**Evolocumab 420 mg QM at 52 weeks** −57.0 (2.1) all patients vs. placebo[b] −55.7 (4.2) + diet alone vs. placebo[b] −61.6 (2.6) + diet with atorvastatin 10 mg vs. placebo[b] −56.8 (5.3) + diet with atorvastatin 80 mg vs. placebo[b] −48.5 (5.2) + diet with atorvastatin 80 mg and ezetimibe 10 mg vs. placebo[b]

Table A-1: Summary of Phase 3 Short-Term Surrogate Outcome Trials

Trial Name	N	Study Details	Study Groups	Mean Treatment Difference[a] in LDL-C (95% CI or SE)
ODYSSEY CHOICE I[49]	803	**Design** Multi-centre, double-blind, randomized, placebo-controlled **Patient population** Patients with moderate to very high CV risk receiving a maximally tolerated statin, moderate CV risk not receiving a statin, or moderate to very high CV risk and muscle-related statin intolerance **Background therapy** Lipid-lowering therapy ± statin	**Alirocumab dose(s)** 75 mg SC Q2W[f] 300 mg SC QM[f] **Placebo control** Placebo SC Q2W	**Alirocumab 75/150 mg Q2W at 24 weeks** NR **Alirocumab 300 mg QM/150 mg Q2W at 24 weeks** −52.4 (3.3) vs. placebo[b] −58.7 (2.8) + statin vs. placebo[b]
Statin intolerance				
GAUSS-2[39,84]	307	**Design** Multi-centre, double-blind, double-dummy, randomized, active-controlled **Patient population** Age 18 to 80 years with hypercholesterolemia with LDL-C above treatment goal based on CV risk and documented intolerance to two or more statins **Background Therapy** Non-ezetimibe lipid-lowering therapy[h]	**Evolocumab dose(s)** 140 mg SC Q2W 420 mg SC QM **Active control** Ezetimibe 10 mg PO QD	**Evolocumab 140 mg Q2W at 12 weeks** −38.1 (−43.7 to −32.4) vs. ezetimibe[b] **Evolocumab 420 mg QM at 12 weeks** −37.6 (−42.2 to −32.9) vs. ezetimibe[b]
ODYSSEY ALTERNATIVE[50,85]	314	**Design** Multi-centre, double-blind, double-dummy, randomized, active-controlled **Patient population** Patients aged 18 years and over and moderate or high (LDL-C ≥ 2.6 mmol/L), or very high (LDL-C ≥ 1.8 mmol/L) CV risk who are intolerant to statins **Background therapy** Lipid-lowering therapy with bile acid sequestrants, nicotinic acid, fenofibrate, or omega-3 fatty acids	**Alirocumab dose(s)** 75 mg SC Q2W[f] **Active control** Ezetimibe 10 mg PO QD	**Alirocumab 75/150 mg Q2W at 24 weeks** −30.4 (−36.6 to −24.2) vs. ezetimibe[b]

Table A-1: Summary of Phase 3 Short-Term Surrogate Outcome Trials

Trial Name	N	Study Details	Study Groups	Mean Treatment Difference[a] in LDL-C (95% CI or SE)
ODYSSEY CHOICE II[49,86]	231	**Design** Multi-centre, double-blind, randomized, placebo-controlled **Patient population** Patients with moderate to very high CV risk with muscle-related statin intolerance or moderate cardiovascular risk not receiving statin therapy **Background Therapy** Ezetimibe, fenofibrate, or diet alone	**Alirocumab dose(s)** 75 mg SC Q2W[f] 150 mg SC QM[f] **Placebo control** Placebo SC Q2W	**Alirocumab 75/150 mg Q2W at 24 weeks** NR **Alirocumab 150 mg QM/150 mg Q2W at 24 weeks** −56.4 (3.3) vs. placebo[b]
Heterozygous familial hypercholesterolemia				
RUTHERFORD-2[40]	329	**Design** Multi-centre, double-blind, randomized, placebo-controlled **Patient population** Patients aged 18 to 80 years with heterozygous familial hypercholesterolemia on a stable dose of statin with or without ezetimibe for at least 4 weeks prior with LDL-C ≥ 2.6 mmol/L **Background therapy** Statin ± lipid-lowering therapies[e]	**Evolocumab dose(s)** 140 mg SC Q2W 420 mg SC QM **Placebo control** Placebo SC (Q2W or QM)	**Evolocumab 140 mg Q2W at 12 weeks** −59.2 (−65.1 to −53.4) vs. placebo[b] **Evolocumab 420 mg QM at 12 weeks** −61.3 (−69.0 to −53.6) vs. placebo[b]
ODYSSEY FH I[51,53]	486	**Design** Multi-centre, double-blind, randomized, placebo-controlled **Patient population** Patients with heterozygous familial hypercholesterolemia not adequately controlled on stable maximally tolerated statin with or without other lipid-modifying therapy with LDL-C ≥ 1.8 mmol/L with documented CVD or 2.6 mmol/L without CVD **Background therapy** Statin ± lipid-lowering therapies[e]	**Alirocumab dose(s)** 75 mg SC Q2W[c] **Placebo control** Placebo SC Q2W	**Alirocumab 75/150 mg Q2W at 24 weeks** −57.9 (−63.3 to −52.6) vs. placebo[b]

Table A-1: Summary of Phase 3 Short-Term Surrogate Outcome Trials

Trial Name	N	Study Details	Study Groups	Mean Treatment Difference[a] in LDL-C (95% CI or SE)
ODYSSEY FH II[51,53]	249	**Design** Multi-centre, double-blind, randomized, placebo-controlled **Patient population** Patients with heterozygous familial hypercholesterolemia not adequately controlled on stable maximally tolerated statin with or without other lipid-modifying therapy with LDL-C ≥ 1.8 mmol/L with documented CVD or 2.6 mmol/L without history of CVD **Background therapy** Statin ± lipid-lowering therapies[e]	**Alirocumab dose(s)** 75 mg SC Q2W[c] **Placebo control** Placebo SC Q2W	**Alirocumab 75/150 mg Q2W at 24 weeks** −51.4 (−58.1 to −44.8) vs. placebo[b]
ODYSSEY HIGH FH[52,87]	107	**Design** Multi-centre, double-blind, randomized, placebo-controlled **Patient population** Patients with heterozygous familial hypercholesterolemia not adequately controlled on stable maximally tolerated statin with or without other lipid-modifying therapy with LDL-C ≥ 4.1 mmol/L **Background therapy** Statin ± lipid-lowering therapies[e]	**Alirocumab dose(s)** 150 mg SC Q2W **Placebo control** Placebo SC Q2W	**Alirocumab 150 Q2W at 24 weeks** −39.1 (−51.1 to −27.1) vs. placebo[b]

Table A-1: Summary of Phase 3 Short-Term Surrogate Outcome Trials

Trial Name	N	Study Details	Study Groups	Mean Treatment Difference[a] in LDL-C (95% CI or SE)
Homozygous familial hypercholesterolemia				
TESLA Part B[41]	49	**Design** Multi-centre, double-blind, randomized, placebo-controlled **Patient population** Patients aged 12 to 80 years with homozygous familial hypercholesterolemia on a stable lipid-lowering therapies for at least 4 weeks prior but not receiving lipoprotein apheresis with LDL-C ≥ 3.4 mmol/L **Background therapy** Statin ± lipid-lowering therapies[e]	**Evolocumab dose(s)** 420 mg SC QM **Placebo control** Placebo SC QM	**Evolocumab 420 mg QM at 12 weeks** −30.9 (−43.9 to −18.0) vs. placebo[b]

CHD = coronary heart disease; CI = confidence interval; CV = cardiovascular; CVD = cardiovascular disease; CKD = chronic kidney disease; LDL-C = low-density lipoprotein cholesterol; NR = not reported; PO = orally; Q2W = once every 2 weeks; QD = once every day; QM = once every month; SC = subcutaneously; SE = standard error; vs. = versus; yr = year.

[a] The mean difference between evolocumab or alirocumab and its comparator with respect to per cent change in LDL-C from baseline to the primary outcome time point.

[b] $P < 0.001$.

[c] Dose was up-titrated to 150 mg Q2W at week 12 if LDL-C ≥ 1.8 mmol/L at week 8.

[d] All patients randomized to moderate-intensity statin (atorvastatin 10 mg, simvastatin 40 mg, rosuvastatin 5 mg) PO QD or high-intensity statin (atorvastatin 80 mg or rosuvastatin 40 mg) PO QD.

[e] All patients received a stable, maximally tolerated statin (atorvastatin ≥ 40 mg, rosuvastatin ≥ 20 mg, or simvastatin 80 mg) PO QD with or without other lipid-lowering therapy (ezetimibe, bile acid sequestrant, niacin, omega-3).

[f] Dose was up-titrated to 150 mg Q2W at week 12 if LDL-C ≥ 1.8 mmol/L at week 8 in very high-risk patients and LDL ≥ 2.6 mmol/L in high- or moderate-risk patients.

[g] Patients assigned to background lipid-lowering therapy based on LDL-C level at screening and National Cholesterol Education Program Adult Treatment Panel III risk categories: diet alone, diet plus atorvastatin 10 mg PO QD, diet plus atorvastatin 80 mg PO QD, or diet plus atorvastatin 80 mg PO QD and ezetimibe 10 mg PO QD.

[h] At screening, low-dose statins permitted: atorvastatin ≤ 70 mg, simvastatin ≤ 140 mg, pravastatin ≤ 140 mg, rosuvastatin ≤ 35 mg, lovastatin ≤ 140 mg, or fluvastatin ≤ 280 mg.

Table A-2: Unpublished Ongoing Phase 3 Surrogate Outcome and Safety Trials[88]

Trial Name ClinicalTrials.gov Identifier	Study Design	Patient Population	Primary Outcome
EVOLOCUMAB			
EBBINGHAUS NCT02207634	Multi-centre, double-blind, placebo-controlled study **Interventions** Evolocumab 140 mg SC Q2W or, Evolocumab 420 mg SC QM[a] **Comparators** Placebo SC Q2W or QM	Patients aged 40 to 85 years with cardiovascular disease receiving statin therapy who were previously randomized into FOURIER cardiovascular outcomes study (N = 4,000)	Mean change in Spatial Working Memory (SWM) index of executive function of data collected over study duration (up to 4 years)
TAUSSIG NCT01624142	Multi-centre, open-label, long-term extension study **Interventions** Evolocumab 420mg SC Q2W, or Evolocumab 420mg SC QM[a] **Comparator** NA	Patients 12 to 80 years with severe familial hypercholesterolemia, including homozygous familial hypercholesterolemia (N = 300)	Incidence of treatment-emergent adverse events over 5 years
GAUSS-3 NCT01984424	Multi-centre trial in 3 parts: **Part A** — Double-blind, placebo-controlled, two-period, crossover statin re-challenge **Part B** — 24-week, double-blind, double-dummy comparison of evolocumab and ezetimibe **Part C** — 2-year, open-label evolocumab extension **Interventions/Comparators** **Part A** Placebo PO QD Atorvastatin 20 mg PO QD **Part B** Placebo SC QM + ezetimibe 10 mg PO QD Evolocumab 420 mg SC QM + placebo PO QD **Part C** Evolocumab 420 mg SC QM or, Evolocumab SC 140 mg Q2W	Adult patients 18 to 80 years with primary hyperlipidemia (heterozygous familial and non-familial) and mixed dyslipidemia with a history of statin intolerance (N = 519)	Mean per cent change from baseline in LDL-C of weeks 22 and 24 Per cent change from baseline in LDL-C at week 24

Table A-2: Unpublished Ongoing Phase 3 Surrogate Outcome and Safety Trials[88]

Trial Name ClinicalTrials.gov Identifier	Study Design	Patient Population	Primary Outcome
GLAGOV NCT01813422	Multi-centre, double-blind, randomized, placebo-controlled study **Intervention** Evolocumab 420 mg SC QM **Comparator** Placebo SC QM	Adult patients 18 years and older with coronary artery disease requiring angiography for a clinical indication who are already receiving therapy with statins, niacin, or ezetimibe. Patients intolerant to statin may also be included. (N = 970)	Nominal change in per cent atheroma volume from baseline to week 78 post-randomization, as determined by intravascular ultrasound
Extension (OLE) Study NCT02304484	Multi-centre, open-label, extension study **Intervention** Evolocumab 420 mg SC QM **Comparator** NA	Adult patients who completed week 80 of Study 20120153 (GLAGOV) (N = 642)	Number of participants with adverse effects at week 52
HAUSER-RCT NCT02392559	Multi-centre, double-blind, randomized, placebo-controlled **Intervention** Evolocumab 420 mg SC QM **Comparator** Placebo SC QM	Pediatric patients 10 to 17 years of age with a diagnosis of heterozygous familial hypercholesterolemia on a stable statin dose plus other lipid-lowering therapy stable for ≥ 4 weeks (N = 150)	Percentage change from baseline in LDL-C levels at week 24
ALIROCUMAB			
ODYSSEY JAPAN NCT02107898	Multi-centre, double-blind, randomized, placebo-controlled **Intervention** Alirocumab 75 mg SC Q2W[b] **Comparator** Placebo SC Q2W	Patients 20 years or older with heterozygous familial hypercholesterolemia or non-familial hypercholesterolemia who are not adequately controlled with a stable dose of statin with or without other lipid-modifying therapy (N = 216)	Percentage change from baseline in LDL-C levels at week 24
ODYSSEY ESCAPE NCT02326220	Multi-centre, double-blind, randomized, placebo-controlled **Intervention** Alirocumab 75 mg SC Q2W[b] **Comparator** Placebo SC Q2W	Patients 18 years or older with heterozygous familial hypercholesterolemia currently undergoing LDL apheresis therapy weekly or every 2 weeks for at least 8 weeks prior to screening visit (N = 63)	Rate of apheresis treatments during a 12-week period normalized by the number of planned apheresis treatments according to each patient's established schedule at screening

Table A-2: Unpublished Ongoing Phase 3 Surrogate Outcome and Safety Trials[88]

Trial Name ClinicalTrials.gov Identifier	Study Design	Patient Population	Primary Outcome
NCT02476006	Multi-centre, open-label, single-group **Intervention** Alirocumab 75 mg SC Q2W[b] **Comparator** NA	Patients 18 years or older with heterozygous familial hypercholesterolemia or with established coronary heart disease or cardiovascular disease not adequately controlled with maximally tolerated dose of statin with or without other lipid-modifying therapy (N = 1,100)	Proportion of patients with adverse events at up to 30 months follow-up
ODYSSEY OLE NCT01954394	Multi-centre, open-label, single-group **Intervention** Alirocumab 75 mg SC Q2W[b] **Comparator** NA	Patients 18 years or older with heterozygous familial hypercholesterolemia who have completed one of the following four studies (ODYSSEY FH I, ODYSSEY FH II, ODYSSEY HIGH FH, and ODYSSEY LONG TERM) (N = 1,200)	Assessment of safety parameters (adverse events, laboratory data, vital signs) up to 120 weeks
NCT02289963	Multi-centre, double-blind, randomized, placebo-controlled **Intervention** Alirocumab 75 mg SC Q2W[b] **Comparator** Placebo SC Q2W	Patients 18 years or older in South Korea or Taiwan with hypercholesterolemia and established coronary heart disease or coronary heart disease risk equivalents not adequately controlled on maximally tolerated dose of statin with or without other lipid-modifying therapy (N = 184)	Percentage change from baseline in LDL-C levels at week 24
BOCOCIZUMAB			
SPIRE-HR NCT01968954	Multi-centre, double-blind, randomized, placebo-controlled **Intervention** Bococizumab 150 mg SC Q2W **Comparator** Placebo SC Q2W	Adults 18 years and older with primary hyperlipidemia or mixed dyslipidemia, receiving a maximally tolerated dose of a highly effective statin, at high or very high risk of a CV event (N = 600)	Per cent change from baseline in LDL-C at week 12

Table A-2: Unpublished Ongoing Phase 3 Surrogate Outcome and Safety Trials[88]

Trial Name ClinicalTrials.gov Identifier	Study Design	Patient Population	Primary Outcome
SPIRE-LDL NCT01968967	Multi-centre, double-blind, randomized, placebo-controlled **Intervention** Bococizumab 150 mg SC Q2W **Comparator** Placebo SC Q2W	Adults 18 years and older with primary hyperlipidemia or mixed dyslipidemia, receiving a maximally tolerated dose of a highly effective statin, at high or very high risk of a CV event (N = 1,932)	Per cent change from baseline in LDL-C at week 12
SPIRE-FH NCT01968980	Multi-centre, double-blind, randomized, placebo-controlled **Intervention** Bococizumab 150 mg SC Q2W **Comparator** Placebo SC Q2W	Adults 18 years and older with heterozygous familial hypercholesterolemia receiving a maximally tolerated dose of a highly effective statin, at high or very high risk of a CV event (N = 300)	Per cent change from baseline in LDL-C at week 12
SPIRE-SI NCT02135029	Multi-centre, double-blind, randomized, placebo-controlled and active-controlled **Intervention** Bococizumab 150 mg SC Q2W **Active comparator** Atorvastatin PO QD **Placebo comparator** Placebo SC Q2W Placebo PO QD	Adults 18 years and older with primary hyperlipidemia or mixed dyslipidemia who are statin intolerant (N = 150)	Per cent change from baseline in LDL-C at week 12
SPIRE-LL NCT02100514	Multi-centre, double-blind, randomized, placebo-controlled **Intervention** Bococizumab 150 mg SC Q2W **Comparator** Placebo SC Q2W	Adults 18 years and older with primary hyperlipidemia or mixed dyslipidemia, receiving background statin therapy, at high or very high risk of a CV event (N = 690)	Per cent change from baseline in LDL-C at week 12

Table A-2: Unpublished Ongoing Phase 3 Surrogate Outcome and Safety Trials[88]

Trial Name ClinicalTrials.gov Identifier	Study Design	Patient Population	Primary Outcome
SPIRE-AI NCT02458287	Multi-centre, double-blind, randomized, placebo-controlled **Intervention** Bococizumab 75 mg or 150 mg auto-injector (pre-filled pen) SC Q2W **Comparator** Placebo auto-injector (pre-filled pen) SC Q2W	Adults 18 years and older with primary or mixed dyslipidemia who are receiving the maximum tolerated dose statin (N = 300)	Per cent change from baseline in LDL-C at week 12 and delivery system success rate (proportion of patients who successfully operate the drug delivery system)

CV = cardiovascular; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; NA = not applicable; PO = orally; Q2W = once every 2 weeks; QD = once every day; QM = once every month; SC = subcutaneously.

[a] Based on investigator and/or patient preference for biweekly or monthly regimen.

[b] The initial dose of alirocumab is 75 mg Q2W with up-titration to 150 mg Q2W for LDL-C not at target after 8 weeks.