Common Drug Review
Clinical Review Report

February 2016

Drug	Evolocumab (Repatha)
Indication	1. As an adjunct to diet and maximally tolerated statin therapy in adult patients with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C). 2. As an adjunct to diet and other LDL-lowering therapies (eg, statins, ezetimibe, LDL apheresis) in adult patients and adolescent patients aged 12 years and over with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.
Listing request	1. High-risk patients with primary hyperlipidemia or mixed dyslipidemia who have experienced a prior cardiovascular event and who cannot reach the LDL-C target with standard of care. 2. Heterozygous familial hypercholesterolemia patients who are not at the LDL-C target with standard of care.
Dosage Form	140 mg/mL Pre-filled auto-injector/pre-filled syringe
NOC Date	Sept. 10 2015
Manufacturer	Amgen Canada Inc.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

TABLE OF CONTENTS

Tables

Figures

ABBREVIATIONS

AE	adverse event
AI	auto-injector
apo B	apolipoprotein B
ATP	Adult Treatment Panel
CAS	completer analysis set
CCS	Canadian Cardiovascular Society
CDR	CADTH Common Drug Review
CHD	coronary heart disease
CI	confidence interval
CK	creatine kinase
CNS	central nervous system
DB	double-blind
FAS	full analysis set
FH	familial hypercholesterolemia
HCV	hepatitis C virus
HDL	high-density–lipoprotein
HeFH	heterozygous familial hypercholesterolemia
HoFH	homozygous familial hypercholesterolemia
HMG-CoA	3-hydroxy-3-methyl-glutaryl-CoA
LDL	low-density–lipoprotein
LOCF	last observation carried forward
Lp(a)	lipoprotein(a)
LSM	least squares mean
NCEP	National Cholesterol Education Program
PCSK9	proprotein convertase subtilisin/kexin type 9
RCT	randomized controlled trial
SAE	serious adverse event
SC	subcutaneous
VLDL	very–low-density–lipoprotein

EXECUTIVE SUMMARY

Introduction

Low-density–lipoprotein (LDL) cholesterol is the key component in total cholesterol and is believed to play a crucial role in the formation of atherosclerotic plaques. Familial hypercholesterolemia (FH) is a common genetic disorder of lipid metabolism affecting between 14 million and 34 million people worldwide and is characterized by markedly elevated plasma levels of LDL cholesterol.[1] FH is subdivided into heterozygous (HeFH) or homozygous (HoFH) disease,[1-4] with HoFH being the more severe and rare form.[1,5] In Canada, it is estimated that HeFH affects 83,500 persons, while HoFH affects 60 persons.[6] Patients with untreated FH have a 20-fold increased risk, irrespective of the underlying genetic mutation, of developing premature coronary artery disease compared with people without FH.[2] Hyperlipidemia is typically defined by an elevated LDL cholesterol value, and although the cut-off for therapy is also affected by the patients' risk factors, for patients with established cardiovascular disease, the recommended target LDL cholesterol value is 2.0 mmol/L or lower. For primary prevention in FH, and for treatment in patients in whom therapy is limited by intolerance, and who fail to achieve an LDL cholesterol of 2.0 mmol/L or lower, the Canadian Cardiovascular Society (CCS) guidelines recommend a reduction in LDL cholesterol of at least 50% from baseline.[6]

Initial interventions for hyperlipidemia include diet and lifestyle modifications. The standard lipid-lowering therapy for the last few decades has been 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors, more commonly known as "statins." The next most commonly used drug in management of hyperlipidemia is ezetimibe, an inhibitor of cholesterol absorption. Ezetimibe is typically used in combination with a statin, most commonly atorvastatin.

Evolocumab is a fully human monoclonal antibody that binds to human proprotein convertase subtilisin/kexin type 9 (PCSK9). Binding of PCSK9 to LDL cholesterol receptors leads to destruction of those receptors. Therefore, when evolocumab binds PCSK9, it prevents PCSK9 from destroying LDL cholesterol receptors, which leads to an increase in LDL cholesterol receptor density at the surface of the liver and enhanced clearance of LDL cholesterol from the blood. Evolocumab is administered by subcutaneous injection, at a dose of either 140 mg every two weeks or 420 mg once monthly.

Indication under review
As an adjunct to diet and maximally tolerated statin therapy in adult patients with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C. The effect of evolocumab on cardiovascular morbidity and mortality has not been determined.
Listing criteria requested by sponsor
Amgen Canada is requesting listing for evolocumab in the following patient groups: 1. High-risk patients with primary hyperlipidemia or mixed dyslipidemia who have experienced a prior CV event and who cannot reach the LDL-C target with standard of care; 2. HeFH patients who are not at the LDL-C target with standard of care.

The objective of this report was to perform a systematic review of the beneficial and harmful effects of evolocumab for the treatment of primary hyperlipidemia (HeFH or non-familial) or mixed dyslipidemia in combination with a statin or with another lipid-lowering drug in patients who are intolerant of statins or in whom statins are not considered clinically appropriate.

Results and Interpretation

Included Studies

Four double-blind (DB), randomized controlled trials (RCTs) met the inclusion criteria for this review. In LAPLACE-2, patients were initially randomized to background regimens of various statins (atorvastatin 10 mg or 80 mg, rosuvastatin 5 mg or 40 mg, or simvastatin 40 mg, all daily). Once stabilized, 1,899 patients were then randomized 2:2:1:1:1:1 to evolocumab (140 mg or 420 mg), matching placebo, or matching placebo plus ezetimibe 10 mg daily (only patients on atorvastatin received ezetimibe), for a period of 12 weeks. RUTHERFORD-2 was a placebo-controlled study, with 331 patients with HeFH randomized 2:2:1:1 to evolocumab (140 mg or 420 mg) or matching placebo for 12 weeks. DESCARTES (N = 905) was also a placebo-controlled study (randomized 2:1, evolocumab to placebo), with all evolocumab patients receiving the 420 mg dose with a variety of different background therapies (atorvastatin 10 mg/day or atorvastatin 80 mg/day or atorvastatin 80 mg/day plus ezetimibe, or diet alone), over 52 weeks. GAUSS-2 was ezetimibe-controlled, randomizing 307 patients with statin intolerance (2:2:1:1) to either of the two approved doses of evolocumab (140 mg or 420 mg) or to matching placebo plus ezetimibe 10 mg daily, over a treatment period of 12 weeks.

Key critical appraisal issues included the fact that studies were not powered or of sufficient duration to assess long-term harms. Power and duration are particularly important in assessing harms in a novel drug class such as this, which has a novel molecular target. Although the proportion of patients discontinuing the study drug was relatively low across studies, in a few instances there was a numerical difference in discontinuations between groups within studies. The manufacturer employed a repeated measures analysis to assess change from baseline in LDL cholesterol; however, no imputation methods were employed to account for missing data.

Efficacy

The co-primary outcome of all included studies was the change from baseline in LDL cholesterol, reported as a percentage change from baseline to mean of weeks 10 and 12 as well as at week 12 alone in the 12-week studies, and after 52 weeks in DESCARTES. All studies were designed to assess the superiority of evolocumab versus either ezetimibe or placebo, depending on the comparator in the study. In all studies and for all background therapies, results showed evolocumab was superior to ezetimibe or placebo. This statistically significant treatment effect was consistent across subgroups of interest for this review, such as baseline LDL cholesterol, background use of statins, or number of risk factors for coronary heart disease. These percentage reductions in LDL cholesterol were large (consistently greater than 50% versus placebo across studies) and considered clinically significant by the clinical expert. Although the studies were not designed to make such comparisons, there were no obvious differences in efficacy between groups on a background therapy of high- versus low-intensity statins, and there was no clear difference in efficacy between the two evolocumab doses studied (140 mg every two weeks or 420 mg once monthly). Additionally, based on subgroup analyses, it appears that a similar treatment effect was observed regardless of baseline LDL cholesterol, which ranged from 2 mmol/L to 5 mmol/L.

Deaths were infrequent across the studies; therefore, no conclusions could be drawn regarding the effect of evolocumab on mortality. The same was true for morbidity, assessed by adjudicated cardiovascular events, as there were too few of these events across studies to establish a clear or consistent effect of evolocumab on reducing risk of morbidity. Quality of life, another key efficacy outcome of this review, was not investigated in any of the included studies.

Other efficacy outcomes of interest for this review included a variety of lipid parameters and biomarkers. Of the five selected a priori to be of greatest relevance to this review, apolipoprotein B, lipoprotein(a), and non–high-density–lipoprotein cholesterol were consistently improved by both evolocumab doses compared with both ezetimibe and placebo. These differences were statistically significant regardless of background therapy. Conversely, very–low-density–lipoprotein cholesterol and triglycerides, considered less important, were not as consistently improved with evolocumab versus ezetimibe or placebo across studies. Other outcomes of interest for this review — health care resource utilization and vascular imaging — were not investigated in the included trials.

Harms

The included studies were not powered to assess harms such as adverse events (AEs), serious adverse events (SAEs), or withdrawals due to AEs. Numerical differences in the proportion of patients with an AE were noted between groups in some studies; however, there was no consistent pattern of increased risk of an AE in either the intervention or control groups across studies. The most common AEs were nasopharyngitis, upper respiratory tract infection, myalgia, and headache; there was no consistent numerical differences noted in the proportion of patients with these harms between groups within studies.

The proportion of patients with serious AEs was low (no more than 6% of patients in any group in any study), and there were no clear and consistent patterns of increased risk of serious AEs in either the intervention or control groups.

The proportion of patients discontinuing the study drug due to an AE was less than 5% in any group across the LAPLACE-2, RUTHERFORD-2, and DESCARTES studies, with no clear differences between groups. In GAUSS-2, the proportion of patients discontinuing the study drug due to an AE was higher than in the other studies (approximately 11%), and there were numerical differences in the rates between groups, with the highest being in the placebo monthly/ezetimibe group (18%) and the lowest in the evolocumab 140 mg group (6%).

There were numerous notable harms identified a priori to be of interest for this review, including injection-site and hypersensitivity reactions, hepatic and muscle-related symptoms, hepatitis C, and neurocognitive events. There was no clear and consistent pattern of increased risk of any of these harms in either the intervention or control groups across studies.

Other Considerations

Evolocumab was submitted before a notice of compliance had been issued by Health Canada, and the protocol and subsequent inclusion of studies was based on the following indication:

> Treatment of primary hyperlipidemia (HF or non-familial) or mixed dyslipidemia in combination with a statin or in combination with another lipid-lowering agent in patients who are intolerant of statins or in whom statins are not considered clinically appropriate.

Late in the review process, the wording of the official indication changed to the following:

> As an adjunct to diet and maximally tolerated statin therapy in adult patients with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C. The effect of evolocumab on cardiovascular morbidity and mortality has not been determined.

At the time of completion of this report, the Health Canada reviewers' report was not available; therefore, clarification of the reasons for the change in wording was not available. The following explanation for the change in wording was provided by the manufacturer in its response to the clinical review:

> The change of wording reflects the fact that statins are the current first-line [standard of care] in lipid management and should remain that way. Health Canada and Amgen agreed that evolocumab should not be a replacement therapy for statins and should rather be prescribed as an add-on to a statin therapy. While it is recognized that some patients may have tolerability issues with statins, every effort should be made by clinicians to try a "tolerable" dose of a statin. Hence the reason for the new terminology of "maximally tolerated statin therapy." This statement is also reflected in guidance issued by the US National Lipid Association, which suggests that for patients intolerant to statins, a less-than-daily statin dosing regimen should be considered as an option alongside non-statin therapy either as monotherapy or in co-administration with less-than-daily statin administration.
>
> Maximally tolerated statin therapy therefore refers to the highest statin dose each individual patient can tolerate, which may include no statin at all for patients who cannot tolerate statin.

Conclusions

Four DB RCTs (LAPLACE-2, RUTHERFORD-2, DESCARTES, and GAUSS-2) assessed the efficacy and safety of evolocumab (140 mg or 420 mg or both) compared with placebo, with or without concurrent ezetimibe treatment, on a background of statin therapy. The studies ranged in duration from 12 to 52 weeks and included between 307 and 1,899 patients. Only the RUTHERFORD-2 study required patient to have HeFH, and only the GAUSS-2 study targeted statin-intolerant patients. In all studies, regardless of length of treatment (12 or 52 weeks) or the type of background therapy, evolocumab was statistically significantly superior to placebo with or without ezetimibe in reducing LDL cholesterol levels. This result was consistent regardless of baseline LDL cholesterol levels or coronary heart disease risk factors. The included studies were not powered for and were not of sufficient duration to assess hard clinical outcomes such as mortality and morbidity, and there were very few of these events across the studies, with no clear or consistent differences in frequency between comparison groups. The included studies were also not powered to assess harms, and there were no clear or consistent differences among treatment groups with respect to the proportion of patients with AEs, SAEs, or discontinuation due to AE. There were also no clear or consistent differences in the proportion of patients with notable muscle- and hepatic-related harms, injection-site or hypersensitivity reactions, or with neurocognitive-related harms. Finally, the long-term potential harms associated with evolocumab are unknown, as safety data are limited to only two years of exposure.

TABLE 1: SUMMARY OF RESULTS — LAPLACE-2

High-Intensity, Atorvastatin 80 mg Background						
LDL-C[a], % Change	**EVO 140 mg q.2w. N = 110**	**EVO 420 mg q.m. N = 110**	**EZE/PLA q.2w. N = 56**	**EZE/PLA q.m. N = 54**	**PLA q.2w. N = 55**	**PLA q.m. N = 55**
Mean (SD) baseline, mmol/L	2.4 (0.9)	2.4 (0.8)	2.6 (0.9)	2.4 (0.5)	2.6 (0.9)	2.5 (0.8)
LSM[b] (SE) % change, weeks 10/12	−61.80 (2.77)	−65.05 (2.42)	−16.85 (3.88)	−21.25 (3.42)	13.12 (3.99)	9.76 (3.39)
Treatment difference (95% CI)	**Versus EZE** **EVO 140 mg vs. EZE/PLA q.2w.:** −44.9 (−54.3 to −35.6), *P* < 0.001 **EVO 420 mg vs. EZE/PLA q.m.:** −43.8 (−52.1 to −35.6), *P* < 0.001			**Versus placebo** **EVO 140 mg vs. PLA q.2w.:** −74.9 (−84.5 to −65.4), *P* < 0.001 **EVO 420 mg vs. PLA q.m.:** −74.8 (−83.0 to −66.6), *P* < 0.001		
	EVO 140 mg vs. EVO 420 mg: −3.25 (−10.48 to 3.97), *P* = NR					
LSM[b] (SE) % change, week 12	−61.80 (3.04)	−58.68 (2.74)	−14.60 (4.29)	−19.80 (3.85)	14.49 (4.42)	11.83 (3.85)
Treatment difference (95% CI)	**Versus EZE** **EVO 140 mg vs. EZE/PLA q.2w.:** −47.20 (−57.54 to −36.86), *P* < 0.001 **EVO 420 mg vs. EZE/PLA q.m.:** −38.88 (−48.21 to −29.56), *P* < 0.001			**Versus placebo** **EVO 140 mg vs. PLA q.2w.:** −76.29 (−86.87 to −65.72), *P* < 0.001 **EVO 420 mg vs. PLA q.m.:** −70.51 (−79.81 to −61.20), *P* < 0.001		
	EVO 140 mg vs. EVO 420 mg: 3.13 (−4.92 to 11.18), *P* = NR					
Patients with LDL-C < 1.8 mmol/L at mean of weeks 10 and 12, % (95% CI)	94.4 (88.4 to 97.4)	92.5 (85.9 to 96.2)	50.9 (38.1 to 63.6)	62.3 (48.8 to 74.1)	13.7 (6.8 to 25.7)	9.3 (4.0 to 19.9)
Moderate-Intensity, Atorvastatin 10 mg Background						
LDL-C[a], % Change	**N = 110**	**N = 110**	**N = 56**	**N = 55**	**N = 56**	**N = 55**
Mean (SD) baseline	3.2 (1.1)	3.3 (1.3)	3.3 (1.3)	3.1 (0.7)	3.2 (1.2)	3.2 (1.2)
LSM[b] (SE) % change, weeks 10/12	−61.41 (1.61)	−62.47 (1.83)	−23.88 (2.34)	−18.98 (2.57)	8.54 (2.24)	0.35 (2.60)
Treatment difference (95% CI)	**Versus EZE** **EVO 140 mg vs. EZE/PLA q.2w.:** −37.5 (−43.0 to −32.0), *P* < 0.001 **EVO 420 mg vs. EZE/PLA q.m.:** −43.5 (−49.7 to −37.3), *P* < 0.001			**Versus placebo** **EVO 140 mg vs. PLA q.2w.:** −70.0 (−75.4 to −64.5), *P* < 0.001 **EVO 420 mg vs. PLA q.m.:** −62.8 (−69.1 to −56.6), *P* < 0.001		
	EVO 140 mg vs. EVO 420 mg: −1.06 (−5.84 to 3.72), P = NR					
LSM[b] (SE) % change, week 12	−64.56 (1.90)	−60.05 (2.04)	−20.92 (2.78)	−17.05 (2.87)	9.86 (2.65)	1.03 (2.89)
Treatment difference (95% CI)	**Versus EZE** **EVO 140 mg vs. EZE/PLA q.2w.:** −39.60 (−45.81 to −33.40), *P* < 0.001 **EVO 420 mg vs. EZE/PLA q.m.:** −41.10 (−47.83 to −34.37), *P* < 0.001			**Versus placebo** **EVO 140 mg vs. PLA q.2w.:** −71.42 (−77.55 to −65.29), *P* < 0.001 **EVO 420 mg vs. PLA q.m.:** −59.16 (−65.94 to −52.38), *P* < 0.001		
	EVO 140 mg vs. EVO 420 mg: 3.38 (−1.91 to 8.66), *P* = NR					

Moderate-Intensity, Atorvastatin 10 mg Background						
Patients with LDL-C < 1.8 mmol/L at mean of weeks 10 and 12, % (95% CI)	88.1 (80.7 to 92.9)	85.8 (78.0 to 91.2)	20.0 (11.2 to 33.0)	16.7 (9.0 to 28.7)	5.7 (1.9 to 15.4)	5.6 (1.9 to 15.1)
All Atorvastatin Backgrounds						
	N = 219	**N = 220**	**N = 112**	**N = 109**	**N = 111**	**N = 110**
Mortality[c]						
Deaths, N (%)	0	0	0	0	0	0
Morbidity[d]						
Adjudicated CV event, n (%)	2 (1)	1 (1)	0	2 (2)	0	0
Quality of life						
Not investigated						
Harms						
Patients with > 0 AEs, N (%)	85 (39)	77 (35)	48 (43)	41 (38)	45 (41)	40 (36)
Patients with > 0 SAEs, N (%)	7 (3)	3 (1)	1 (1)	1 (1)	3 (3)	3 (3)
WDAEs, N (%)	6 (3)	4 (2)	3 (3)	1 (1)	2 (2)	4 (4)

AE = adverse event; CI = confidence interval; CV = cardiovascular; EVO = evolocumab; EZE = ezetimibe; LDL-C = low-density–lipoprotein cholesterol; LSM = least squares mean; PLA = placebo; q.2w. = every two weeks; q.m. = once monthly; SAE = serious adverse event; SD = standard deviation; SE = standard error; vs. = versus; WDAE = withdrawal due to adverse event.
[a] When the calculated LDL-C is < 40 mg/dL or triglycerides are > 400 mg/dL, calculated LDL-C will be replaced with ultracentrifugation LDL-C from the same blood sample, if available.
[b] LSM is from the repeated measures model, which includes treatment group, stratification factor (from IVRS), scheduled visit, and the interaction of treatment with scheduled visit as covariates.
[c] In the pooled analysis, there was one death in the group receiving placebo (every two weeks) plus rosuvastatin 40 mg background.
[d] Adjudicated CV events reported only for pooled atorvastatin groups.
Source: Clinical Study Report for LAPLACE-2.[7]

TABLE 2: SUMMARY OF RESULTS — LAPLACE-2 (CONTINUED)

High-Intensity, Rosuvastatin 40 mg				
LDL-C[a], % Change	**EVO 140 mg q.2w. N = 111**	**EVO 420 mg q.m. N = 112**	**PLA q.2w. N = 56**	**PLA q.m. N = 55**
Mean (SD) baseline	2.3 (0.8)	2.3 (0.8)	2.0 (0.5)	2.7 (1.3)
LSM[b] (SE) % change, weeks 10/12	–59.08 (2.23)	–62.94 (2.44)	6.57 (3.11)	–0.02 (3.51)
Treatment difference versus placebo (95% CI)	**EVO 140 mg vs. PLA q.2w. :** –65.7 (–73.2 to –58.1), *P* < 0.001 **EVO 420 mg vs. PLA q.m.:** –62.9 (–71.4 to –54.5), *P* < 0.001			
	EVO 140 mg vs. EVO 420 mg: –3.85 (–10.36 to 2.66), *P* = NR			
LSM[b] % (SE) change, week 12	–58.89 (2.58)	–52.40 (2.98)	9.42 (3.60)	2.59 (4.30)
Treatment difference versus placebo (95% CI)	**EVO 140 mg vs. PLA q.2w.:** –68.31 (–77.04 to –59.57), *P* < 0.001 **EVO 420 mg vs. PLA q.m.:** –54.98 (–65.31 to –44.65), *P* < 0.001			
	EVO 140 mg vs. EVO 420 mg: 6.49 (–1.27 to 14.26), *P* = NR			
Patients with LDL-C < 1.8 mmol/L at mean of weeks 10 and 12, % (95% CI)	93.5 (87.1 to 96.8)	94.5 (88.6 to 97.5)	38.9 (27.0 to 52.2)	28.8 (18.3 to 42.3)
Moderate-Intensity, Rosuvastatin 5 mg				
LDL-C[a], % Change	**N = 111**	**N = 112**	**N = 56**	**N = 55**
Mean (SD) baseline	3.1 (1.1)	3.2 (1.1)	3.0 (1.0)	3.1 (1.0)
LSM[b] (SE) % change, weeks 10/12	–59.33 (1.74)	–63.79 (1.76)	7.55 (2.39)	2.79 (2.50)

Moderate-Intensity, Rosuvastatin 5 mg				
Treatment difference versus placebo (95% CI)	**EVO 140 mg vs. PLA q.2w.:** −66.9 (−72.7 to −61.1), *P* < 0.001 **EVO 420 mg vs. PLA q.m.:** −66.6 (−72.6 to −60.6), *P* < 0.001			
	EVO 140 mg vs. EVO 420 mg: –4.46 (–9.32 to 0.41) , *P* = NR			
LSM[b] % (SE) change, week 12	–60.09 (1.94)	–59.40 (1.87)	8.12 (2.68)	5.10 (2.62)
Treatment difference versus placebo (95% CI)	**EVO 140 mg vs. PLA q.2w.:** –68.21 (–74.72 to –61.70), *P* < 0.001 **EVO 420 mg vs. PLA q.m.:** –64.49 (–70.84 to –58.14), *P* < 0.001			
	EVO 140 mg vs. EVO 420 mg: 0.70 (–4.61 to 6.00) , *P* = NR			
Patients with LDL-C < 1.8 mmol/L at mean of weeks 10 and 12, % (95% CI)	88.7 (81.2 to 93.4)	89.9 (82.8 to 94.3)	7.0 (2.8 to 16.7)	5.3 (1.8 to 14.4)
Moderate-Intensity, Simvastatin 40 mg				
LDL-C[a], % Change	**N = 111**	**N = 112**	**N = 56**	**N = 55**
Mean (SD) baseline	3.0 (0.9)	3.2 (1.3)	2.9 (0.7)	2.8 (0.8)
LSM[b] (SE) % change, weeks 10/12	–66.17 (2.93)	–62.45 (3.85)	3.26 (3.40)	6.00 (4.80)
Treatment difference versus placebo (95% CI)	**EVO 140 mg vs. PLA q.2w.:** −69.4 (−74.9 to −64.0), *P* < 0.001 **EVO 420 mg vs. PLA q.m.:** −68.5 (−76.7 to −60.2), *P* < 0.001			
	EVO 140 mg vs. EVO 420 mg: 3.72 (–5.79 to 13.23) , *P* = NR			
LSM[b] % (SE) change, week 12	–65.86 (3.05)	–57.02 (3.93)	4.70 (3.61)	3.40 (4.94)
Treatment difference versus placebo (95% CI)	**EVO 140 mg vs. PLA q.2w.:** –70.56 (–76.72 to –64.41), *P* < 0.001 **EVO 420 mg vs. PLA q.m.:** –60.41 (–69.11 to –51.72), *P* < 0.001			
	EVO 140 mg vs. EVO 420 mg: 8.84 (–0.93 to 18.62) , *P* = NR			
Patients with LDL-C < 1.8 mmol/L at mean of weeks 10 and 12, % (95% CI)	93.6 (87.3 to 96.9)	88.5 (81.3 to 93.2)	1.9 (0.3 to 9.8)	3.9 (1.1 to 13.2)
HARMS				
Not reported for these cohorts				

CI = confidence interval; CV = cardiovascular; EVO = evolocumab; LDL-C = low-density–lipoprotein cholesterol; LSM = least squares mean; PLA = placebo; q.2w. = every two weeks; q.m. = once monthly; SD = standard deviation; SE = standard error; vs. = versus.

[a] When the calculated LDL-C is < 40 mg/dL or triglycerides are > 400 mg/dL, calculated LDL-C will be replaced with ultracentrifugation LDL-C from the same blood sample, if available.

[b] LSM is from the repeated measures model, which includes treatment group, stratification factor (from IVRS), scheduled visit, and the interaction of treatment with scheduled visit as covariates.

Source: Clinical Study Report for LAPLACE-2.[7]

TABLE 3: SUMMARY OF RESULTS — RUTHERFORD-2

	RUTHERFORD-2			
LDL-C[a], % Change	EVO 140 mg q.2w. N = 110	EVO 420 mg q.m. N = 110	PLA q.2w. N = 54	PLA q.m. N = 55
Mean (SD) baseline, mmol/L	4.18 (1.32)	3.98 (1.12)	3.91 (0.95)	3.93 (1.10)
LSM[b] % change, week 12	–61.3 (–64.7 to –57.8)	–55.7 (–60.2 to –51.3)	–2.0 (–6.9 to 2.9)	5.5 (–0.9 to 12.0)
Treatment difference (95% CI)	**EVO 140 mg vs. PLA q.2w.:** –59.2% (–65.1 to –53.4), *P* < 0.0001 **EVO 420 mg vs. PLA q.m.:** –61.3% (–69.0 to –53.6), *P* < 0.0001			
	EVO 140 mg vs. EVO 420 mg: 5.51 (–0.12 to 11.14), *P* = NR			
LSM[b] (95% CI) % change, weeks 10 and 12	–61.2 (–64.6 to –57.9)	–63.3 (–66.6 to –59.9)	–1.1 (–5.8 to 3.7)	2.3 (–2.5 to 7.1)
Treatment difference (95% CI)	**EVO 140 mg vs. PLA q.2w.:** –60.2% (–65.8 to –54.5), *P* < 0.0001 **EVO 420 mg vs. PLA q.m.:** –65.6% (–71.3 to –59.8), *P* < 0.0001			
	EVO 140 mg vs. EVO 420 mg: –2.02 (–6.77 to 2.73), *P* = NR			

	RUTHERFORD-2			
LDL-C[a], % Change	EVO 140 mg q.2w. N = 110	EVO 420 mg q.m. N = 110	PLA q.2w. N = 54	PLA q.m. N = 55
Mortality, N				
N	0	0	0	0
Morbidity				
Cardiovascular events, N	2	1	0	0
Quality of life				
Not investigated				
Harms				
Patients with > 0 AEs, N (%)	61 (55)	63 (57)	23 (43)	30 (55)
Patients with > 0 SAEs, N (%)	3 (3)	4 (4)	2 (4)	3 (5)
WDAEs, N (%)	0	0	0	0

AE = adverse event; CI = confidence interval; CV = cardiovascular; EVO = evolocumab; LDL-C = low-density–lipoprotein cholesterol; LSM = least squares mean; NR = not reported. PLA = placebo; q.2w. = every two weeks; q.m. = once monthly; SAE = serious adverse event; SD = standard deviation; SE = standard error; vs. = versus; WDAE = withdrawal due to adverse event.
[a] The primary efficacy analysis used a reflexive approach, where the calculated LDL-C was employed unless the calculated LDL-C was < 1.0 mmol/L) or triglycerides were > 4.5 mmol/L, in which case UC LDL-C was determined and utilized.
[b] LSM is from the repeated measures model, which includes treatment group, stratification factors (from IVRS), scheduled visit, and the interaction of treatment with scheduled visit as covariates.
Source: Clinical Study Report for RUTHERFORD-2.[8]

TABLE 4: SUMMARY OF RESULTS — DESCARTES

	DESCARTES	
LDL-C[a], % Change	**EVO 420 mg q.m. N = 599**	**PLA q.m. N = 302**
Mean (SD) baseline, mmol/L	2.7 (0.6)	2.7 (0.6)
LSM[b] (SE) % change, week 52	–50.14% (1.24)	6.83% (1.75)
Treatment difference (95% CI)	–56.97 (–61.08 to –52.85), *P* < 0.001	
MORTALITY		
Deaths	2	0
MORBIDITY		
Cardiovascular events N (%)	6 (1)	2 (1)
QUALITY OF LIFE		
Not investigated		
HARMS		
Patients with > 0 AEs, N (%)	448 (75)	224 (74)
Patients with > 0 SAEs, N (%)	33 (6)	13 (4)
WDAEs, N (%)	13 (2)	3 (1)

AE = adverse event; CI = confidence interval; CV = cardiovascular; EVO = evolocumab; LDL-C = low-density–lipoprotein cholesterol; LSM = least squares mean; PLA = placebo; q.m. = once monthly; SAE = serious adverse event; SD = standard deviation; SE = standard error; vs. = versus; WDAE = withdrawal due to adverse event.
[a] Ultracentrifugation LDL-C.
[b] LSM is from the repeated measures model, which includes treatment group, stratification factor(s) (from IVRS), scheduled visit, and the interaction of treatment with scheduled visit as covariates.
Source: Clinical Study Report for DESCARTES.[9]

TABLE 5: SUMMARY OF RESULTS — GAUSS-2

	GAUSS-2			
LDL-C[a], % change	**EVO 140 mg q.2w. N = 103**	**EVO 420 mg q.m. N = 102**	**EZE/PLA q.2w. N = 51**	**EZE/PLA q.m. N = 51**
Mean (SD) baseline, mmol/L	4.97 (1.48)	4.98 (1.58)	5.04 (1.65)	5.06 (1.34)
LSM[b] (SE), week 12	–56.14 (1.91)	–52.60 (1.58)	–18.08 (2.52)	–15.05 (2.13)
Treatment difference (95% CI)[b]	**EVO 140 mg vs. EZE/PLA q.2w.:** –38.06 (–43.73 to –32.39), *P* < 0.001 **EVO 420 mg vs. EZE/PLA q.m.:** –37.55 (–42.16 to –32.94), *P* < 0.001			
	EVO 140 mg vs. EVO 420 mg: 3.54 (–1.34 to 8.42)			
LSM[b] (SE), weeks 10 and 12	–56.11 (1.83)	–55.31 (1.53)	–19.21 (2.40)	–16.62 (2.03)
Treatment difference (95% CI)[b]	**EVO 140 mg vs. EZE/PLA q.2w.:** –36.90 (–42.26 to –31.55), *P* < 0.001 **EVO 420 mg vs. EZE/PLA q.m.:** –38.69 (–43.06 to –34.32), *P* < 0.001			
	EVO 140 mg vs. EVO 420 mg: 0.80 (–3.90 to 5.49)			
Mortality, N				
N (%)	0	0	0	0
Morbidity				
Cardiovascular events, N (%)	0	0	0	0
Quality of life				
Not investigated				
Harms				
Patients with > 0 AEs, N (%)	63 (61)	72 (71)	35 (69)	39 (77)
Patients with > 0 SAEs, N (%)	5 (5)	1 (1)	1 (2)	3 (6)
WDAEs, N (%)	6 (6)	11 (11)	4 (8)	9 (18)

AE = adverse event; CI = confidence interval; EVO = evolocumab; EZE = ezetimibe; LDL-C = low-density–lipoprotein cholesterol; LSM = least squares mean; PLA = placebo; q.2w. = every two weeks; q.m. = once monthly; SAE = serious adverse event; SD = standard deviation; SE = standard error; vs. = versus; WDAE = withdrawal due to adverse event.

[a] When the calculated LDL-C is < 40 mg/dL, or triglycerides are > 400 mg/dL, calculated LDL-C will be replaced with ultracentrifugation LDL-C from the same blood sample, if available.

[b] LSM is from the repeated measures model, which includes treatment group, stratification factors (from IVRS), scheduled visit, and the interaction of treatment with scheduled visit as covariates.

Source: Clinical Study Report for GAUSS-2.[10]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Low-density–lipoprotein (LDL) cholesterol is the key component in total cholesterol and is believed to play a crucial role in the formation of atherosclerotic plaques. Familial hypercholesterolemia (FH) is a common genetic disorder of lipid metabolism affecting between 14 million and 34 million people worldwide.[1] FH is characterized by markedly elevated plasma levels of LDL cholesterol, the chronic exposure to which leads to an increased susceptibility to premature coronary artery disease and cardiac death,[1] sometimes before the age of 10 in the most severe presentation of the disease.[2] FH is subdivided into heterozygous (HeFH) or homozygous (HoFH) disease,[1-4] with HoFH being the more severe and rare form.[1,5] Patients with untreated FH have a 20-fold increased risk, irrespective of the underlying genetic mutation, of developing premature coronary artery disease compared with people without FH.[2] In Canada, it is estimated that HeFH affects 83,500 persons, while HoFH affects about 60 persons.[6] In their input to the CADTH Common Drug Review (CDR), patients with FH described the fear of death from their disease and the challenges associated with trying to get their LDL cholesterol levels down to target. They described being made to feel guilty about their weight or lack of exercise, and caregivers described the challenges associated with getting those under their care to take medications regularly for an asymptomatic condition in which the benefits of drug therapy are not readily apparent.

Hyperlipidemia is typically defined by an elevated LDL cholesterol value, and although the cut-off for therapy is also affected by patients' risk factors, for patients with established cardiovascular disease, the recommended target LDL cholesterol value is 2.0 mmol/L or lower. For primary prevention in FH, and for treatment in patients in whom therapy is limited by intolerance and who fail to achieve an LDL cholesterol of 2.0 mmol/L or lower, the Canadian Cardiovascular Society (CCS) guidelines recommend a reduction in LDL cholesterol of at least 50% from baseline.[6]

1.2 Standards of Therapy

Initial interventions for hyperlipidemia include diet and lifestyle modifications. The standard lipid-lowering therapy for the last few decades has been 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors, more commonly known as "statins." These drugs reduce cholesterol synthesis and have been the standard of care since their entry onto the market. The next most commonly used drug in management of hyperlipidemia is ezetimibe, an inhibitor of cholesterol absorption. Ezetimibe is typically used in combination with a statin, most commonly atorvastatin. Other drugs sometimes used in the management of hyperlipidemia include bile acid sequestrants, which work by reducing the availability of bile acids, a precursor to cholesterol, and fibrates, which through a variety of mechanisms reduce triglyceride levels and increase high-density–lipoprotein (HDL) cholesterol. Niacin has also been used for hyperlipidemia for a number of years, and its use is waning, according to the clinical expert, as a result of poor evidence regarding its use.

1.3 Drug

Evolocumab is a fully human monoclonal antibody that binds to human proprotein convertase subtilisin/kexin type 9 (PCSK9). Binding of PCSK9 to LDL cholesterol receptors leads to destruction of those receptors. Therefore, when evolocumab binds PCSK9, it prevents PCSK9 from destroying LDL cholesterol receptors, which leads to an increase in LDL cholesterol receptor density at the surface of the liver and enhanced clearance of LDL cholesterol from the blood. Evolocumab is approved as an adjunct to diet and maximally tolerated statin therapy in adult patients with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease who require additional lowering

of LDL cholesterol. Evolocumab is administered by subcutaneous injection, at a dose of either 140 mg every two weeks or 420 mg once monthly. It is also approved as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in adult and adolescent patients aged 12 years and over with HoFH who require additional lowering of LDL cholesterol.

Indication under review
As an adjunct to diet and maximally tolerated statin therapy in adult patients with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C. The effect of evolocumab on cardiovascular morbidity and mortality has not been determined.
Listing criteria requested by sponsor
Amgen Canada is requesting listing criteria for evolocumab in the following patient groups in which the unmet need is considered greatest: 1. High-risk patients with primary hyperlipidemia or mixed dyslipidemia who have experienced a prior CV event and who cannot reach the LDL-C target with standard of care; 2. HeFH patients who are not at the LDL-C target with standard of care.

TABLE 6: KEY CHARACTERISTICS OF STATINS, EZETIMIBE, RESINS, AND FIBRATES

	Statins	Ezetimibe	Bile acid sequestrants ("resins")
Available Drugs	Atorvastatin; fluvastatin; lovastatin; pravastatin; rosuvastatin; simvastatin		Cholestyramine; colesevelam; colestipol
Mechanism of Action	Inhibits the HMG-CoA reductase enzyme, the key enzyme involved in cholesterol synthesis	Reduces absorption of cholesterol by inhibiting the intestinal transporter Niemann-Pick C1 Like1 (NPC1L1)	Prevents intestinal reabsorption of bile acids, resulting in increased fecal excretion of LDL-C-bound bile acids and consequent LDL receptor up-regulation
Indication[a]	All: Primary hypercholesterolemia Mixed dyslipidemia Various also indicated for: Dysbetalipoproteinemia Hypertriglyceridemia HeFH and HoFH HeFH in children	Monotherapy or in combination with statins for: Primary hypercholesterolemia (HeFH or non-FH) In combination with a statin: Homozygous familial hypercholesterolemia (HoFH)	*Colesevelam*: In primary hypercholesterolemia (Type IIa)[c] as an adjunct to diet and lifestyle changes when statin therapy alone is inadequate **or** when statin therapies are not tolerated
Route of Administration	Oral	Oral	Oral
Recommended Dose	Varies by drug	10 mg once daily	*Cholestyramine*: 4 g three to four times daily *Colesevelam*: 1,875 mg twice daily or 3,750 mg daily *Colestipol*: 2 g to 16 g once daily or in divided doses

	Statins	Ezetimibe	Bile acid sequestrants ("resins")
Serious Side Effects/ Safety Issues	Contraindicated in active liver disease or unexplained, persistently abnormal transaminases Warnings/precautions: elevated transaminases; myalgia; small risk of type 2 diabetes with high-dose, high-potency statins	Contraindicated in active liver disease or unexplained, persistently elevated transaminases Warnings: hepatitis; pancreatitis; myopathy, rhabdomyolysis, or myalgia	Contraindicated in complete bowel biliary obstruction Warnings/precautions: may worsen pre-existing constipation; can impair absorption of fat-soluble vitamins such as vitamin K, which can affect coagulation
Other	Although the extent of effect varies between drugs in the class, all are able to reduce LDL-C, increase HDL-C, and reduce TG		
	Fibrates		
Available Drugs	bezafibrate; fenofibrate; gemfibrozil		
Mechanism of Action	PPAR-alpha agonist: increases LPL activity, VLDL catabolism, and plasma TG clearance May increase LDL-C slightly if baseline TG elevated		
Indication[a]	Primary hypercholesterolemia (Type IIa) as an adjunct to diet and other therapeutic measures		
Route of Administration	Oral		
Recommended Dose	*Bezafibrate*: 400 mg daily *Fenofibrate*: 145 mg daily *Gemfibrozil*: 600 mg twice daily		
Serious Side Effects / Safety Issues	Contraindicated in hepatic insufficiency, pre-existing gallbladder disease, severe renal dysfunction, chronic or acute pancreatitis Warnings/precautions: combination with statins increases risk of myopathy with possibility of acute renal failure; abnormal liver function tests; risk of cholelithiasis; mild decreases in hemoglobin, hematocrit, and WBC may occur		
Other			

FH = familial hypercholesterolemia; HDL-C = high-density–lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; HMG-CoA = 3-hydroxy-3-methyl-glutaryl-CoA; LDL-C = low-density–lipoprotein cholesterol; LPL = lipoprotein lipase; PPAR = peroxisome proliferator-activated receptor; TG = triglyceride; VLDL = very–low-density–lipoprotein; WBC = white blood cell count.
[a] Health Canada indication.

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of evolocumab for the treatment of heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase 3 studies were selected for inclusion based on the selection criteria presented in Table 7.

TABLE 7: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic CVD Subgroups: • Baseline LDL-C • Established CVD at baseline • Concomitant use of anti-hyperlipidemic drugs during study • Patients who are not candidates for or are intolerant to statins
Intervention	Evolocumab 140 mg SC every 2 weeks or 420 mg once monthly, in combination with a statin, or a statin and other lipid-lowering drugs (e.g., ezetimibe); or alone; or in combination with other lipid-lowering drugs in patients who are intolerant of statins, or for whom statins are not considered clinically appropriate
Comparators	Ezetimibe Statins Placebo

Outcomes	**Key efficacy outcomes:**
	• Mortality
	• Morbidity (cardiovascular-related)
	  ○ Cardiovascular events
	  ○ Hospitalizations
	  ○ Minimally invasive cardiovascular interventions (e.g., PCI)
	• Changes in LDL-C
	• Quality of life
	  ○ HRQoL
	Other efficacy outcomes:
	• Health care resource utilization
	• Vascular imaging
	• Other laboratory parameters:
	  ○ Apo B
	  ○ Lp(a)
	  ○ Non-HDL-C
	  ○ TG
	  ○ VLDL-C
	Harms outcomes:
	AEs, SAEs, WDAEs
	Notable harms: immune reactions, injection-site reactions, muscle symptoms

Study Design	Published and unpublished DB RCTs

AE = adverse event; apo = apolipoprotein; CVD = cardiovascular disease; DB = double-blind; HDL-C = high-density–lipoprotein cholesterol; HRQoL = health-related quality of life; LDL-C = low-density–lipoprotein cholesterol; Lp(a) = lipoprotein(a); PCI = percutaneous coronary intervention; RCT = randomized controlled trial; SAE = serious adverse event; SC = subcutaneous; TG = triglycerides; VLDL-C = very–low-density–lipoprotein cholesterol; WDAE = withdrawal due to adverse event.

The literature search was performed by an information specialist using a peer-reviewed search strategy. Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records & daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Inspiolto Respimat (tiotropium and olodaterol).

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on July 29, 2015. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee on November 18, 2015. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the CADTH Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Databases (free), Internet Search and Open Access Journals. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4 8, 9, and 10; excluded studies (with reasons) are presented in Appendix 3: EXCLUDED STUDIES.

3. RESULTS

3.1 Findings From the Literature

A total of four studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Tables 8, 9, and 10, and described in section 3.2. A list of excluded studies is presented in APPENDIX 3: EXCLUDED STUDIES.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

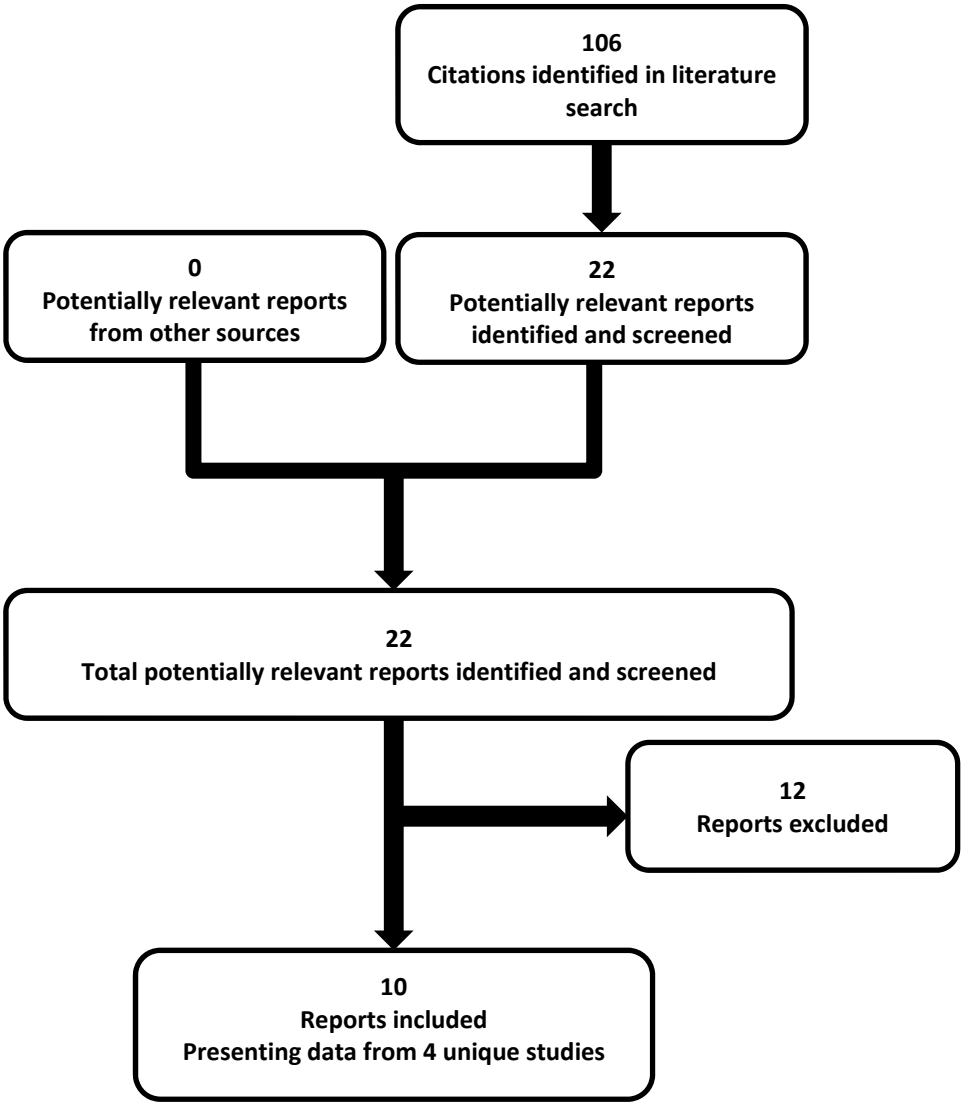


TABLE 8: DETAILS OF INCLUDED STUDIES — LAPLACE-2, RUTHERFORD-2

		LAPLACE-2	RUTHERFORD-2
DESIGNS & POPULATIONS	**Study Design**	DB RCT	DB RCT
	Locations	198 centres: North America (including Canada), EU, Hong Kong	39 sites: North America (including Canada), EU, Australia, NZ, Asia, South Africa
	Randomized (N)	N = 1,899	N = 331
	Study Period	January 15, 2013 to December 4, 2013	February 7, 2013 to December 19, 2013
	Inclusion Criteria	Aged 18 to 80 years Screening LDL-C level of: • ≥ 3.9 mmol/L (no statin at screening) • ≥ 2.6 mmol/L (non-intensive statin at screening) • ≥ 2.1 mmol/L (intensive statin at screening) and fasting triglyceride levels of ≤ 4.5 mmol/L At screening, intensive statin use was defined as daily atorvastatin (40 mg or greater), rosuvastatin (20 mg or greater), simvastatin (80 mg), or any statin plus ezetimibe	Patients 18 to 80 years of age with heterozygous familial hypercholesterolemia according to Simon Broome criteria at screening and on a stable dose of a statin with or without other approved lipid-modifying therapy (e.g., ezetimibe, resins, stanols, or niacin, but excluding fibrates) for at least 4 weeks before screening with fasting LDL-C ≥ 2.6 mmol/L and fasting triglycerides ≤ 4.5 mmol/L
	Exclusion Criteria	Current or prior history of statin intolerance (as determined by investigator) or any intolerance to rosuvastatin, atorvastatin, or simvastatin	Homozygous familial hypercholesterolemia or lipoprotein apheresis within the previous 4 months
DRUGS	**Intervention**	Evolocumab 140 mg SC every 2 weeks Evolocumab 420 mg SC once monthly	Evolocumab 140 mg SC every 2 weeks Evolocumab 420 mg SC once monthly
	Comparator(s)	Placebo (2 groups, each matched to an evolocumab dose) Placebo + ezetimibe 10 mg PO daily (atorvastatin background only: 2 groups, each matched to an evolocumab dose)	Placebo (2 groups, each matched to an evolocumab dose regimen)
DURATION	**Phase**		
	Run-in	8 weeks maximum (including lipid stabilization)	6 weeks
	DB	12 weeks	12 weeks
	Follow-up	0 to 2 weeks	0 to 2 weeks
OUTCOMES	**Primary End Point**	Per cent change from baseline in LDL-C level at the mean of weeks 10 and 12 and at week 12	Per cent change from baseline in LDL-C level at the mean of weeks 10 and 12 and at week 12
	Other End Points	• Mean at weeks 10 and 12 and at week 12 for the change from baseline in LDL-C level • Per cent change from baseline in additional lipid parameters • Proportion of patients achieving LDL-C levels lower than 70 mg/dL Exploratory: • Subject incidence of adjudicated cardiovascular end point events • Subject incidence of non-coronary revascularization	• Mean at weeks 10 and 12 and at week 12 for the change from baseline in LDL-C level • Per cent change from baseline in additional lipid parameters • Proportion of patients achieving LDL-C levels lower than 1.8 mmol/L

		LAPLACE-2	RUTHERFORD-2
NOTES	**Publications**	Robinson et al. 2014[11]	Raal et al. 2015[12]

DB = double-blind; EU = European Union; EVO = evolocumab; LDL-C = low-density–lipoprotein cholesterol; NZ = New Zealand; PO = by mouth; SC = subcutaneous; RCT = randomized controlled trial.
Note: Four additional reports were included (manufacturer's submission,[13] Health Canada Review,[14] Clinical Study Reports for LAPLACE-2[7] and RUTHERFORD-2[8]).
Source: Clinical Study Reports for LAPLACE-2[7] and RUTHERFORD-2[8].

TABLE 9: DETAILS OF INCLUDED STUDIES — DESCARTES

		DESCARTES
DESIGNS & POPULATIONS	**Study Design**	DB RCT
	Locations	88 centres: 9 countries (US, Canada, Australia, South Africa, EU)
	Randomized (N)	N = 905
	Study Period	January 5, 2012 to November 7, 2013
	Inclusion Criteria	Adults 18 to 75 years of age with an LDL-C of ≥ 1.94 mmol/L, fasting TG level of ≤ 4.52 mmol/L
	Exclusion Criteria	Patients diagnosed with CHD or CHD risk equivalent and not receiving statin therapy with LDL-C at screening ≤ 2.6 mmol/L Heart failure, recent MI, recent or planned revascularization procedure, uncontrolled hypertension, hyperthyroidism or hypothyroidism, moderate to severe renal dysfunction, and active liver disease or hepatic dysfunction
DRUGS	**Intervention**	Evolocumab 420 mg SC once monthly plus atorvastatin 10 mg/day Evolocumab 420 mg SC once monthly plus atorvastatin 80 mg/day Evolocumab 420 mg SC once monthly plus atorvastatin 80 mg/day and ezetimibe 10 mg/day Diet alone
	Comparator(s)	Placebo (matched to each group)
DURATION	**Phase**	
	Run-in	4 to 12 weeks (OL background lipid-lowering therapy)
	DB	52 weeks
	Follow-up	0 weeks
OUTCOMES	**Primary End Point**	Per cent change from baseline in the LDL cholesterol level at week 52
	Other End Points	Absolute change from baseline in the LDL-C at week 52 Per cent change from baseline in LDL-C, week 12 Percentage of patients with LDL-C < 1.81 mmol/L at week 52
NOTES	**Publications**	Blom et al. 2014[15]

CHD = coronary heart disease; DB = double-blind; EU = European Union; EVO = evolocumab; LDL-C = low-density–lipoprotein cholesterol; MI = myocardial infarction; OL = open-label; RCT = randomized controlled trial; SC = subcutaneous; TG = triglycerides.
Note: Three additional reports were included (manufacturer's submission,[13] Health Canada Review,[14] Clinical Study Report for DESCARTES[9]).
Source: Clinical Study Report for DESCARTES.[9]

TABLE 10: DETAILS OF INCLUDED STUDIES — GAUSS-2

		GAUSS-2
DESIGNS & POPULATIONS	**Study Design**	DB RCT
	Locations	51 centres: North America (including Canada), EU, Australia, Hong Kong
	Randomized (N)	N = 307
	Study Period	January 24, 2013, to November 19, 2013
	Inclusion Criteria	Men and women 18 to 80 years of age tried at least 2 statins and have been unable to tolerate any dose or an increase in statin dose above the total weekly maximum doses specified due to intolerable myopathy, i.e., myalgia (muscle pain, ache, or weakness without CK elevation), myositis (muscle symptoms with increased CK levels), or rhabdomyolysis (muscle symptoms with marked CK elevation). Statin symptoms must have resolved when the statin was discontinued or the dose reduced. Met the following fasting LDL-C (determined by central laboratory) criteria at screening: • ≥ 2.6 mmol/L for subjects with CHD or CHD risk equivalent • ≥ 3.4 mmol/L for subjects without diagnosed CHD or risk equivalent and 2 or more risk factors • ≥ 4.1 mmol/L for subjects without diagnosed CHD or risk equivalent and with 1 risk factor • ≥ 4.9 mmol/L for subjects without diagnosed CHD or risk equivalent and with no risk factors Fasting triglycerides must have been ≤ 4.5 mmol/L.
	Exclusion Criteria	History or evidence of clinically significant diseases and conditions that would pose a risk to their safety or interfere with the study evaluation, procedures, or completion
DRUGS	**Intervention**	Evolocumab 140 mg SC q.2w. and placebo PO q.d. Evolocumab 420 mg SC q.m. and placebo PO q.d.
	Comparator(s)	Placebo SC q.2w. and ezetimibe 10 mg PO q.d. Placebo SC q.m. and ezetimibe 10 mg PO q.d.
DURATION	**Phase**	
	Screening	6 weeks (training)
	DB	12 weeks
	Follow-up	0 to 2 weeks
OUTCOMES	**Primary End Point**	The co-primary end points were: • Per cent change from baseline in LDL-C at week 12 • Mean per cent change from baseline in LDL-C at weeks 10 and 12
	Other End Points	Co-secondary end points were at week 12 and the means at weeks 10 and 12 for: Tier 1 end points • Change from baseline in LDL-C • Per cent of subjects with LDL-C < 1.8 mmol/L • Per cent change from baseline in non-HDL-C • Per cent change from baseline in apo B • Per cent change from baseline in the total cholesterol/HDL-C ratio • Per cent change from baseline in apo B/apo A-I ratio Tier 2 end points • Per cent change from baseline in Lp(a) • Per cent change from baseline in triglycerides • Per cent change from baseline in VLDL-C • Per cent change from baseline in HDL-C

		GAUSS-2
NOTES	**Publications**	Stroes et al. 2014[16]

apo = apolipoprotein; CHD = coronary heart disease; CK = creatine kinase; DB = double-blind; EU = European Union; EVO = evolocumab;
HDL-C = high-density–lipoprotein cholesterol; LDL-C = low-density–lipoprotein cholesterol; Lp(a) = lipoprotein(a);
PO = by mouth; q.2w. = every two weeks; q.d. = once daily; q.m. = once monthly; RCT = randomized controlled trial;
sC = subcutaneous; VLDL-C = very–low-density–lipoprotein cholesterol.
Note: Three additional reports were included (manufacturer's submission,[13] Health Canada Review,[14] Clinical Study Report for GAUSS-2[10]).
Source: Clinical Study Report for GAUSS-2.[10]

3.2 Included Studies

3.2.1 Description of studies

Four multi-centre, manufacturer-sponsored double-blind (DB) randomized controlled trials (RCTs) met the inclusion criteria for this review (Table 8, 9, and 10). These studies were described as key studies in the manufacturer's executive summary; however, it is not clear whether they are considered pivotal by Health Canada, as its review was not yet available at the time of completion of this CDR report. In LAPLACE-2, patients were initially randomized to background regimens of various statins (atorvastatin 10 mg or 80 mg, rosuvastatin 5 mg or 40 mg, or simvastatin 40 mg, all daily). Once stabilized, patients were then randomized to evolocumab (140 mg or 420 mg), matching placebo, or ezetimibe (only patients on atorvastatin received ezetimibe) for a period of 12 weeks. RUTHERFORD-2 was a placebo-controlled study, with patients randomized to evolocumab (140 mg or 420 mg) or matching placebo for 12 weeks. DESCARTES was also a placebo-controlled study, with all evolocumab patients receiving the 420 mg dose, on a variety of different backgrounds (atorvastatin 10 mg/day, or atorvastatin 80 mg/day, or atorvastatin 80 mg/day plus ezetimibe, or diet alone), over 52 weeks. GAUSS-2 was ezetimibe-controlled, comparing the two approved doses of evolocumab (140 mg or 420 mg) with ezetimibe 10 mg daily, over a treatment period of 12 weeks. Specific details regarding study design for each study are described in the paragraphs that follow.

a) LAPLACE-2

This study was designed to evaluate the efficacy and safety of 12 weeks of evolocumab compared with placebo when administered in combination with statin therapy in hyperlipidemic patients. Before the first randomization, patients entered a screening period to determine eligibility. During screening, placebo was administered by subcutaneous (SC) injection to confirm tolerability of SC administration before randomization. After the screening period, eligible patients were randomized to one of five open-label statin cohorts (atorvastatin 10 mg or 80 mg, rosuvastatin 5 mg or 40 mg, or simvastatin 40 mg, all daily) for a four-week lipid stabilization period based on statin therapy at the time of study entry (no statin use, non-intensive statin use, or intensive statin use). Following the lipid stabilization period, eligible patients were randomized within each statin dose cohort to blinded IP. Due to changes in simvastatin labelling, randomization into IP was stratified by use of certain concomitant medications (any verapamil or diltiazem versus amlodipine, amiodarone or ranolazine alone versus none).

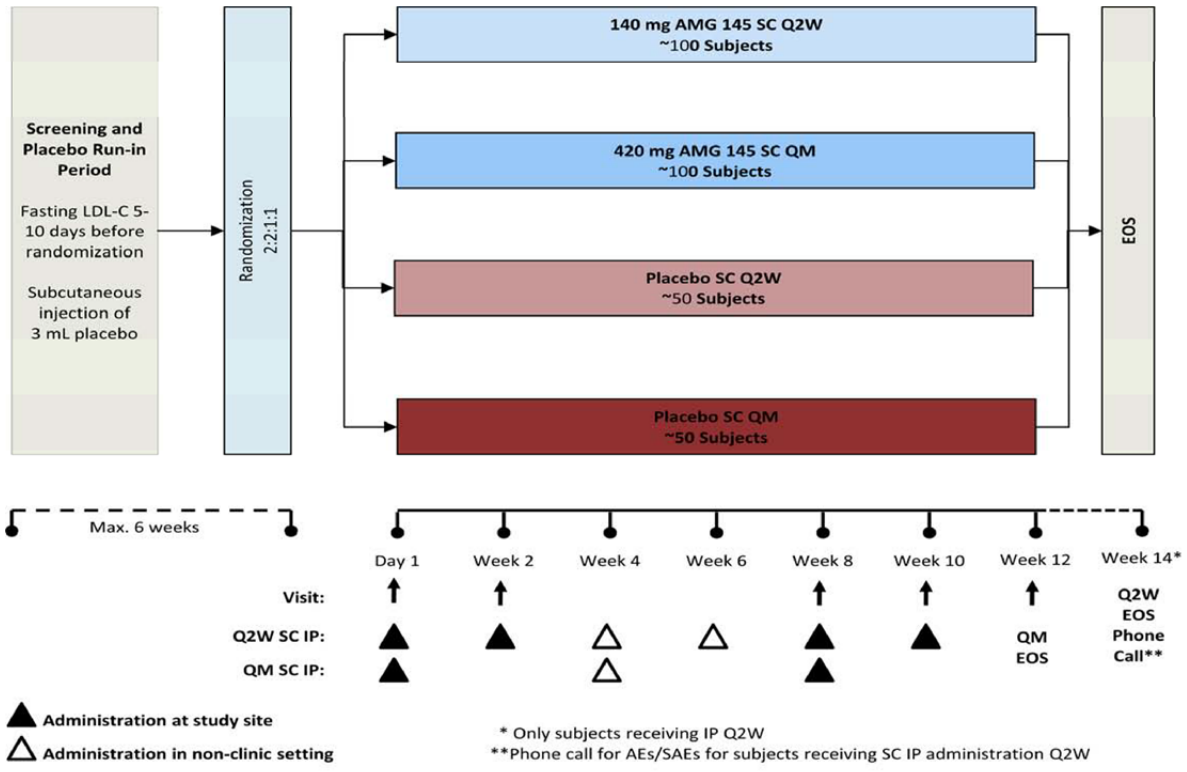
FIGURE 2: DESIGN OF LAPLACE-2

Source: Clinical Study Report for LAPLACE-2.[7]

b) RUTHERFORD-2

This study was designed to evaluate the effect of 12 weeks of evolocumab SC compared with placebo administered every two weeks or once monthly on per cent change from baseline in LDL cholesterol in patients with HeFH on stable doses of a statin. Before randomization, patients entered a six-week screening period to determine eligibility. During screening, SC administration of placebo was performed to confirm tolerability of SC administration before randomization. All patients received placebo SC that corresponded to the once-monthly dose volume (3.0 mL) using three consecutively administered auto-injector pens. During the screening period, the patient (or designee) was trained by study site staff to prepare and self-administer (or administer) the investigational product. Patients who completed the screening period and met final eligibility criteria were randomized in a ratio of 2:2:1:1 to four treatment groups. Randomization was stratified by screening LDL cholesterol level (lower than 4.2 mmol/L or 4.2 mmol/L or higher) and whether ezetimibe was being used at baseline.

FIGURE 3: DESIGN OF RUTHERFORD-2



AE = adverse event; AMG = ; EOS = end of study; IP = ; LDL-C = low-density–lipoprotein cholesterol; Q2W = every two weeks; QM = once monthly; SAE = serious adverse event; SC = subcutaneously.
Source: Clinical Study Report for Rutherford-2.[8]

c) DESCARTES

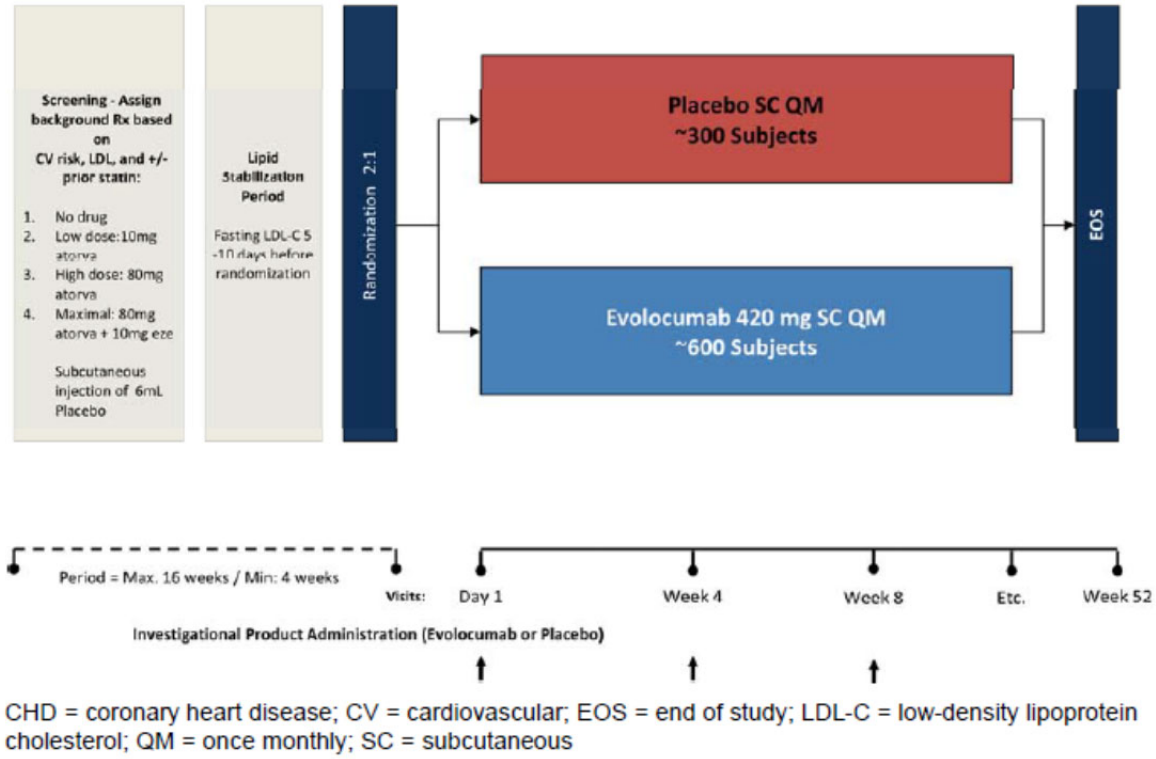
This was a phase 3, multi-centre, DB, double-dummy, randomized placebo-controlled study of evolocumab. Eligible patients with screening central laboratory LDL cholesterol values 1.9 mmol/L or higher were instructed to follow National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP) Therapeutic Lifestyle Changes diet. They were also assigned to one of the following four background lipid-lowering therapies for a four-week stabilization period based on their screening LDL cholesterol and its distance from the individual patient's required goal, as stipulated by his or her NCEP

ATP III risk category:

1. No drug therapy required — diet alone
2. Low-dose drug therapy required — diet plus atorvastatin 10 mg orally once daily
3. High-dose drug therapy required — diet plus atorvastatin 80 mg orally once daily
4. Maximal drug therapy required — diet plus atorvastatin 80 mg orally once daily plus ezetimibe 10 mg orally once daily

At the end of the four-week stabilization period, patients who still exceeded the goal LDL cholesterol value for their NCEP risk category underwent background therapy up-titration to the next therapy level and entered an additional four-week stabilization period, after which study eligibility based on LDL cholesterol was reassessed. A maximum of two up-titrations were permitted. If the patients met entry criteria, they were then randomized entry criteria were achievement of NCEP risk category LDL cholesterol goal (LDL cholesterol lower than 100 mg/dL for those with coronary heart disease [CHD] or CHD risk equivalents, or lower than 130 mg/dL for those without CHD or CHD risk) and LDL cholesterol value 1.9 mmol/L or higher. Patients who were on maximal drug therapy (diet plus atorvastatin 80 mg orally once daily plus ezetimibe 10 mg orally once daily) were eligible if their LDL cholesterol value was 1.9 mmol/L or higher at the end of the four-week stabilization period. Patients on maximal background therapy whose LDL cholesterol was lower than 1.9 mmol/L at the end of the four-week stabilization period were allowed to undergo a single background therapy down-titration to diet plus atorvastatin 80 mg orally once daily and enter an additional four-week lipid stabilization period, after which study eligibility was reassessed based on a final LDL cholesterol blood sample**.** Randomization was stratified by background therapy.

FIGURE 4: DESIGN OF DESCARTES



CHD = coronary heart disease; CV = cardiovascular; EOS = end of study; LDL-C = low-density lipoprotein cholesterol; QM = once monthly; SC = subcutaneous

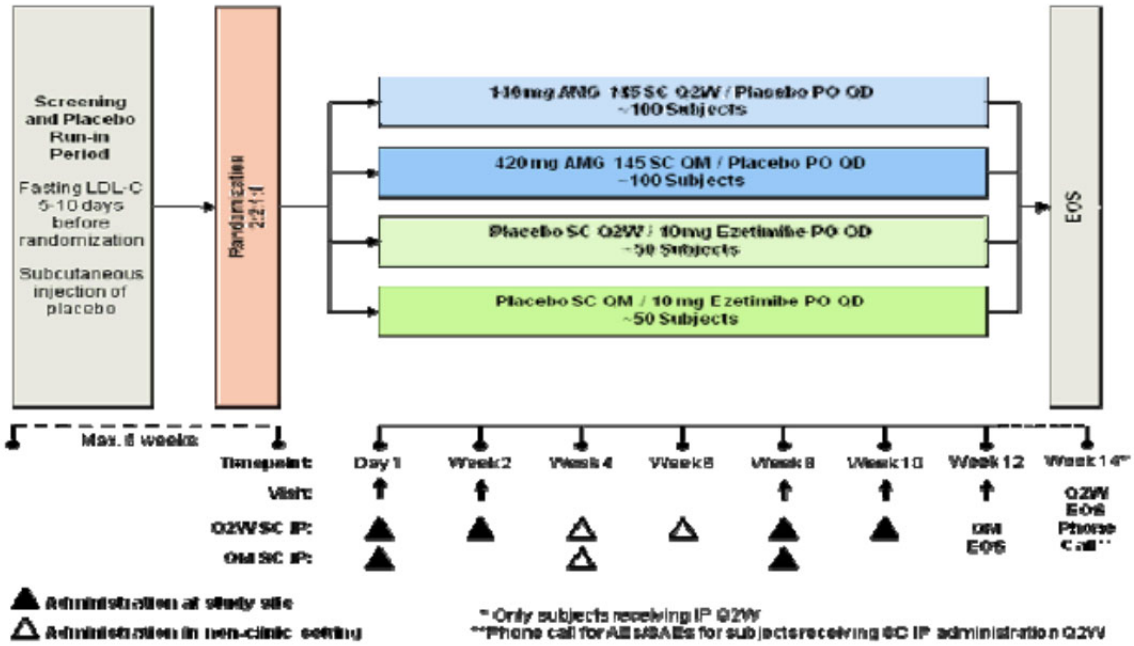
Source: Clinical Study Report for DESCARTES.[9]

d) GAUSS-2

This study enrolled patients who had tried at least two statins and were unable to tolerate either any dose or an increase in statin dose above total weekly maximum doses specified in the protocol, because of intolerable myopathy, i.e., myalgia (muscle pain, ache, or weakness without creatine kinase [CK] elevation), myositis (muscle symptoms with increased CK levels), or rhabdomyolysis (muscle symptoms with marked CK elevation). Randomization was stratified by screening LDL cholesterol level (lower than 4.7 mmol/L or 4.7 mmol/L or higher) and by whether statins were being used at baseline.

Before randomization, all patients entered a six-week screening period to determine eligibility. During screening, placebo was administered to confirm tolerability of SC administration prior to randomization. All patients received SC placebo that corresponded to the once-monthly dose volume (3.0 mL) using three consecutively administered auto-injector (AI) pens. During the screening period, the patient (or designee) was trained by study site staff to prepare and administer the AI pen and was provided the appropriate IFU.

FIGURE 5: DESIGN OF GAUSS-2



AMG = ?; EOS = end of study; IP = ?; LDL-C = low-density–lipoprotein cholesterol; PO = by mouth; Q2W = every two weeks; QD = once daily; SC = subcutaneously.
Source: Clinical Study Report for GAUSS-2.[10]

3.2.2 Populations

a) Inclusion and exclusion criteria

Studies enrolled patients primarily based on LDL cholesterol levels and triglyceride levels; with the exception of RUTHERFORD-2, which specified patients with HeFH, studies did not require patients to have a genetic cause of hypercholesterolemia (Table 8, 9, and Table 10). In LAPLACE-2, eligible LDL cholesterol levels for enrolment varied depending on whether the patient was on a statin at screening and on the intensity of the statin dose. In RUTHERFORD-2, patients were on a stable dose of statin, and the cut-off LDL cholesterol value (minimum 2.6 mmol/L) was the same for all patients. Patients in DESCARTES were not receiving statins at baseline, and the minimum LDL cholesterol in this study was also 2.6 mmol/L. Finally, enrolment criteria for LDL cholesterol in GAUSS-2 were based on a combination of established CHD and risk factors, and all patients had exhibited signs of statin intolerance. Patients with established CHD had the lowest cut-off for LDL cholesterol (again, minimum 2.6 mmol/L), and minimum LDL cholesterol increased as patients had fewer risk factors, up to a minimum of 4.9 mmol/L for patients with no risk factors. In all studies, patients had fasting triglyceride levels of 4.5 mmol/L or lower.

b) Baseline characteristics

At baseline across studies, patients were generally in their 50s and early 60s, with the oldest population in GAUSS-2 (mean age 61 years) and the youngest in RUTHERFORD-2 (mean age 51) (Table 11, Table 12, Table 13, and Table 14). There was a similar proportion of males and females across studies. The proportion of patients with coronary artery disease at baseline ranged from 22% in LAPLACE-2 to 30% in RUTHERFORD-2, although in DESCARTES the proportions varied widely between groups, with the highest proportion (47%) in patients on the most intensive background of atorvastatin 80 mg plus ezetimibe.

TABLE 11: SUMMARY OF BASELINE CHARACTERISTICS — LAPLACE-2

	LAPLACE-2					
	EVO 140 mg q.2w. + any statin N = 555	EVO 420 mg q.m. + any statin N = 562	PLA q.2w. + atorvastatin/ EZE N = 112	PLA q.m. + atorvastatin/EZ E N = 109	PLA q.2w. + statin N = 281	PLA q.m.+ statin N = 277
Mean (SD) age, years	59.2 (9.7)	60.0 (10.1)	60.7 (9.6)	60.9 (9.0)	59.8 (9.7)	60.0 (10.6)
Male, n (%)	317 (57)	308 (55)	59 (53)	53 (49)	147 (52)	144 (52)
Mean (SD) LDL-C, mmol/L	2.80 (1.03)	2.88 (1.16)	2.92 (1.16)	2.74 (0.72)	2.73 (1.00)	2.85 (1.08)
CHD, n (%)	129 (23)	137 (24)	19 (17)	19 (17)	62 (22)	61 (22)
NCEP CHD risk						
High	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderately high	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lower	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Statin use	394 (71)	391 (70)	80 (71)	68 (62)	184 (66)	193 (70)

CHD = coronary heart disease; EVO = evolocumab; EZE = ezetimibe; LDL-C = low-density–lipoprotein cholesterol; NCEP = National Cholesterol Education Program; PLA = placebo; q.2w. = every two weeks; q.m. = once monthly; SD = standard deviation.
Source: Clinical Study Report for LAPLACE-2.[7]

TABLE 12: SUMMARY OF BASELINE CHARACTERISTICS — RUTHERFORD-2

	RUTHERFORD-2			
	EVO 140 mg q.2w. N = 110	EVO 420 mg q.m. N = 110	PLA q.2w. N = 54	PLA q.m. N = 55
Mean (SD) age, years	52.6 (12.3)	51.9 (12.0)	51.1 (14.2)	46.8 (12.1)
Male, n (%)	66 (60)	64 (58)	29 (54)	31 (56)
CHD, n (%)	38 (35)	39 (35)	16 (30)	10 (18)
Mean (SD) LDL-C[a], mmol/L	4.2 (1.3)	4.0 (1.1)	3.9 (0.9)	3.9 (1.1)
NCEP CHD risk categories, n (%)				
High	[redacted]	[redacted]	[redacted]	[redacted]
Moderately high	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]
Lower	[redacted]	[redacted]	[redacted]	[redacted]
Patients with coronary artery disease, n (%)	38 (35)	39 (36)	16 (30)	10 (18)

CHD = coronary heart disease; EVO = evolocumab; LDL-C = low-density–lipoprotein cholesterol; NCEP = National Cholesterol Education Program; q.2w. = every two weeks; q.m. = once monthly; SD = standard deviation.
[a] Established by the Friedewald formula with reflexive testing through preparative ultracentrifugation when calculated LDL cholesterol was ≤ 1.0 mmol/L or triglyceride concentrations were ≥ 4.5 mmol/L.
Source: Clinical Study Report for RUTHERFORD-2.[8]

TABLE 13: SUMMARY OF BASELINE CHARACTERISTICS — DESCARTES

	DESCARTES							
	EVO 420 mg q.m./ ATO 10 mg q.d. N = 254	PLA q.m./ ATO 10 mg q.d. N = 129	EVO 420 mg q.m./ ATO 80 mg q.d. N = 145	PLA q.m./ ATO 80 mg q.d. N = 73	EVO 420 mg q.m./ ATO 80 mg q.d. + EZE N = 126	PLA q.m./ ATO 80 mg q.d. + EZE N = 63	EVO 420 mg q.m./ diet N = 74	PLA q.m./ diet N = 37
Mean (SD) age, years	57.2 (10.3)	57.0(10.6)	57.8 (9.4)	58.4 (8.7)	54.2 (11.5)	55.9 (9.0)	50.7 (10.6)	53.5 (12.4)
Male, n (%)	109 (43)	59 (46)	76 (52)	33 (45)	70 (56)	33 (52)	35 (47)	15 (41)
CHD, n (%)	8 (3)	2 (2)	23 (16)	11 (15)	61 (48)	29 (46)	2 (3)	0
Mean (SD) LDL-C, mmol/L	2.6 (0.4)	2.5 (0.4)	2.4 (0.3)	2.5 (0.3)	3.0 (0.9)	3.1 (0.8)	2.9 (0.4)	2.9 (0.4)
ATP III risk category, n (%)								
High	28 (11)	13 (10)	44 (30)	23 (32)	80 (64)	41 (65)	4 (5)	2 (5)
Moderately high	27 (11)	15 (12)	12 (8)	7 (10)	7 (6)	3 (5)	10 (14)	4 (11)
Moderate	92 (36)	46 (36)	62 (43)	24 (33)	24 (19)	11 (18)	25 (34)	16 (43)
Low	107 (42)	55 (43)	27 (19)	19 (26)	15 (12)	8 (13)	35 (47)	15 (41)

ATO = atorvastatin; ATP = Adult Treatment Panel; CHD = coronary heart disease; EVO = evolocumab; EZE = ezetimibe; LDL-C = low-density–lipoprotein cholesterol; PLA = placebo; q.d. = once daily; q.m. = once monthly; SD = standard deviation.
Source: Clinical Study Report for DESCARTES.[9]

TABLE 14: SUMMARY OF BASELINE CHARACTERISTICS — GAUSS-2

	GAUSS-2	
	EVO N = 205	EZE N = 102
Mean (SD) age, years	61.7 (10.0)	61.0 (9.4)
Male, n (%)	113 (55)	53 (52)
CHD, n (%)	90 (29)	28 (28)
Mean (SD) LDL-C, mmol/L	4.98 (1.53)	5.05 (1.50)
NCEP CHD risk categories, n (%)		
High	109 (53)	64 (63)
Moderately high	32 (16)	13 (13)
Moderate	36 (18)	17 (17)
Lower	28 (14)	8 (8)
Number of patients reporting statin intolerance in medical history	205 (100)	102 (100)
Intolerance to statins (number of statins per patient)		
Two statins	96 (47)	42 (41)
Three statins	69 (34)	35 (34)
Four or more statins	40 (20)	25 (25)
Worst muscle-related side effect for any statin, n (%)		
Myalgia (muscle symptoms without CK elevation)	161 (79)	85 (83)
Myositis (muscle symptoms with CK elevation)	39 (19)	15 (15)
Rhabdomyolysis (muscle symptoms with significant CK elevation)	4 (2)	2 (2)

	GAUSS-2	
	EVO N = 205	EZE N = 102
LDL-C treatment goals based on risk category		
LDL-C < 100 mg/dL for diagnosed CHD or CHD risk equivalent	103 (50)	50 (49)
LDL-C < 130 mg/dL for 2 or more risk factors without diagnosed CHD or CHD risk equivalent	53 (26)	33 (32)
LDL-C < 160 mg/dL for 1 risk factor without diagnosed CHD or CHD risk equivalent	35 (17)	12 (12)
LDL-C < 190 mg/dL for no risk factors without diagnosed CHD or CHD risk equivalent	14 (7)	7 (7)

CHD = coronary heart disease; CK = creatine kinase; EVO = evolocumab; EZE = ezetimibe; LDL-C = low-density–lipoprotein cholesterol; SD = standard deviation.
Source: Clinical Study Report for GAUSS-2.[10]

3.2.3 Interventions

a) LAPLACE-2

The SC study drug administration was either 140 mg evolocumab or placebo in 1.0 mL (one injection by AI pen) every two weeks, or 420 mg evolocumab or placebo in 3.0 mL (three injections by AI pen) monthly. The three injections for the monthly administration could be administered at different injection sites but were administered consecutively within 30 minutes. After administration at the first dosing visit, patients were required to remain at the study centre for observation for at least 30 minutes before being discharged. The remaining doses were administered in the clinic or in a home-use setting.

b) RUTHERFORD-2

The SC study drug administration was either 140 mg evolocumab or placebo in 1.0 mL (one injection by pre-filled AI pen) every two weeks, or 420 mg evolocumab or placebo in 3.0 mL (three injections by pre-filled AI pen) monthly. The three injections for the monthly administration could be administered at different injection sites but were administered consecutively within 30 minutes. After administration at the first dosing visit, patients were required to remain at the study centre for observation for at least 30 minutes before being discharged. It was anticipated that patients would remain on a stable dose of statin and of any other approved lipid-lowering drugs, from screening until the end of study. Patients were required to maintain their current regimen of diet and exercise and to refrain from unaccustomed intensive exercise (e.g., heavy lifting or long runs) 48 hours before each visit.

TABLE 15: RUTHERFORD-2 — LIPID-REGULATING CONCOMITANT MEDICATIONS USED BY MORE THAN 10% OF PATIENTS

	Baseline		Post-baseline	
	Evolocumab (N = 220)	Placebo (N = 109)	Evolocumab (N = 220)	Placebo (N = 109)
Number of patients reporting use of medications of interest, N (%)				
Atorvastatin	74 (34)	41 (38)	74 (34)	41 (38)
Rosuvastatin	109 (50)	52 (48)	109 (50)	52 (48)
Simvastatin	29 (13)	11 (10)	29 (13)	11 (10)
Ezetimibe	135 (61)	69 (63)	136 (62)	69 (63)

Source: Clinical Study Report for RUTHERFORD-2.[8]

c) DESCARTES

Evolocumab or placebo was administered by SC injection of 6 mL once monthly. The dose was split (e.g., three injections of 2 mL each) and administered at different injection sites in a consecutive manner, all within 30 minutes. Investigators were instructed to maintain the patients on stable background lipid-lowering therapy (e.g., diet, atorvastatin, and ezetimibe) from screening until the end of study. Also, patients were encouraged to maintain their usual exercise regimen.

d) GAUSS-2

The study drug was administered by a SC injection of either 140 mg evolocumab or placebo in 1.0 mL (one injection by pre-filled AI pen) every two weeks, or 420 mg evolocumab or placebo in 3.0 mL (three injections by pre-filled AI pen) monthly. The three injections for the monthly administration could be administered at different injection sites but were administered consecutively within 30 minutes. Patients were required to maintain their current regimen of diet and exercise and to refrain from unaccustomed intensive exercise (e.g., heavy lifting or long runs) 48 hours before each visit.

TABLE 16: GAUSS-2 — CHANGE IN LIPID-REGULATING MEDICATION USE DURING STUDY

	GAUSS-2			
	EVO 140 mg q.2w. N = 103	**EVO 420 mg q.m. N = 102**	**EZE/PLA q.2w. N = 51**	**EZE/PLA q.m. N = 51**
None at baseline	[redacted]	[redacted]	[redacted]	[redacted]
None post-baseline	[redacted]	[redacted]	[redacted]	[redacted]
Non-statin lipid-modifying therapy usage post-baseline	[redacted]	[redacted]	[redacted]	[redacted]
Statin usage post-baseline	[redacted]	[redacted]	[redacted]	[redacted]
Non-statin lipid-modifying therapy usage at baseline	[redacted]	[redacted]	[redacted]	[redacted]
None post-baseline	[redacted]	[redacted]	[redacted]	[redacted]
Non-statin lipid-modifying therapy usage post-baseline	[redacted]	[redacted]	[redacted]	[redacted]
Statin usage post-baseline	[redacted]	[redacted]	[redacted]	[redacted]
Statin usage at baseline	[redacted]	[redacted]	[redacted]	[redacted]
None post-baseline	[redacted]	[redacted]	[redacted]	[redacted]
Non-statin lipid-modifying therapy usage post-baseline	[redacted]	[redacted]	[redacted]	[redacted]
Statin usage post-baseline	[redacted]	[redacted]	[redacted]	[redacted]

EVO = evolocumab; EZE = ezetimibe; PLA = placebo; q.2w. = every two weeks; q.m. = once monthly.
Source: Clinical Study Report for GAUSS-2.[10]

3.2.4 Outcomes

The primary outcome of all studies was the percentage change from baseline in LDL cholesterol. In the 12-week studies, this was assessed as a co-primary end point at week 12 and at a mean of weeks 10 and 12. According to the clinical expert, the rationale for assessing LDL cholesterol at both weeks 10 and 12, as well as week 12 alone, is that when evolocumab is dosed monthly, LDL cholesterol rises near the end of the four-week dose interval, and that might lead to an underestimation of effect if LDL cholesterol is assessed only at week 12. In the 52-week DESCARTES study, percentage change from baseline in LDL cholesterol was reported at a single time point of 52 weeks. Across the included studies, level of LDL cholesterol was generally determined by the Friedewald formula, unless calculated LDL cholesterol was

lower than 40 mg/dL or triglyceride levels were greater than 400 mg/dL; in those cases, the LDL cholesterol level was measured by preparative ultracentrifugation. Fasting lipid levels were taken at baseline and at weeks 2, 8, 10, and 12 for the 12-week studies, and apolipoprotein (apo) B and lipoprotein(a) [Lp(a)] were taken at baseline and at weeks 10 and 12. In the 52-week DESCARTES study, fasting lipids and apo B were assessed at baseline and at weeks 12, 13, 24, 36, 37, and 52.

Across all studies, cardiovascular end points were adjudicated by an Independent Clinical Endpoint Committee (CEC). The CEC comprised independent adjudicators who were blinded to patient identity, treatment assignment, and LDL cholesterol concentrations. The following events were adjudicated for this study based on Clinical Data Interchange Standards Consortium definitions provided in the "Standardized Definitions for Endpoint Events in Cardiovascular Trials" in order to facilitate integrated analyses across the program:

- death by any cause
- cardiovascular death
- myocardial infarction
- hospitalization for unstable angina
- coronary revascularization
- stroke
- transient ischemic attack
- hospitalization for heart failure

3.2.5 Statistical analysis

The power calculations for the included studies appeared to be based on observations of treatment effect for LDL cholesterol in the phase 2 studies. The sample size was determined using a pre-specified treatment effect of 15% (DESCARTES) or 16.5% (other studies) for reduction in LDL cholesterol, and common standard deviation of between 20% and 23%, depending on the study.

Across the included studies, to assess the primary end point (mean per cent change from baseline in LDL cholesterol), a repeated measures linear effects model was used on the full analysis set (FAS), separately in each group, to compare the efficacy of evolocumab with comparators. The repeated measures model included terms for treatment group, stratification factor, scheduled visit, and the interaction of treatment group with scheduled visit. In RUTHERFORD-2, randomization was stratified by screening LDL cholesterol level (lower than 4.2 mmol/L or 4.2 mmol/L and higher) and by whether ezetimibe was being used baseline. In DESCARTES, randomization was stratified by background therapy. In GAUSS-2, randomization was stratified by screening LDL cholesterol level (lower than 4.7 mmol/L or 4.7 mmol/L and higher) and by whether statins were being used at baseline. In LAPLACE-2, the stratification factor was the background therapy group.

Missing values were not imputed when the repeated measures linear effects model was used. For missing LDL cholesterol response (achievement of LDL cholesterol lower than 70 mg/dL), the model considered the patient but not the response. If LDL cholesterol values at either week 10 or 12 were missing, the mean achievement of LDL cholesterol lower than 70 mg/dL at weeks 10 and 12 was defined using the mean of non-missing values at those two time points (if one was missing, the mean equalled the available one).

To adjust for multiplicity for primary and selected secondary end points, the included studies used the same general approach. Testing of each co-end point pair resulted in a single *P* value, and for co-secondary end points, these *P* values were then used in the Hochberg procedure. The following method

was used to preserve the familywise error rate for the co-primary and co-secondary end points for testing within each dose frequency:

1. If the treatment effect from the primary analysis of the co-primary end points was significant at the 0.05 level for both end points, statistical testing of the tier 1 co-secondary end points followed the Hochberg procedure at a significance level of 0.005.
2. If all tier 1 co-secondary end points were significant, the tier 2 co-secondary end points were tested using the Hochberg procedure at a significance level of 0.05.
3. If not all tier 1 co-secondary end points were significant, the tier 2 co-secondary end points were tested using the Hochberg procedure at a significance level of 0.045.

Unless specified otherwise, all other hypothesis testing was two-sided, with a significance level of 0.05.

Sensitivity analyses were as follows:

LAPLACE-2

To evaluate the robustness of the analysis results, sensitivity analyses were performed as follows:

- The primary analysis was repeated on the completer analysis set (CAS).
- Non-parametric analyses (Quade tests) were performed using the CAS.

RUTHERFORD-2

To evaluate the robustness of the analysis results, sensitivity analyses were performed as follows:

- The primary analysis was repeated using the CAS.
- Non-parametric analyses (Quade tests) were performed using the CAS.

DESCARTES

Sensitivity analyses were performed as follows:

- The primary analysis was repeated using the CAS. When the non-completion rate was high, this was an important analysis to evaluate the robustness of treatment effect durability.
- The analysis of covariance (ANCOVA) model was used to assess the effect of evolocumab 420 mg once monthly compared with placebo once monthly. The model included terms for treatment group and stratification factor. The dependent variable in this analysis was the per cent change from baseline at week 52. ANCOVA analyses were performed using two analytical approaches to handling LDL cholesterol missing values:
  - "On-treatment approach": for patients who terminated the study drug early, LDL cholesterol values measured after termination of study drug were censored. Any missing week 52 data after this censoring were imputed using the last observation carried forward (LOCF), carrying forward the last LDL cholesterol value obtained while on study drug.
  - "As-observed" approach: all available week 52 LDL cholesterol values measured on study were used, regardless of study drug status at time of assessment. Missing week 52 data were imputed using LOCF.
- Non-parametric analyses were performed when missing week 52 data were imputed using LOCF.

a) Analysis populations

In all studies, the FAS included all randomized patients who received at least one dose of study drug (either SC or oral). The FAS was used for both efficacy and safety analyses in the DB treatment period. In efficacy analyses, patients were grouped according to their randomized treatment group assignment, regardless of the treatment received. For safety analyses, patients were grouped according to their actual treatment group.

The CAS included patients in the FAS who adhered to the scheduled study drug and statin therapy, and who had observed values for the co-primary end points. The CAS was used in sensitivity analyses of the co-primary end points.

3.3 Patient Disposition

Discontinuations were generally around 10% or less, with similar rates between groups within studies Table 17, Table 18, Table 19, and Table 20). High discontinuation rates were recorded in the placebo every-two-weeks/atorvastatin 80 mg group (22%) and the ezetimibe/placebo every-two-weeks/atorvastatin 10 mg (25%) group in LAPLACE-2. Numerical differences between groups were seen in RUTHERFORD-2, in which both the evolocumab and placebo every-two-weeks groups had higher discontinuation rates (9% and 11%, respectively) than the evolocumab and placebo once-monthly groups (2% in each). The same difference was evident in GAUSS-2: the every-two-weeks groups for both evolocumab and ezetimibe had higher discontinuation rates (9% and 12%, respectively) than the once-monthly regimens of evolocumab and ezetimibe (1% and 2%, respectively). In DESCARTES, the highest discontinuation rates were seen in the evolocumab 420 mg plus diet and the diet alone groups (11% and 13%, respectively).

TABLE 17: PATIENT DISPOSITION — LAPLACE-2

	LAPLACE-2					
	EVO 140 mg q.2w.	**EVO 420 mg q.m.**	**EZE/PLA q.2w.**	**EZE/PLA q.m.**	**PLA q.2w.**	**PLA q.m.**
Screened, N	3,590					
High-intensity, atorvastatin 80 mg: 487 randomized initially, then 47 excluded						
Randomized to atorvastatin	487					
Excluded	47 (4 never received statin, 43 discontinued statin and ended study)					
Randomized, N	110	110	56	54	55	55
Randomized and treated, N (%)	109	110	56	54	55	55
Discontinued study drug, N (%)	12 (11)	10 (9)	5 (9)	7 (13)	12 (22)	5 (9)
Adverse event	6	3	3	1	3	2
Participant request	3	0	0	6	7	0
Other	3	4	0	0	1	3
Sponsor decision	0	2	0	0	0	0
Physician decision	0	1	2	0	0	0
Lost to follow-up	0	0	0	0	1	0
Moderate-intensity, atorvastatin 10 mg						
Randomized to atorvastatin	485					
Excluded	43 (5 never received statin, 38 discontinued statin and ended study)					
Randomized, N	110	110	56	55	56	55
Randomized and treated, N (%)	110	110	56	55	56	54
Discontinued study drug, N (%)	6 (5)	10 (9)	14 (25)	2 (4)	6 (11)	5 (9)
Adverse event	3	5	2	2	2	4
Participant request	2	3	11	0	2	1
Other	1	2	1	0	2	0
High-intensity, rosuvastatin 40 mg						
Randomized to rosuvastatin	366					
Excluded	31 (2 never received statin, 29 discontinued statin and ended study)					
Randomized, N	111	112			56	56

	LAPLACE-2					
	EVO 140 mg q.2w.	**EVO 420 mg q.m.**	**EZE/PLA q.2w.**	**EZE/PLA q.m.**	**PLA q.2w.**	**PLA q.m.**
Randomized and treated, N (%)	111	112			56	55
Discontinued study drug, N (%)	3 (3)	3 (3)			2 (4)	2 (4)
Adverse event	0	1			1	1
Participant request	1	2			0	1
Other	0	0			1	0
Sponsor decision	1	0			0	0
Physician decision	0	0			0	0
Lost to follow-up	1	0			0	0
Moderate-intensity, rosuvastatin 5 mg						
Randomized to rosuvastatin	365					
Excluded	21 (2 never received statin, 19 discontinued statin and ended study)					
Randomized, N	114	115			58	57
Randomized and treated, N (%)	113	115			58	57
Discontinued study drug, N (%)	8 (7)	6 (5)			3 (5)	1 (2)
Adverse event	6	2			1	0
Participant request	2	3			1	0
Other	0	1			0	1
Sponsor decision	0	0			0	0
Physician decision	0	0			0	0
Lost to follow-up	0	0			1	0
Simvastatin 40 mg						
Randomized to simvastatin	364					
Excluded	26 (2 never received statin, 24 discontinued statin and ended study)					
Randomized, N	112	115			56	55
Randomized and treated, N (%)	112	115			56	55
Discontinued study drug, N (%)	3 (3)	3 (3)			3 (5)	4 (7)
Adverse event	2	1			2	1
Participant request	1	1			1	2
Other	0	0			0	0
Sponsor decision	0	0			0	0
Physician decision	0	0			0	1
Lost to follow-up	0	1			0	0
All cohorts combined						
Completed study	526 (94)	550 (98)	104 (93)	108 (99)	263 (94)	275 (99)
Discontinued study	31 (6)	12 (2)	8 (7)	1 (1)	18 (6)	3 (1)
Withdrew consent	11 (2)	10 (2)	5 (5)	1 (1)	10 (4)	3 (1)
Death	0	0	0	0	1 (< 1)	0
Decision by sponsor	18 (3)	0	3 (3)	0	5 (2)	0
Lost to follow-up	2 (< 1)	2 (< 1)	0	0	2 (1)	0

EVO = evolocumab; EZE = ezetimibe; PLA = placebo; q.2w. = every two weeks; q.m. = once monthly.
Source: Clinical Study Report for LAPLACE-2.[7]

TABLE 18: PATIENT DISPOSITION — RUTHERFORD-2

	RUTHERFORD-2			
	EVO 140 mg q.2w.	**EVO 420 mg q.m.**	**PLA q.2w.**	**PLA q.m.**
Screened, N	415			
Randomized, N (%)	111	110	55	55
Randomized and treated, n (%)	110	110	54	55
Discontinued study, N (%)	10 (9)	2 (2)	6 (11)	2 (2)
Withdrew consent	1 (1)	2 (2)	2 (4)	2 (2)
Death	0	0	0	0
Decision by sponsor	9 (8)	0	4 (7)	0
Lost to follow-up	0	0	0	0
Full analysis set, N	110 (99)	110 (100)	54 (98)	55 (100)
Completer analysis set, N	NR	NR	NR	NR

EVO = evolocumab; PLA = placebo; NR = not reported; q.2w. = every two weeks; q.m. = once monthly.
Source: Clinical Study Report for RUTHERFORD-2.[8]

TABLE 19: PATIENT DISPOSITION — DESCARTES

	DESCARTES							
	EVO 420 mg q.m. ATO 10 mg N = 254	**PLA ATO 10 mg N = 129**	**EVO 420 mg q.m. ATO80 N = 145**	**PLA ATO 80 mg N = 73**	**EVO 420 mg q.m. ATO 80 mg + EZE N = 126**	**PLA ATO 80 mg + EZE N = 63**	**EVO 420 mg q.m. + diet N = 74**	**PLA + diet N = 37**
Screened, N	2,120							
Randomized, N	256	129	146	73	126	63	74	38
Randomized and treated, N (%)	254	129	145	73	126	63	74	37
Discontinued study, N (%)	12 (5)	6 (5)	9 (6)	2 (3)	5 (4)	3 (5)	8 (11)	5 (13)
Lost to follow-up	2 (1)	1 (1)	2 (1)	0	2 (2)	0	5 (7)	1 (3)
Withdrew consent	6 (2)	3 (2)	2 (1)	1 (1)	2 (2)	2 (3)	1 (1)	3 (8)
Death	1 (< 1)	0	1 (1)	0	0	0	0	0
Study termination	0	0	0	0	0	0	0	0
Other	3 (1)	2 (2)	4 (3)	1 (1)	1 (1)	1 (2)	2 (3)	1 (3)
ITT, N	NR	NR	NR	NR	NR	NR	NR	NR
Per protocol, N	NR	NR	NR	NR	NR	NR	NR	NR
Safety, N	NR	NR	NR	NR	NR	NR	NR	NR

ATO = atorvastatin; EVO = evolocumab; EZE = ezetimibe; ITT = intention to treat; NR = not reported; PLA = placebo; q.2w. = every two weeks; q.m. = once monthly.
Source: Clinical Study Report for DESCARTES.[9]

TABLE 20: PATIENT DISPOSITION — GAUSS-2

	GAUSS-2			
	EVO 140 mg q.2w.	**EVO 420 mg q.m.**	**EZE 10 mg / PLA q.2w.**	**EZE 10 mg / PLA q.m.**
Screened, N				
Randomized, N (%)	103	102	51	51
Randomized and treated, N (%)	103	102	51	51
Discontinued study, N (%)	9 (9)	1 (1)	6 (12)	1 (2)
Withdrew consent	0	1 (1)	1 (2)	1 (2)
Death	0	0	0	0
Decision by sponsor	8 (8)	0	5 (10)	0
Lost to follow-up	1 (1)	0	0	0
ITT, N	NR	NR	NR	NR
Per protocol, N	NR	NR	NR	NR
Safety, N	NR	NR	NR	NR

EVO = evolocumab; EZE = ezetimibe; ITT = intention to treat; PLA = placebo; NR = not reported; q.2w. = every two weeks; q.m. = once monthly.
Source: Clinical Study Report for GAUSS-2.[10]

3.4 Exposure to Study Treatments

The extent of exposure to study drug was consistent with the treatment duration of the studies; therefore, in the 12-week studies the duration of exposure was approximately 2.7 months, while in the 52-week DESCARTES study the duration of exposure was approximately 12 months. There were no numerical differences in the extent of exposure between groups within studies.

3.5 Critical Appraisal

3.5.1 Internal validity

The included studies were all DB, and patients in control groups were required to administer placebo injections. Training appears to have been provided for injections to increase the likelihood of adequate delivery of drug and reduce risk of injection-site reactions. Adequate measures appear to have been taken during the randomization process to ensure allocation concealment. Injection-site reactions and, more notably, hypersensitivity reactions are a known complication associated with the use of monoclonal antibodies; however, neither was common in the included studies, and therefore this is less likely to have compromised blinding.

The rates of discontinuation of study or of study drug were generally less than 20% across studies. Numerical differences in discontinuation rates were evident in some studies, although there was no clear and consistent pattern of increased withdrawals with evolocumab or its comparators. In GAUSS-2, the rate of discontinuations was lower (1% to 2% of patients) in the evolocumab once-monthly group and corresponding control ezetimibe/placebo once-monthly group when compared with either of the every-two-weeks groups (9% to 12% of patients). This higher discontinuation rate in the every-two-weeks groups, both intervention and control, was also observed in LAPLACE-2 and RUTHERFORD-2. The manufacturer employed a repeated measures analysis for assessment of the co-primary end points (per cent change from baseline in LDL cholesterol) across studies; however, no imputation was employed to account for missing data for these end points. This assumes that any missing values are missing at random, which is not an appropriate assumption to make. The higher the withdrawal rate, such as the rates noted above in the every-two-weeks groups, the lower the confidence in the reported findings. In

its statistical review, the US Food and Drug Administration conducted its own sensitivity analysis, which accounted for this and other missing data, and found the treatment effect to be reduced by between 1% and 3% across studies.[17] Given the large treatment effect seen in each of the studies, this would not be expected to change the overall conclusions regarding the primary end points.

Adjustments for multiplicity were made in order to test of multiple study end points, in a hierarchical approach, employing the Hochberg procedure. However, the LAPLACE-2 study, which featured multiple comparison groups (24 in all), appeared to adjust only for multiple comparisons between groups for the atorvastatin cohorts, and the adjustment appeared to be relatively small, changing the threshold for statistical significance to $P = 0.01$ (comparisons with placebo) or $P = 0.04$ (comparisons with ezetimibe). For the rosuvastatin and simvastatin cohorts, the threshold for statistical significance remained at $P = 0.05$. The other studies also appeared to adjust only for multiplicity with respect to outcomes, rather than comparison groups, although the number of comparison groups in these studies was much smaller than in LAPLACE-2 (either two or four comparison groups, depending on the study).

3.5.2 External validity

The included studies were not designed to assess hard clinical outcomes such as mortality and morbidity; therefore, the evidence supporting the efficacy of evolocumab relative to comparators such as ezetimibe and placebo relies on a surrogate marker, LDL cholesterol. LDL cholesterol is considered to be a well-validated and widely accepted surrogate for this indication.

The baseline characteristics across studies were generally consistent with the population that would be expected to use evolocumab in Canada, according to the clinical expert. There were Canadian sites in the included studies. However, one of the two groups identified in the manufacturer's requested listing criteria, patients with established CHD, made up only a minority of patients at baseline (20% to 30% of patients) in the included studies. No subgroup analyses were performed based on patients with established CHD versus those without. The manufacturer also stated in its listing criteria that patients could be at high risk of CHD. Subgroup analysis was performed based on CHD risk factors, and results were statistically significant regardless of whether evolocumab was used in patients at high or lower risk of CHD. Other high-risk groups included in the CCS guidelines, such as those with diabetes or chronic kidney disease, were not studied in the included trials. Therefore, the efficacy and harms of evolocumab in this population are not known, despite the fact that they may represent groups likely to receive this drug.

With the exception of DESCARTES, which was a 52-week study, the included studies were all 12 weeks in duration, and none of these would be considered adequate follow-up to assess the potential for harms associated with long-term use of evolocumab. In most patients evolocumab will be a long-term therapy, and the identification of harms that are more likely to be associated with long-term therapy, such as neurocognitive events, suggests that there are generalizability issues when assessing harms of evolocumab. The included studies were also not powered to assess harms, and the relatively small sample size within groups (50 to 100 patients in many cases) is unlikely to be large enough to reveal rare safety issues. The exclusion of high-risk patients (with cardiovascular disease, uncontrolled hypertension, or chronic kidney disease) in DESCARTES also limits the assessment of harms in the only study with a follow-up beyond 12 weeks.

The indication for evolocumab states that it is intended for patients who have failed to reach the LDL cholesterol target on maximally tolerated statin therapy. The only one of the four included studies that specifically addressed the issue of statin intolerance was GAUSS-2, which was a relatively small study

(100 patients in each of the evolocumab groups, 50 patients in the corresponding control groups) of only 12 weeks' duration. In the other studies, one could argue that patients could have reached target LDL cholesterol without having reached maximally tolerated statin therapy, and in LAPLACE-2, patients on high-dose rosuvastatin background therapy were at target at the start of the treatment period.

Patients who are statin-intolerant are likely to constitute a large proportion of the target population for evolocumab; however, at present the definition of statin intolerance is wide-ranging and subjective. At the most severe end of the range, statin intolerance is clearly defined by rhabdomyolysis; however, this is a relatively infrequent harm associated with statin therapy. At the other end of the spectrum, myalgia is both the least severe and by far the most common manifestation of statin intolerance but is also the most subjective. In GAUSS-2, which included patients with statin intolerance, approximately 80% of the cases of intolerance at enrolment were defined based on myalgia. According to the clinical expert, statin intolerance is very difficult to assess consistently, and determination of statin intolerance relies heavily on the patient's perception.

According to the clinical expert, lipids would only be tested every six months rather than weekly or monthly, as they were in the included trials.

In LAPLACE-2, ezetimibe was tested as background therapy only when combined with atorvastatin, and not with rosuvastatin or simvastatin. Therefore, the results comparing evolocumab with ezetimibe from LAPLACE-2 are only generalizable when atorvastatin is combined with ezetimibe. At the time of planning for this study, atorvastatin was the only statin that had clinical trial evidence in combination with ezetimibe, according to the clinical expert.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2). See APPENDIX 4: DETAILED OUTCOME DATA for detailed efficacy data.

3.6.1 Mortality

There were few deaths across the studies, with no clear pattern of deaths in any one group.

3.6.2 Morbidity

Adjudicated cardiovascular events were an outcome in the included trials. There were few adjudicated cardiovascular events, affecting no more than 2% of patients in any group, across the included trials, and no clear difference in proportions between groups (Table 21, Table 22, Table 23, Table 24, Table 25, and Table 26).

3.6.3 Change in LDL cholesterol

The per cent change from baseline in LDL cholesterol was the primary outcome of all included studies. In the 12-week studies this was a co-primary outcome, as per cent changes in LDL cholesterol were reported at both week 12 and a mean of weeks 10 and 12 ("weeks 10/12") versus baseline. In the 52-week DESCARTES study, per cent change in LDL cholesterol was reported at 52 weeks.

a) GAUSS-2

In GAUSS-2, the least squares mean (LSM) (95%) per cent reduction in LDL cholesterol was greater for evolocumab than for ezetimibe at weeks 10/12 in both the evolocumab 140 mg (–38.06; 95% confidence interval [CI], –43.73 to –32.39; $P < 0.001$) and evolocumab 420 mg (–37.55; 95% CI, –42.16 to

–32.94; *P* < 0.001) groups, and at week 12 in both the evolocumab 140 mg (–36.90; –42.26 to –31.55; *P* < 0.001) and evolocumab 420 mg groups (–38.69; –43.06 to –34.32; *P* < 0.001) (Table 26).

b) LAPLACE-2

Atorvastatin background (high-intensity)

In LAPLACE-2, for weeks 10/12 data, in those on an atorvastatin 80 mg background, the LSM difference of per cent change for evolocumab 140 mg versus ezetimibe was −44.9 (95% CI, −54.3 to −35.6; *P* < 0.001) and for evolocumab 420 mg versus ezetimibe was −43.8 (95% CI, −52.1 to −35.6; *P* < 0.001) (Table 21). Similar results were seen for the week 12 data, at both the evolocumab 140 mg (–47.20; 95% CI, –57.54 to –36.86; *P* < 0.001) and evolocumab 420 mg doses (–38.88; 95% CI, –48.21 to –29.56; *P* < 0.001) versus ezetimibe (Table 21).

Atorvastatin background (low-intensity)

Similar results for comparisons with ezetimibe were seen for patients on an atorvastatin 10 mg background, at weeks 10/12 for evolocumab 140 mg (−37.5; 95% CI, −43.0 to −32.0; *P* < 0.001) and evolocumab 420 mg (−43.5; 95% CI, −49.7 to −37.3; *P* < 0.001) and at week 12 for evolocumab 140 mg (–39.60; 95% CI, –45.81 to –33.40; *P* < 0.001) and evolocumab 420 mg (–41.10; 95% CI, –47.83 to –34.37; *P* < 0.001)(Table 21). Compared with placebo, statistically significant percentage reductions in LDL cholesterol were reported at both the evolocumab 140 mg and evolocumab 420 mg doses, regardless of background, at both weeks 10/12 and week 12.

Other statins

Similar statistically significant reductions in LDL cholesterol versus placebo were reported in groups on a rosuvastatin (5 mg or 40 mg) or simvastatin (40 mg) background (Table 22).

c) RUTHERFORD-2

In RUTHERFORD-2, at weeks 10/12 the difference from corresponding placebo in LSM per cent change from baseline was –60.2% (95% CI, –65.8 to –54.5; *P* < 0.0001) for the evolocumab 140 mg group and –65.6% (95% CI, –71.3 to –59.8; *P* < 0.0001) for the evolocumab 420 mg group (Table 24). Similar results were also seen at week 12, for both the evolocumab 140 mg group (–59.2%; 95% CI, –65.1 to –53.4; *P* < 0.0001) and the evolocumab 420 mg group (–61.3%; 95% CI, –69.0 to –53.6; *P* < 0.0001) when compared with placebo (Table 24).

d) DESCARTES

In DESCARTES, after 52 weeks there was a statistically significant reduction versus placebo in the LSM (95% CI) per cent change in LDL cholesterol in the evolocumab 420 group (–56.97; 95% CI, –61.08 to –52.85; *P* < 0.001) (Table 25).

Sensitivity analyses

In LAPLACE-2, results of sensitivity analyses of the co-primary end points for per cent change from baseline in LDL cholesterol using the reflexive approach, including the completer analysis and the non-parametric analysis, were consistent and similar in magnitude to the primary efficacy analysis. In RUTHERFORD-2, an additional analysis of the co-primary end points was conducted using only calculated LDL cholesterol concentrations to allow for an informal comparison with the results obtained using the reflexive approach. These results were generally consistent with previous evidence that the use of calculated LDL cholesterol can result in lower values when calculated LDL cholesterol concentrations are lower than 40 mg/dL or triglycerides are high. However, the results were not as pronounced in this study, which may be owing to the high baseline concentrations of LDL cholesterol in this HeFH patient

population. Results of sensitivity analyses of the co-primary end points for per cent change from baseline in LDL cholesterol using the reflexive approach, including the completer analysis and the non-parametric analysis, were consistent and similar in magnitude to the primary efficacy analysis. In DESCARTES, results of the sensitivity analyses for per cent change from baseline in [redacted] LDL cholesterol at week 52 in the completer analysis and the non-parametric analysis were consistent and appeared comparable in magnitude to the primary efficacy analysis, as were results from the sensitivity analyses using an ANCOVA model performed using an on-treatment approach and an as-observed approach. Statistically significant reductions in per cent LDL cholesterol were seen regardless of the method used to measure LDL cholesterol (ultracentrifugation, reflexive or calculated). In GAUSS-2, results of sensitivity analyses of the co-primary end points for per cent change from baseline in LDL cholesterol using the reflexive approach, including the completer analysis and the non-parametric analysis, were consistent and similar in magnitude to the primary efficacy analysis. Statistically significant reductions in per cent LDL cholesterol were seen, regardless of whether a reflexive or calculated approach to measure LDL cholesterol was used.

Subgroup data

In subgroup analysis based on baseline LDL cholesterol value, results for either dose of evolocumab remained statistically significant regardless of baseline LDL cholesterol value across studies and versus either placebo or ezetimibe, and regardless of background therapy in LAPLACE-2. Interaction *P* values were generally greater than 0.05 across studies for this subgroup.

Regardless of the number of baseline CHD risk factors (less than two, or two or more), results for per cent change in LDL cholesterol remained statistically significant for all doses of evolocumab when compared with either ezetimibe or placebo. Interaction *P* values were generally greater than 0.05 in LAPLACE-2, with the exception of the evolocumab 420 mg group versus placebo (atorvastatin 80 mg background) and all comparisons of evolocumab versus placebo on a simvastatin background. In patients on a simvastatin background, the treatment effect versus placebo appeared to be larger in patients with at least two risk factors, compared with those with less than two risk factors (Table 43). In DESCARTES, the interaction *P* value was 0.031, although there was a larger treatment effect versus placebo in patients with less than two risk factors (Table 45). In RUTHERFORD-2 and in GAUSS-2, interaction *P* values were greater than 0.05 (Table 44 and Table 46).

LAPLACE-2 was designed to compare groups based on baseline statin use as part of the primary analysis, and results for all groups receiving evolocumab were statistically significant versus either ezetimibe (atorvastatin groups only) or placebo, regardless of background statin used or statin dose. In DESCARTES, regardless of background therapy (diet alone, diet plus atorvastatin 10 mg or 80 mg, or diet plus atorvastatin 80 mg plus ezetimibe), results for reduction in LDL cholesterol were statistically significant for evolocumab 420 mg versus placebo. The interaction *P* value was greater than 0.05 (Table 45). In GAUSS-2, results were statistically significant for evolocumab versus ezetimibe, regardless of whether statins were used at baseline, and the interaction *P* value was greater than 0.05 (Table 46).

3.6.4 Quality of life

Quality of life was not investigated in any of the included studies.

3.6.5 Other efficacy outcomes

All of the protocol-defined lipid biomarkers identified as other efficacy outcomes for this review were reported in each of the included studies. Apo B, Lp(a), and non-HDL cholesterol were all consistently improved versus either ezetimibe or placebo in each of the included studies, regardless of background therapy. Results for triglycerides and very–low-density–lipoprotein (VLDL) cholesterol were less consistent. In LAPLACE-2, in patients on a rosuvastatin background, both the evolocumab 140 mg and 420 mg doses resulted in statistically significantly improvement versus placebo for both VLDL cholesterol and triglycerides at both weeks 10/12 and week 12 time points. Conversely, for those on an atorvastatin or a simvastatin background, results were statistically significant versus placebo for most, but not all, doses and time points.

Health care resource utilization and vascular imaging were not investigated.

TABLE 21: KEY EFFICACY OUTCOMES — LAPLACE-2

High-Intensity, Atorvastatin 80 mg Background						
LDL-C[a], % Change	**EVO 140 mg q.2w. N = 110**	**EVO 420 mg q.m. N = 110**	**EZE/PLA q.2w. N = 56**	**EZE/PLA q.m. N = 54**	**PLA q.2w. N = 55**	**PLA q.m. N = 55**
Mean (SD) baseline, mmol/L	2.4 (0.9)	2.4 (0.8)	2.6 (0.9)	2.4 (0.5)	2.6 (0.9)	2.5 (0.8)
LSM[b] (SE) % change, weeks 10/12	–61.80 (2.77)	–65.05 (2.42)	–16.85 (3.88)	–21.25 (3.42)	13.12 (3.99)	9.76 (3.39)
Treatment difference (95% CI)	**Versus EZE** **EVO 140 mg vs. EZE/PLAq.2w.:** −44.9 (−54.3 to −35.6), *P* < 0.001 **EVO 420 mg vs. EZE/PLA q.m.:** −43.8 (−52.1 to −35.6), *P* < 0.001			**Versus placebo** **EVO 140 mg vs. PLA q.2w.:** −74.9 (−84.5 to −65.4), *P* < 0.001 **EVO 420 mg vs. PLA q.m.:** −74.8 (−83.0 to −66.6), *P* < 0.001		
	EVO 140 mg vs. EVO 420 mg: –3.25 (–10.48 to 3.97), *P* = NR					
LSM[b] (SE) % change, week 12	–61.80 (3.04)	–58.68 (2.74)	–14.60 (4.29)	–19.80 (3.85)	14.49 (4.42)	11.83 (3.85)
Treatment difference (95% CI)	**Versus EZE** **EVO 140 mg vs. EZE/PLA q.2w.:** –47.20 (–57.54 to –36.86), *P* < 0.001 **EVO 420 mg vs. EZE/PLA q.m.:** –38.88 (–48.21 to –29.56), *P* < 0.001			**Versus placebo** **EVO 140 mg vs. PLA q.2w.:** –76.29 (–86.87 to –65.72), *P* < 0.001 **EVO 420 mg vs. PLA q.m.:** –70.51 (–79.81 to –61.20), *P* < 0.001		
	EVO 140 mg vs. EVO 420 mg: 3.13 (–4.92 to 11.18) *P* = NR					
Patients with LDL-C < 1.8mmol/L at mean of weeks 10 and 12, % (95% CI)	94.4 (88.4 to 97.4)	92.5 (85.9 to 96.2)	50.9 (38.1 to 63.6)	62.3 (48.8 to 74.1)	13.7 (6.8 to 25.7)	9.3 (4.0 to 19.9)
Moderate-Intensity, Atorvastatin 10 mg Background						
LDL-C[a], % Change	**N = 110**	**N = 110**	**N = 56**	**N = 55**	**N = 56**	**N = 55**
Mean (SD) baseline, mmol/L	3.2 (1.1)	3.3 (1.3)	3.3 (1.3)	3.1 (0.7)	3.2 (1.2)	3.2 (1.2)
LSM[b] (SE) % change, weeks 10/12	–61.41 (1.61)	–62.47 (1.83)	–23.88 (2.34)	–18.98 (2.57)	8.54 (2.24)	0.35 (2.60)

Moderate-Intensity, Atorvastatin 10 mg Background						
Treatment difference (95% CI)	**Versus EZE** **EVO 140 mg vs. EZE/PLA q.2w.:** −37.5 (−43.0 to −32.0), *P* < 0.001 **EVO 420 mg vs. EZE/PLA q.m.:** −43.5 (−49.7 to −37.3), *P* < 0.001			**Versus placebo** **EVO 140 mg vs. PLA q.2w.:** −70.0 (−75.4 to −64.5), *P* < 0.001 **EVO 420 mg vs. PLA q.m.:** −62.8 (−69.1 to −56.6), *P* < 0.001		
	EVO 140 mg vs. EVO 420 mg: –1.06 (–5.84 to 3.72), *P* = NR					
LSM[b] (SE) % change, week 12	–64.56 (1.90)	–60.05 (2.04)	–20.92 (2.78)	–17.05 (2.87)	9.86 (2.65)	1.03 (2.89)
Treatment difference (95% CI)	**Versus EZE** **EVO 140 mg vs. EZE/PLA q.2w.:** –39.60 (–45.81 to –33.40), *P* < 0.001 **EVO 420 mg vs. EZE/PLA q.m.:** –41.10 (–47.83 to –34.37), *P* < 0.001			**Versus placebo** **EVO 140 mg vs. PLA q.2w.:** –71.42 (–77.55 to –65.29), *P* < 0.001 **EVO 420 mg vs. PLA q.m.:** –59.16 (–65.94 to –52.38), *P* < 0.001		
	EVO 140 mg vs. EVO 420 mg: 3.38 (–1.91 to 8.66) *P* = NR					
Patients with LDL-C < 1.8mmol/L at mean of weeks 10 and 12, % (95% CI)	88.1 (80.7 to 92.9)	85.8 (78.0 to 91.2)	20.0 (11.2 to 33.0)	16.7 (9.0 to 28.7)	5.7 (1.9 to 15.4)	5.6 (1.9 to 15.1)
Pooled Atorvastatin Groups						
Mortality						
Deaths, N (%)	0	0	0	0	0	0
Morbidity						
Adjudicated CV event, n (%)	2 (1)	1 (1)	0	2 (2)	0	0
Quality of life						
Not investigated						

CI = confidence interval; CV = cardiovascular; EVO = evolocumab; EZE = ezetimibe; LDL-C = low-density–lipoprotein cholesterol; LSM = least squares mean; PLA = placebo; q.2w. = every two weeks; q.m. = once monthly; SD = standard deviation; SE = standard error; vs. = versus.

[a] When the calculated LDL-C is < 40 mg/dL or triglycerides are > 400 mg/dL, calculated LDL-C will be replaced with ultracentrifugation LDL-C from the same blood sample, if available.

[b] LSM is from the repeated measures model, which includes treatment group, stratification factor (from IVRS), scheduled visit, and the interaction of treatment with scheduled visit as covariates.

[c] In the pooled analysis there was one death in a placebo (every-two-weeks) group, rosuvastatin 40 mg background.

[d] Adjudicated CV events reported only for pooled atorvastatin groups.

Source: Clinical Study Report for LAPLACE-2.[7]

TABLE 22: KEY EFFICACY OUTCOMES — LAPLACE-2, CONTINUED

High-intensity, rosuvastatin 40 mg				
LDL-C[a], % Change	**EVO 140 mg q.2w. N = 111**	**EVO 420 mg q.m. N = 112**	**PLA q.2w. N = 56**	**PLA q.m. N = 55**
Mean (SD) baseline, mmol/L	2.3 (0.8)	2.3 (0.8)	2.0 (0.5)	2.7 (1.3)
LSM[b] (SE) % change, weeks 10/12	–59.08 (2.23)	–62.94 (2.44)	6.57 (3.11)	–0.02 (3.51)
Treatment difference versus placebo (95% CI)	**EVO 140 mg vs. PLA q.2w.:** −65.7 (−73.2 to −58.1), *P* < 0.001 **EVO 420 mg vs. PLA q.m.:** −62.9 (−71.4 to −54.5), *P* < 0.001			
	EVO 140 mg vs. EVO 420 mg: –3.85 (–10.36 to 2.66), *P* = NR			
LSM[b] % (SE) change, week 12	–58.89 (2.58)	–52.40 (2.98)	9.42 (3.60)	2.59 (4.30)
Treatment difference versus placebo (95% CI)	**EVO 140 mg vs. PLA q.2w.:** –68.31 (–77.04 to –59.57), *P* < 0.001 **EVO 420 mg vs. PLA q.m.:** –54.98 (–65.31 to –44.65), *P* < 0.001			
	EVO 140 mg vs. EVO 420 mg: 6.49 (–1.27 to 14.26), *P* = NR			
Patients with LDL-C < 1.8mmol/L at mean of weeks 10 and 12, % (95% CI)	93.5 (87.1 to 96.8)	94.5 (88.6 to 97.5)	38.9 (27.0 to 52.2)	28.8 (18.3 to 42.3)
Moderate-intensity, rosuvastatin 5 mg				
LDL-C[a], % Change	**N = 111**	**N = 112**	**N = 56**	**N = 55**
Mean (SD) baseline, mmol/L	3.1 (1.1)	3.2 (1.1)	3.0 (1.0)	3.1 (1.0)
LSM[b] (SE) % change, weeks 10/12	–59.33 (1.74)	–63.79 (1.76)	7.55 (2.39)	2.79 (2.50)
Treatment difference versus placebo (95% CI)	**EVO 140 mg vs. PLA q.2w.:** −66.9 (−72.7 to −61.1), *P* < 0.001 **EVO 420 mg vs. PLA q.m.:** −66.6 (−72.6 to −60.6), *P* < 0.001			
	EVO 140 mg vs. EVO 420 mg: –4.46 (–9.32 to 0.41), *P* = NR			
LSM[b] % (SE) change, week 12	–60.09 (1.94)	–59.40 (1.87)	8.12 (2.68)	5.10 (2.62)
Treatment difference versus placebo (95% CI)	**EVO 140 mg vs. PLA q.2w.:** –68.21 (–74.72 to –61.70), *P* < 0.001 **EVO 420 mg vs. PLA q.m.:** –64.49 (–70.84 to –58.14), *P* < 0.001			
	EVO 140 mg vs. EVO 420 mg: 0.70 (–4.61 to 6.00), *P* = NR			
Patients with LDL-C < 1.8 mmol/L at mean of weeks 10 and 12, % (95% CI)	88.7 (81.2 to 93.4)	89.9 (82.8 to 94.3)	7.0 (2.8 to 16.7)	5.3 (1.8 to 14.4)
Moderate-intensity, simvastatin 40 mg				
LDL-C[a], % Change	**N = 111**	**N = 112**	**N = 56**	**N = 55**
Mean (SD) baseline, mmol/L	3.0 (0.9)	3.2 (1.3)	2.9 (0.7)	2.8 (0.8)
LSM[b] (SE) % change, weeks 10/12	–66.17 (2.93)	–62.45 (3.85)	3.26 (3.40)	6.00 (4.80)
Treatment difference versus placebo (95% CI)	**EVO 140 mg vs. PLA q.2w.:** −69.4 (−74.9 to −64.0), *P* < 0.001 **EVO 420 mg vs. PLA q.m.:** −68.5 (−76.7 to −60.2), *P* < 0.001			
	EVO 140 mg vs. EVO 420 mg: 3.72 (–5.79 to 13.23), *P* = NR			
LSM[b] % (SE) change, week 12	–65.86 (3.05)	–57.02 (3.93)	4.70 (3.61)	3.40 (4.94)
Treatment difference versus placebo (95% CI)	**EVO 140 mg vs. PLA q.2w.:** –70.56 (–76.72 to –64.41), *P* < 0.001 **EVO 420 mg vs. PLA q.m.:** –60.41 (–69.11 to –51.72), *P* < 0.001			
	EVO 140 mg vs. EVO 420 mg: 8.84 (–0.93 to 18.62), *P* = NR			
Patients with LDL-C < 1.8 mmol/L at mean of weeks 10 and 12, % (95% CI)	93.6 (87.3 to 96.9)	88.5 (81.3 to 93.2)	1.9 (0.3 to 9.8)	3.9 (1.1 to 13.2)

CI = confidence interval; EVO = evolocumab; LDL-C = low-density–lipoprotein cholesterol; LSM = least squares mean; NR = not reported; PLA = placebo; q.2w. = every two weeks; q.m. = once monthly; SD = standard deviation; SE = standard error; vs. = versus.

[a] When the calculated LDL-C is < 40 mg/dL or triglycerides are > 400 mg/dL, calculated LDL-C will be replaced with ultracentrifugation LDL-C from the same blood sample, if available.

[b] LSM is from the repeated measures model, which includes treatment group, stratification factor (from IVRS), scheduled visit, and the interaction of treatment with scheduled visit as covariates.

Source: Clinical Study Report for LAPLACE-2.[7]

TABLE 23: KEY EFFICACY OUTCOMES — LAPLACE-2, COMBINED STATIN ANALYSIS

	LAPLACE-2		LAPLACE-2	
LDL-C[a], % Change	**EVO 140 mg q.2w.**	**PLA 2 weeks**	**EVO 420 mg q.m.**	**PLA q.m.**
Treatment difference versus placebo (95% CI), week 10/12	–69.22 (–72.19 to –66.25), *P* < 0.001		–67.33 (–70.68 to –63.98), *P* < 0.001	
Treatment difference versus placebo (95% CI), week 12	–70.79 (–74.13 to –67.44), *P* < 0.001		–62.18 (–65.93 to –58.43), *P* < 0.001	

CI = confidence interval; EVO = evolocumab; EZE = ezetimibe; LDL-C = low-density–lipoprotein cholesterol.
[a] When the calculated LDL-C is < 40 mg/dL or triglycerides are > 400 mg/dL, calculated LDL-C will be replaced with ultracentrifugation LDL-C from the same blood sample, if available.
Source: Clinical Study Report for LAPLACE-2.[7]

TABLE 24: KEY EFFICACY OUTCOMES — RUTHERFORD-2

	RUTHERFORD-2			
LDL-C[a], % Change	**EVO 140 mg q.2w. N = 110**	**EVO 420 mg q.m. N = 110**	**PLA q.2w. N = 54**	**PLA q.m. N = 55**
Mean (SD) baseline, mmol/L	4.18 (1.32)	3.98 (1.12)	3.91 (0.95)	3.93 (1.10)
LSM[b] % change, week 12	–61.3 (–64.7 to –57.8)	–55.7 (–60.2 to –51.3)	–2.0 (–6.9 to 2.9)	5.5 (–0.9 to 12.0)
Treatment difference (95% CI)	**EVO 140 mg vs. PLA q.2w.:** –59.2% (–65.1 to –53.4), *P* < 0.0001 **EVO 420 mg vs. PLA q.m.:** –61.3% (–69.0 to –53.6), *P* < 0.0001			
	EVO 140 mg vs. EVO 420 mg: 5.51 (–0.12, 11.14), *P* = NR			
LSM[b] (95% CI) % change, (weeks 10 and 12)	–61.2 (–64.6 to –57.9)	–63.3 (–66.6 to –59.9)	–1.1 (–5.8 to 3.7)	2.3 (–2.5 to 7.1)
Treatment difference (95% CI)	**EVO 140 mg vs. PLA q.2w.:** –60.2% (–65.8 to –54.5), *P* < 0.0001 **EVO 420 mg vs. PLA q.m.:** –65.6% (–71.3 to –59.8), *P* < 0.0001			
	EVO 140 mg vs. EVO 420 mg: –2.02 (–6.77, 2.73), *P* = NR			
Mortality, N				
N (%)	0	0	0	0
Morbidity				
Cardiovascular events, N (%)	2	1	0	0
Reasons	MI (non-fatal) Surgical coronary revascularization	PCI		
Quality of Life				
Not investigated				

CI = confidence interval; EVO = evolocumab; LSM = least squares mean; MI = myocardial infarction; NR = not reported; PCI = percutaneous coronary intervention; q.2w. = every two weeks; q.m. = once monthly; SD = standard deviation; vs. = versus.
[a] The primary efficacy analysis used a reflexive approach, in which the calculated LDL-C was employed unless the calculated LDL-C was < 1.0 mmol/L) or triglycerides were > 4.5 mmol/L, in which case UC LDL-C was determined and used.
[b] LSM is from the repeated measures model, which includes treatment group, stratification factors (from IVRS), scheduled visit, and the interaction of treatment with scheduled visit as covariates.
Source: Clinical Study Report for RUTHERFORD-2.[8]

TABLE 25: KEY EFFICACY OUTCOMES — DESCARTES

	DESCARTES	
LDL-C[a], % Change	**EVO 420 mg q.m. N = 599**	**PLA q.m. N = 302**
Mean (SD) baseline, mmol/L	2.7 (0.6)	2.7 (0.6)
LSM[b] (SE) % change, week 52	–50.14% (1.24)	6.83% (1.75)
Treatment difference (95% CI)	–56.97 (–61.08 to –52.85), *P* < 0.001	
Mortality		
Deaths	2	0
	Cardiac failure MI	
Morbidity		
Patients, n (%)	6 (1)	2 (1)
Quality of Life		
Not investigated		

CI = confidence interval; EVO = evolocumab; LDL-C = low-density–lipoprotein cholesterol; LSM = least squares mean; q.m. = once monthly; SD = standard deviation; SE = standard error.
[a] Ultracentrifugation LDL-C.
[b] LSM is from the repeated measures model, which includes treatment group, stratification factor(s) (from IVRS), scheduled visit, and the interaction of treatment with scheduled visit as covariates.
Source: Clinical Study Report for DESCARTES.[9]

TABLE 26: KEY EFFICACY OUTCOMES — GAUSS-2

	GAUSS-2			
LDL-C[a], % Change	**EVO 140 mg q.2w. N = 103**	**EVO 420 mg q.m. N = 102**	**EZE/ PLA q.2w. N = 51**	**EZE/PLA q.m. N = 51**
Mean (SD) baseline, mmol/L	4.97 (1.48)	4.98 (1.58)	5.04 (1.65)	5.06 (1.34)
LSM[b] (SE), week 12	–56.14 (1.91)	–52.60 (1.58)	–18.08 (2.52)	–15.05 (2.13)
Treatment difference (95% CI)[b]	**EVO 140 mg vs. EZE/PLA q.2w.:** –38.06 (–43.73 to –32.39), *P* < 0.001 **EVO 420 mg vs. EZE/PLA q.m.:** –37.55 (–42.16 to –32.94), *P* < 0.001			
	EVO 140 mg vs. EVO 420 mg: 3.54 (–1.34 to 8.42)			
LSM[b] (SE), weeks 10/12	–56.11 (1.83)	–55.31 (1.53)	–19.21 (2.40)	–16.62 (2.03)
Treatment difference (95% CI)[b]	**EVO 140 mg vs. EZE/PLA q.2w.:** –36.90 (–42.26 to –31.55), *P* < 0.001 **EVO 420 mg vs. EZE/PLA q.m.:** –38.69 (–43.06 to –34.32), *P* < 0.001			
	EVO 140 mg vs. EVO 420 mg: 0.80 (–3.90 to 5.49)			
Mortality, N				
N (%)	0	0	0	0
Morbidity				
Cardiovascular events, N (%)	0	0	0	0
Quality of Life				
Not investigated				

CI = confidence interval; EVO = evolocumab; EZE = ezetimibe; LDL-C = low-density–lipoprotein cholesterol; LSM = least squares mean; PLA = placebo; q.2w. = every two weeks; q.m. = once monthly; SD = standard deviation; SE = standard error.
[a] When the calculated LDL-C is < 40 mg/dL, or triglycerides are > 400 mg/dL, calculated LDL-C will be replaced with ultracentrifugation LDL-C from the same blood sample, if available.
[b] LSM is from the repeated measures model, which includes treatment group, stratification factors (from IVRS), scheduled visit, and the interaction of treatment with scheduled visit as covariates.
Source: Clinical Study Report for GAUSS-2.[10]

3.7 Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol). See APPENDIX 4: DETAILED OUTCOME DATA for detailed harms data.

3.7.1 Adverse events

In the 12-week studies, the proportion of patients experiencing an adverse event (AE) was highest in GAUSS-2 (range of 61% to 77% between groups) and lowest in LAPLACE-2 (35% to 43%) (Table 27, Table 28, and Table 30). In DESCARTES, with a 52-week treatment period, 75% of patients experienced an AE (Table 29).

None of the included studies were designed to assess harms; therefore, no formal statistical comparisons were reported. With respect to between-group differences within studies, the largest numerical differences between evolocumab and placebo groups were noted in RUTHERFORD-2, in which 43% of patients had an AE in the placebo every-two-weeks group, which was numerically lower than in the evolocumab 140 mg (55% of patients), the evolocumab 420 mg (57%), and the placebo monthly (55%) groups (Table 28). The largest numerical differences between evolocumab and ezetimibe were in GAUSS-2, in which 77% of patients had an AE in the placebo monthly/ezetimibe group, which was numerically higher than the evolocumab 140 mg group (61%), as well as the evolocumab 420 mg group (71%) and placebo every-two-weeks/ezetimibe group (69%) (Table 30). The study with the longest treatment period, DESCARTES, had the smallest difference between groups with respect to AEs, occurring in 75% of patients in the evolocumab 420 mg group and 74% of patients in the matching placebo group (Table 29). In LAPLACE-2, AE data were reported only for patients on an atorvastatin background, and the largest numerical difference between groups was a low of 35% of patients reporting an AE in the evolocumab 420 mg group and a high of 43% of patients reporting an AE in the placebo every-two-weeks/ezetimibe group.

The most common AEs reported across studies were nasopharyngitis, upper respiratory tract infection, influenza, myalgia, and headache, with no clear or consistent numerical differences between groups.

3.7.2 Serious adverse events

There were few serious adverse events (SAEs) across the studies. In the 12-week studies, the proportions ranged from 1% to 6% (Table 27, Table 28, and Table 30), and in the 52-week DESCARTES study, the proportion was 6% with evolocumab 420 mg and 4% with matching placebo (Table 29). The largest numerical difference in the proportion of patients with SAEs was in GAUSS-2, with a low of 1% in the evolocumab 420 mg group and a high of 6% in the placebo monthly/ezetimibe group (Table 30).

3.7.3 Withdrawals due to adverse events

There were very few (less than 5% of patients in any one group) discontinuations of study drug due to adverse events in LAPLACE-2 (only atorvastatin cohorts reported), RUTHERFORD-2, and DESCARTES, and there were no clear and consistent numerical differences between groups (Table 27, Table 28, and Table 29). In GAUSS-2, the proportion of patients discontinuing the study drug due to an AE was higher overall than in the other studies (approximately 11% of patients), and there were numerical differences in the proportion of patients discontinuing the study drug between groups (Table 30). The highest proportion of patients discontinuing was in the placebo monthly/ezetimibe group (18%), and the lowest percentage was in the evolocumab 140 mg group (6%). The most common reason for discontinuation across groups was myalgia, and this was highest in the placebo monthly/ezetimibe group (6%). GAUSS-2 was the study that included patients who had previous issues with statin intolerance, and approximately one-third of patients in this study continued to take statins; therefore, it is not clear whether the higher

discontinuation rate, or numerical differences between groups for discontinuations, were due to the background statin rather than the intervention.

3.7.4 Notable harms

The proportion of patients experiencing notable harms was small, with no clear and consistent numerical differences in risk between groups across studies. The largest numerical differences between groups within studies with respect to notable harms were in GAUSS-2, in which potential injection-site reactions occurred in 14% of patients in the placebo monthly/ezetimibe group versus 2% or 3% in each of the other groups (Table 30). Potential muscle-related AEs were also numerically higher in the placebo monthly/ezetimibe group (29%) when compared with the other groups (12% to 16% of patients across groups).

TABLE 27: HARMS — LAPLACE-2 ATORVASTATIN COHORTS

	LAPLACE-2					
AEs	**EVO 140 mg q.2w. N = 219**	**EVO 420 mg q.m. N = 220**	**EZE/ PLA q.2w. N = 112**	**EZE/PLA q.m. N = 109**	**PLA q.2w. N = 111**	**PLA q.m. N = 110**
Patients with > 0 AEs, N (%)	85 (39)	77 (35)	48 (43)	41 (38)	45 (41)	40 (36)
Most common AEs						
Myalgia	1 (1)	3 (1)	3 (3)	1 (1)	2 (2)	6 (6)
SAEs						
Patients with > 0 SAEs, N (%)	7 (3)	3 (1)	1 (1)	1 (1)	3 (3)	3 (3)
WDAEs						
WDAEs, N (%)	6 (3)	4 (2)	3 (3)	1 (1)	2 (2)	4 (4)
Notable harms (all cohorts)						
Injection-site reactions (potential)	4 (1)	11 (2)	NR	NR	2 (1)	6 (2)
Muscle-related AE (potential)	0	0	NR	NR	0	0
Neurocognitive AE						
Development of anti-EVO Ab	0	1	NR	NR	NR	NR
Creatine kinase > 5 × ULN (any post-baseline value)	0	1 (< 1)	0	0	1 (< 1)	1 (< 1)
Transaminase elevations and potential hepatic disorders	[redacted]	[redacted]			[redacted]	[redacted]
Potential hepatitis C	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Potential hypersensitivity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Potential diabetes events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Exposure, mean (SD) months						

Ab = antibody; AE = adverse event; EVO = evolocumab; EZE = ezetimibe; NR = not reported; PLA = placebo; q.2w. = every two weeks; q.m. = once monthly; SAE = serious adverse event; SD = standard deviation; ULN = upper limit of normal; WDAE = withdrawal due to adverse event.
Source: Clinical Study Report for LAPLACE-2.[7]

TABLE 28: HARMS — RUTHERFORD-2

	RUTHERFORD-2			
AEs	**EVO 140 mg q.2w. N = 110**	**EVO 420 mg q.m. N = 110**	**PLA q.2w. N = 54**	**PLA q.m. N = 55**
Patients with > 0 AEs, N (%)	61 (55)	63 (57)	23 (43)	30 (55)
Most common AEs				
Nasopharyngitis	8 (7)	11 (10)	2 (4)	3 (5)
Headache	4 (4)	5 (5)	1 (2)	3 (5)
Confusion	5 (5)	4 (4)	0	1 (2)
Back pain	2 (2)	6 (5)	0	1 (2)
Nausea	5 (5)	3 (3)	0	1 (2)
SAEs[a]				
Patients with > 0 SAEs, N (%)	3 (3)	4 (4)	2 (4)	3 (5)
WDAEs				
WDAEs, N (%)	0	0	0	0
NOTABLE HARMS				
Injection-site reactions	5 (5)	8 (7)	2 (4)	2 (4)
Muscle-related AE	8 (7)	2 (2)	0	1 (2)
Adjudicated CV events	2 (2)	1 (1)	0	0
Neurocognitive AE	0	0	0	0
Hepatitis C	[redacted]	[redacted]	[redacted]	[redacted]
Development of anti-EVO Ab	0	0	NA	NA
ALT or AST > 3 × ULN (any post-baseline value)	0	0	0	0
Creatine kinase > 5 × ULN (any post-baseline value)	0	0	0	2 (4)
Exposure, mean (SD) months	2.78 (0.19)	2.74 (0.29)	2.77 (0.27)	2.75 (0.17)

Ab = antibody; AE = adverse event; CV = cardiovascular; EVO = evolocumab; EZE = ezetimibe; LDL-C = low density lipoprotein cholesterol; NA = not applicable; PLA = placebo; q.2w. = every two weeks; q.m. = once monthly; SAE = serious adverse event; SD = standard deviation; ULN = upper limit of normal; WDAE = withdrawal due to adverse event.
[a] There were no SAEs that occurred in more than two patients.
Source: Clinical Study Report for RUTHERFORD-2.[8]

TABLE 29: HARMS — DESCARTES

	DESCARTES	
AEs	**EVO 420 mg q.m. N = 599**	**PLA q.m. N = 302**
Patients with > 0 AEs, N (%)	448 (75)	224 (74)
Most common AEs		
Upper respiratory tract infection	56 (9)	19 (6)
Influenza	45 (8)	19 (6)
SAEs		
Patients with > 0 SAEs, N (%)	33 (6)	13 (4)
Most common SAEs	None in ≥ 1% of patients	None in ≥ 1% of patients
WDAEs		
WDAEs, N (%)	13 (2)	3 (1)
Notable harms		

	DESCARTES	
AEs	**EVO 420 mg q.m. N = 599**	**PLA q.m. N = 302**
Injection-site reactions (potential)	34 (6)	15 (5)
Muscle-related AE (potential)	0	0
Neurocognitive AE	NR	NR
Development of anti-EVO Ab		
Creatine kinase > 5 × ULN (any post-baseline value)	NR	NR
Transaminase elevations and potential hepatic disorders	[redacted]	[redacted]
Potential hepatitis C	[redacted]	[redacted]
Potential hypersensitivity	[redacted]	[redacted]
Exposure, mean (SD) months	11.8 (2.9)	12.1 (2.6)

Ab = antibody; AE = adverse event; EVO = evolocumab; NR = not reported; PLA = placebo; q.m. = once monthly; SAE = serious adverse event; SD = standard deviation; ULN = upper limit of normal; WDAE = withdrawal due to adverse event.
Source: Clinical Study Report for DESCARTES.[9]

TABLE 30: HARMS — GAUSS-2

	GAUSS-2			
	EVO 140 mg q.2w. N = 103	**EVO 420 mg q.m. N = 102**	**EZE/ PLA q.2w. N = 51**	**EZE/PLA q.m. N = 51**
AEs				
Patients with > 0 AEs, N (%)	63 (61)	72 (71)	35 (69)	39 (77)
Most common AEs				
Myalgia	7 (7)	9 (9)	7 (14)	11 (22)
Headache	4 (4)	12 (12)	3 (6)	6 (12)
Pain in extremity	2 (2)	12 (12)	0	1 (2)
Fatigue	3 (3)	6 (6)	4 (8)	6 (12)
Nausea	3 (3)	6 (6)	2 (4)	5 (10)
SAEs				
Patients with > 0 SAEs, N (%)	5 (5)	1 (1)	1 (2)	3 (6)
Most common SAEs	None in > 1 patient	None in > 1 patient	None in > 1 patient	None in > 1 patient
WDAEs				
WDAEs, N (%)	6 (6)	11 (11)	4 (8)	9 (18)
Notable harms				
Injection-site reactions (potential)	3 (3)	3 (3)	1 (2)	7 (14)
Hypersensitivity reactions (potential)	[redacted]	[redacted]	[redacted]	[redacted]
Muscle-related AE	0	0	0	0
Muscle-related AE (potential)	13 (13)	12 (12)	8 (16)	15 (29)
Neurocognitive AE	NR	NR	NR	NR
Development of anti-EVO Ab	0	0	0	0
Liver function test abnormal	2 (2)	0	0	0
Hepatic enzyme increased	[redacted]	[redacted]	[redacted]	[redacted]
Creatine kinase > 5 × ULN (any post-baseline value)	0	2 (2)	3 (6)	0

	GAUSS-2			
	EVO 140 mg q.2w. N = 103	**EVO 420 mg q.m. N = 102**	**EZE/ PLA q.2w. N = 51**	**EZE/PLA q.m. N = 51**
Hepatitis C (potential)	[redacted]	[redacted]	[redacted]	[redacted]
Exposure, mean (SD) months	2.72 (0.39)	2.74 (0.19)	2.70 (0.41)	2.69 (0.38)

AE = adverse event; EVO = evolocumab; EZE = ezetimibe; NR = not reported; PLA = placebo; q.2w. = every two weeks; q.m. = once monthly; SAE = serious adverse event; SD = standard deviation; ULN = upper limit of normal; WDAE = withdrawal due to adverse event.
Source: Clinical Study Report for GAUSS-2.[10]

4. DISCUSSION

4.1 Summary of Available Evidence

Four DB RCTs met the inclusion criteria for this review; three of the studies had a 12-week treatment duration and one study (DESCARTES) had a 52-week treatment duration. LAPLACE-2 randomized patients on a stable statin regimen (atorvastatin 10 mg or 80 mg, rosuvastatin 5 mg or 40 mg, or simvastatin 40 mg daily) to either evolocumab 140 mg every two weeks or evolocumab 420 mg once monthly, or matching placebo, or matching placebo plus ezetimibe 10 mg daily (atorvastatin groups only). RUTHERFORD-2 compared the two regimens of evolocumab with matching placebo in patients with HeFH stabilized on a lipid regimen, and DESCARTES compared the evolocumab 420 mg monthly regimen with placebo over 52 weeks, in patients on a background of either diet alone, diet plus atorvastatin 10 mg or 80 mg daily, or diet plus ezetimibe or atorvastatin 80 mg daily. Finally, GAUSS-2 enrolled patients who were unable to tolerate statins or had reached the maximum tolerated statin dose, and compared the two evolocumab dose regimens with matching placebo plus ezetimibe 10 mg daily.

In all studies, regardless of background therapy, both doses of evolocumab were statistically significantly superior to placebo or ezetimibe for the primary outcome of per cent change from baseline in LDL cholesterol. The statistically significant superiority versus placebo and ezetimibe was consistent across subgroups based on concomitant use of statins, baseline LDL cholesterol, or number of cardiovascular risk factors. Few deaths and few cardiovascular events occurred across studies; therefore, no clear or consistent differences were found between evolocumab and placebo or ezetimibe for these outcomes. Quality of life was not investigated. Among other efficacy outcomes, three lipid biomarkers — apo B, Lp(a), and non-HDL cholesterol — were consistently improved to a statistically significant extent versus placebo or ezetimibe; however, triglycerides and VLDL cholesterol were not as consistently improved versus placebo or ezetimibe. Health care resource utilization and vascular imaging were not investigated. There were no consistent differences in overall AEs, or SAEs, although the included studies were not powered to assess harms outcomes. Among notable harms, such as injection-site and hypersensitivity reactions, muscle-related events, diabetes, and neurocognitive events, there were no clear and consistent differences between evolocumab groups and either ezetimibe or placebo.

4.2 Interpretation of Results

4.2.1 Efficacy

The indication for evolocumab includes patients who require further LDL cholesterol lowering despite maximally tolerated statin therapy. Statin intolerance can manifest in a wide spectrum, from patients with clearly defined intolerance such as rhabdomyolysis to patients with more subjective intolerance defined by myalgia.[18] The GAUSS-2 study was designed to assess evolocumab use in a population of

patients with statin intolerance, and in this study the majority of patients (approximately 80%) had intolerance defined by myalgia. Although evolocumab demonstrated statistically and clinically significant superiority over ezetimibe in this study, it is not clear how many patients will be candidates for evolocumab in real-world clinical practice. Myalgia has no biomarker associated with it; therefore, this population will likely be defined by the patient, with assistance from his or her health care provider. The reported proportion of patients with statin intolerance in clinical practice varies depending on the setting in which it is studied, but it is likely that statin intolerance in actual use is higher than that reported in clinical trials, possibly as high as 20%.[19,20] There is also the issue of how many statins should be attempted before a patient is declared intolerant, and the indication, as stated, does not appear to address this. The European Atherosclerosis Society Consensus Panel guideline calls for repeated trials of statins (generally three statins) before intolerance is declared.[21] Findings from a recent retrospective database study reinforced the importance of statin re-challenge, finding that, of the 10% of patients reporting statin intolerance, 90% were able to tolerate another statin, or even the same statin, upon re-challenge.[20] It appears clear across the included studies that evolocumab, added to statin therapy, represents a clear advantage over statin therapy alone, regardless of the intensity of the statin regimen being used; therefore, there will likely be a temptation to use the drug based on its efficacy alone, regardless of whether patients are truly unable to tolerate a further increase in their statin dose. While the fact that it must be administered by injection may be a deterrent to the use of evolocumab, this may at least be partially offset by the fact that it does not require daily administration, which is a limitation of currently available therapies identified in patient input to CDR.

In addition to the difficulty in defining "maximally tolerated" statin therapy, another aspect of the indication that is open to interpretation is "clinical atherosclerotic disease." It is not clear whether this means patients who have had a cardiovascular event, or whether it is defined based on risk scores. Only a minority (less than 35% in most studies) of patients across the included studies were defined as having "established cardiovascular disease" at baseline, and no subgroup analyses of this population were planned. Therefore, if this is one of the target populations for evolocumab, the efficacy and harms of evolocumab are not known for these patients. A clinical expert consulted by CDR stated that he or she would consider "clinical atherosclerotic cardiovascular disease" as patients who have had a previous cardiovascular event.

The lack of data for hard clinical end points such as mortality and morbidity is a limitation of the findings from the included studies, particularly given the cost of evolocumab. Over many years of study, various trials have demonstrated a correlation between a lowering of LDL cholesterol and a reduction in hard clinical end points such as these. The data from the included trials in this report suggest that evolocumab will provide additional LDL cholesterol lowering beyond that of the statins; what is not currently known is how much additional benefit in terms of hard clinical end points would be achieved by this additional lowering of LDL cholesterol. PCSK9 was first identified as a therapeutic target early this century, with the observation that patients with mutations conferring low PCSK9, and, therefore, low LDL cholesterol, also had significantly lower risk of developing coronary heart disease.[22] It is therefore tempting to extrapolate these findings, combined with the findings of the relationship between reductions in LDL cholesterol and cardiovascular risk from the statin trials, and arrive at an estimate of the potential risk reduction achievable with exogenous inhibition of PCSK9. However, genetic mutations that confer lifelong low LDL cholesterol levels may manifest different reductions in cardiovascular risk than intervention with a PCSK9 inhibitor in middle age or later. We do not know enough about the relationship between the time course of LDL cholesterol lowering and CHD risk reduction to understand whether large reductions in CHD, seen in these genetic mutations over the course of a lifetime, are achievable with PCSK9 inhibition initiated later in life. In other words, there may be a limit to the

reduction in CHD risk that is achievable with exogenous lowering of LDL cholesterol. The same argument can be made for extrapolation of CHD risk reductions from the statin trials, as the law of diminishing returns may apply once LDL cholesterol has been lowered past a certain value. This may be particularly the case in patients with established CHD, which is a target population for evolocumab. Longer-term safety and efficacy data were reported in the OSLER-2 trial, which was an extension that included a number of the phase 3 studies included in the systematic review. The findings of OSLER-2 are summarized in Appendix 5, and harms data from this trial are reviewed in the next section. A recent published analysis by Sabatine et al.[23] reviewed harms and cardiovascular event data, pooling data from OSLER-2 as well as OSLER-1, which was an extension to the phase 2 trials of evolocumab. These phase 2 studies did not meet the inclusion criteria for the CDR review, which focused on phase 3 studies. In the Sabatine et al. analysis, the total follow-up between the studies was approximately one year, and a total of 4,465 patients were included. Although cardiovascular events were an exploratory end point in each of these studies, Sabatine et al. found a statistically significant difference in cardiovascular events in patients receiving evolocumab (0.95% of patients with a cardiovascular event) when compared with standard therapy (2.18% of patients) for a hazard ratio of 0.47 (95% CI, 0.28 to 0.78; *P* = 0.0003). Due to the exploratory nature of the analysis, these data should be considered hypothesis-generating. A number of ongoing studies of PCSK9 inhibitors seek to answer this question concerning the benefits of this extent of LDL cholesterol lowering, including the FOURIER (Further cardiovascular outcomes research with PCSK9 inhibition in subjects with elevated risk) trial, which is expected to be completed in late 2017 or early 2018.(126)

Evolocumab may be administered in two different dosing regimens: either a single injection of 140 mg evolocumab administered every two weeks, or three injections (total of 420 mg) administered once monthly. The manufacturer considers these two dose regimens to be clinically equivalent, and although the included studies were not designed to assess differences between the two regimens, there were no obvious differences in efficacy or harms between the two. This may be important from an economic perspective because evolocumab will be marketed in Canada as a 140 mg injection and is priced per injection; therefore, three injections of evolocumab once monthly rather than one injection every two weeks will add considerable cost to the use of this new drug. Both dose regimens are approved for use in Canada, so at present a patient and his or her health care provider may, in theory, choose either to administer two or three injections. There are a number of considerations that may determine which regimen is chosen, and fundamentally it appears to come down to a choice between the convenience of once-monthly administration with the pain of three injections versus the relative inconvenience of twice monthly administration of two injections. For patients who rely on injections being administered in a clinic, the once-monthly injection may be desirable, especially in cases where travel to a clinic might be onerous.

The patient input submitted to CDR suggests that quality of life is a consideration in patients with FH. Patients identified issues ranging from fear of sequelae of coronary artery disease to frustration with inability to reach target LDL cholesterol, to dealing with the adverse effects of statin therapy, most notably myalgia. Quality of life was not investigated in the included studies, although a number of these concerns raised by patients are unlikely to have been addressed by these shorter-term, blinded studies. The data from the included studies do not address or allay concerns regarding morbidity and mortality associated with FH, as noted above. The ability of evolocumab to elicit both statistically and clinically significant reductions in LDL cholesterol is clear, and the data suggest that more than 90% of patients treated with evolocumab were able to reach target LDL cholesterol of lower than 70 mg/dL. Many patients in the included studies continued to take a statin; therefore, it is unclear whether evolocumab will reduce the risk of adverse effects such as myalgia. In patients who cannot tolerate a statin, per

indication, evolocumab would presumably be used without statins, and presumably the risk of myalgia would be lower in these patients. However, at present, there is no clear evidence that patients who take evolocumab will be spared adverse effects, or whether evolocumab monotherapy will result in a new set of adverse effects that are unique to this drug.

4.2.2 Harms

From the relatively short-term and small trials included in this review, the overall assessment of harms suggests that evolocumab is a reasonably well-tolerated drug with no clear safety issues at present. However, there are safety issues that have been linked to this class of drugs, either due to the extent to which they lower LDL cholesterol or the role of PCSK9 elsewhere in the body, which has not yet been established. One of the key safety issues cited for PCSK9 inhibitors is neurocognitive effects. Cholesterol is a key component of the central nervous system (CNS), found in abundance in brain tissue, as well as being an essential component of myelin, the sheath that surrounds neurons and promotes conduction of nerve signals within the CNS. However, despite the clear role of cholesterol in the CNS, there is no evidence at present linking extensive LDL cholesterol lowering with loss of neuronal function. As noted in Swiger et al., modern LDL cholesterol levels far exceed those of our ancient ancestors, yet there is no evidence that those very–low-LDL cholesterol values resulted in widespread neurological impairments in those early populations.[24] Indeed, although the mechanism may not be related to LDL cholesterol lowering, statins are currently being investigated as a treatment for Alzheimer's disease. Although concerns over neurocognitive effects of lipid-lowering therapies first emerged with the statins, these were short-term observations, and clearly concern in this area was not enough to discourage use of statins to reduce long-term neurocognitive decline. There were no neurocognitive-related AEs reported across the clinical trials included in this review, although the short-term follow-up (12 weeks in three trials, 52 weeks in the fourth) limits any conclusions that can be drawn regarding neurocognitive effects, at least in the long term. Indeed, few long-term data are available. A two-year open-label extension study of the OSLER trial (OSLER-2) revealed that the overall incidence of AEs and SAEs was generally similar between the evolocumab and control groups (APPENDIX 5). The Sabatine et al. 2015 paper, described in the previous section, which pooled data from OSLER-1 and -2, reported a higher incidence of neurocognitive AEs with evolocumab versus standard therapy (0.9% of patients versus 0.3%).[23]

Another notable harm of interest, this time more closely related to manipulation of PCSK9, is increased risk of hepatitis C infection. PCSK9 may play a role in impairing CD81, which is considered a key component facilitating entry of the hepatitis C virus (HCV) into hepatocytes.[25] Therefore, inhibiting PCSK9 may enhance one's susceptibility to infection with HCV. At present, this appears to be more of a theoretical rather than a practical concern with PCSK9 inhibition, as there does not appear to be any indication of elevated risk of infection with HCV from either the studies included in this review or the wider PCSK9 inhibitor clinical trial program. Because of the prevalence of HCV and the potential for harm associated with infection, there is certainly reason to be vigilant about this possible AE.

Many of the other notable harms identified for this review are those classically associated with statin use, including muscle-related harms (including CK elevations) and hepatic events. There is no evidence from the included trials of a difference in risk of these events between evolocumab and either placebo or ezetimibe; however, it should be noted that these studies were not powered to make such comparisons. The risk of harms classically associated with the use of monoclonal antibodies in general, such as hypersensitivity reactions and injection-site reactions, were also not elevated with evolocumab, although the same caveat applies regarding formal comparisons. Evolocumab is a fully human monoclonal antibody, and, unlike the earlier monoclonal antibodies of chimeric design, these newer monoclonal antibodies are less likely to carry significant risk of hypersensitivity reactions.

4.3 Potential Place in Therapy

This section is based on information provided in draft form by the clinical experts consulted by CDR for the purpose of this review. According to the clinical experts consulted for this review, two broad categories of patients have an unmet need that could be met by treatment with evolocumab, namely (a) patients with HeFH (at least 83,500 patients in Canada) who have uncontrolled hypercholesterolemia (approximately 20,000 patients), and (b) patients with atherosclerotic cardiovascular disease (approximately 1.5 million patients in Canada) who have uncontrolled hypercholesterolemia (up to 4.6% of the population, or approximately 70,000 patients who are not at the recommended LDL cholesterol goal of lower than 2.0 mmol/L).[3] The expert noted that HoFH is a rare disease that affects no more than approximately 60 Canadians. Repatha is indicated as an adjunct to diet and other LDL-lowering therapies in patients with HoFH who require additional lowering of LDL cholesterol.

Clinical experts consulted by CADTH suggested that, based on the clinical evidence available and the existing unmet need, the following subgroups of patients would benefit from treatment with evolocumab.

1. Patients with familial hypercholesterolemia, defined per CCS guidelines[4] AND all of the following:
    a. unable to reach the LDL cholesterol target recommended by the CCS (LDL cholesterol value lower than 2.0 mmol/L)
    b. currently receiving optimally tolerated standard of care (i.e., statins with or without ezetimibe).[2]

2. Patients with atherosclerotic cardiovascular disease AND all of the following:
    a. having had a prior cardiovascular event
    b. unable to achieve the LDL cholesterol target recommended by the CCS (LDL cholesterol value lower than 2.0 mmol/L)
    c. currently receiving optimally tolerated standard of care (i.e., statins with or without ezetimibe).[2]

It is not clear what LDL cholesterol threshold should be used to initiate evolocumab therapy, and this threshold for evolocumab (or other PCSK9 inhibitors) is a matter of continuing debate. The clinical expert suggested that the threshold could, in practice, depend on the absolute risk of atherosclerotic cardiovascular disease, and noted that this will be necessarily arbitrary. He suggested that a conservative threshold for secondary prevention could be LDL cholesterol levels higher than 3.0 or 3.5 mmol/L, and higher than 4.0 or 5.0 mmol/L for primary prevention in patients with FH (subgroup 1). The clinical experts noted that new cardiovascular disease prevention guidelines are being developed and will be published in 2016.

5. CONCLUSIONS

Four DB RCTs (LAPLACE-2, RUTHERFORD-2, DESCARTES, and GAUSS-2) assessed the efficacy and safety of evolocumab (140 mg or 420 mg or both) compared with placebo with or without concurrent ezetimibe treatment on a background of statin therapy. The studies ranged in duration from 12 to 52 weeks and included between 307 and 1,899 patients. Only the RUTHERFORD-2 study required patients to have HeFH, and only the GAUSS-2 study targeted statin-intolerant patients. In all studies, regardless of length of treatment (12 or 52 weeks) or the type of background therapy, evolocumab was statistically significantly superior to placebo with or without ezetimibe in reducing LDL cholesterol levels. This result was consistent regardless of baseline LDL cholesterol levels or CHD risk factors. The included studies were not powered for and were not of sufficient duration to assess hard clinical outcomes such as mortality and morbidity, and there were very few of these events across the studies, with no clear and consistent differences in frequency between comparison groups. The included studies were also not powered to assess harms, and there were no clear or consistent differences among treatment groups with respect to the proportion of patients with an adverse event, serious adverse event, or discontinuation due to adverse event. There were also no clear or consistent differences in the proportion of patients with notable muscle- and hepatic-related harms, injection-site or hypersensitivity reactions, or neurocognitive-related harms. Finally, the long-term potential harms associated with evolocumab are unknown, as safety data are limited to only two years of exposure.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

Two patient groups, the Heart and Stroke Foundation (HSF) of Canada and Familial Hypercholesterolemia Canada Patient Network (FH-CPN), provided input for this review. The HSF is one of Canada's largest and most effective health charities. Its mission is to prevent disease, save lives, and promote recovery. Over the last 60 years, the HSF has invested more than $1.39 billion in heart and stroke research, and the death rate from heart disease and stroke has declined by more than 75% during this period. The FH-CPN is a volunteer-led national non-profit organization. It was organized with the assistance of clinicians in Montreal and Vancouver, with outreach through the FH Canada Registry Network and the FH Foundation in the United States. The objectives of the FH-CPN are to raise awareness about FH, to promote screening and diagnosis, to provide education about the condition, to improve access to appropriate treatment and care, and to provide a forum for advocacy and support.

The HSF has received unrestricted financial support from Aegerion Pharmaceuticals, Amgen, Apotex, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb Canada, Eli Lilly Canada, GlaxoSmithKline Inc., Janssen, McKesson Canada, Merck, Merz Pharma Canada, Novartis, Novo Nordisk, Pfizer Canada Inc., Sanofi, Servier, Takeda, and Valeant. The HSF and the individuals involved in the preparation of this submission have no conflicts of interest to declare. The FH-CPN receives unrestricted educational grants from Sanofi Canada, Pfizer Canada, Amgen, and Aegerion, but whether there is any conflict of interest in preparing this submission was not described.

2. Condition-Related Information

The information provided by HSF was gathered through an online survey and literature searches. Twenty-eight of 32 participants completed the survey. FH-CPN collected the information through one-on-one interviews, focus groups, a survey, questions posed in online forums, and closed discussion groups.

Patients with FH feel that the disease affects their day-to-day life because they have to take medication at specific times. Some patients fear death from the disease. The impact of FH on their daily life was as much emotional as it was physical. One patient mentioned: "I was told I had a stroke but no proof of a stroke or heart attack was proven, I simply fell because I was tired and overworked." Another patient said: "I am on apheresis at least every two weeks, and the last time, I started to get severe chest pains right there in the clinic. I was rushed to emergency where they decided to put in another stent." Symptoms reported by the two patient groups include stress, anxiety, and frustration with not being able to attain or maintain their target cholesterol levels. They reported being "accused" by their health professionals of not adhering to their medications. One patient indicated that "I take them religiously but the doctor just doesn't want to believe me, and keeps increasing the dosage or changing the meds. Now I feel like I've run out of options." They also reported being made to feel guilty about their weight or lack of exercise.

Many of the caregivers were parents of children diagnosed with or at risk for FH. Some caregivers expressed frustration with getting their spouses or older children to stay on therapy, especially when they seemingly experienced no immediate benefit or negative outcome when not followed. The impact of FH on caregivers was described as follows:

"The medication schedule requires that you not take one pill while doing another; you have to space them out and it is not so easy when the [person] is not there with you 24/7."

"We've had to look up all the medications ourselves since the various doctors don't seem to have clue as to what others have prescribed. If it weren't for my pharmacist, I think we would have been in serious trouble."

3. Current Therapy-Related Information

Patients with FH indicated that they have been prescribed statins such as atorvastatin/Caudet/Lipitor, rosuvastatin/Crestor, pravastatin/Pravachol, simvastatin/Zocor, ezetimibe/Ezetrol, and ramipril/Altace for treatment of high cholesterol levels. Some patients were on apheresis. Some respondents were actively taking medication to control their condition (having last taken medication "today" or "yesterday"). Some reported taking medication more than one year ago. Some noted that the aforementioned medications have helped to control their condition, while others reported the opposite. For many, the improvement in their symptoms did not last very long, and one patient said, "the period of time between feeling normal and feeling lousy seems to get shorter and shorter." One patient reported that "I am on apheresis at least every week, which is interferes with my work," and "The last time I was there (for apheresis), I started to experience severe chest pains and was rushed to emergency to have another stent put in."

The patient group reported that muscle pain (myopathy) was the most frequent and difficult side effect related to statins. The other side effects reported by patients were shortness of breath, fatigue, joint and chest pain, headaches, muscle weakness, tenderness or spasms, sleep issues, dry mouth or altered taste, gastrointestinal issues, and skin reactions, among others. Patients reported stress, anxiety, and frustration with not being able to get their cholesterol to target levels or maintain it there:

"No matter how hard I try, nothing seems to work. I just feel like giving up."

"I've been on three different statins and now on a statin with another drug but I can't seem to get my cholesterol level below 15."

"I've tried every statin, high-dose and low-dose, but the pains in my legs, especially my calves, were so bad that I couldn't walk even as far as the bus stop. What else can I do?"

"I switched from atorvastatin to rosuvastatin because I was having extreme pains in my legs and hips. The pain has gone, but now I'm just exhausted all the time. Someone suggested taking CoQ10 and vitamin D, but that brings me up to 11 medications."

"I take them religiously but the doctor just doesn't want to believe me, and keeps increasing the dosage or changing the meds. Now I feel like I've run out of options."

"It (apheresis) is definitely no longer working. I have had with multiple hospitalizations and stents inserted on an emergency basis, but they don't work for long."

4. Expectations About the Drug Being Reviewed

The methods of information collection in this section were the same as those used in the section 3.

In the HSF submission, none of the respondents had experience with evolocumab. Six patients responded to the question, "Other than being cured, what would be the best course of treatment look like for you?" Responses included, "something without serious side effects or liver disease"; "I'm tired of pills"; "continue with medication"; and "just to keep my cholesterol at a low normal level."

In the submission by the FH-CPN, among patients who did not have experience with evolocumab and had not attained optimal blood cholesterol control, most expected that evolocumab would work to lower cholesterol levels, possibly more effectively and without the side effects experienced with statins. Most of them were anticipating evolocumab being listed for reimbursement.

Among patients who have received evolocumab through clinical trials, all were satisfied or very satisfied with the impact of treatment with evolocumab on their cholesterol level and reported both physical and emotional (psychological) benefits. All patients were still on therapy, and some were also taking statins. All patients indicated their cholesterol levels have remained close to target or lower than before taking evolocumab. Several quotes regarding the experience of the use of evolocumab are summarized as below:

"I noticed a difference almost right away, and my numbers stayed down, even between injections."

"This is the first time in a long time that I felt some hope in getting on top of this condition. I had almost given up on getting my cholesterol under control."

"I feel fantastic!"

"I feel so lucky that my doctor enrolled me in the clinical trials. I could tell almost right away that I was on the real therapy and I was right. [I have been on the trial] for two weeks, and the difference was huge."

"With my previous drugs [statins], my doctor was constantly checking my cholesterol and making changes to my medicines. This has been working for me without almost any problems."

"I find it so much easier to do the injections once a month than taking the pills every day. And with the new pen, it is even easier."

Most of the patients experienced few or temporary adverse reactions to evolocumab and showed their appreciation for being free of the side effects they had experienced with statins. The quotes on the injection experience included the following:

"I had some soreness with the injections initially, but that has gone away almost completely."

"I thought it would be difficult to give myself an injection, but I got the hang of it pretty quickly."

None of the patients in the survey had discontinued evolocumab, although some were worried about the eventual cost of the therapy and whether it would be covered. One patient said: “I can’t imagine going back to statins or something else. Maybe, now that my cholesterol is down, they would work but I don’t want to take the chance.”

As acknowledged by the two patient groups, a limitation of the patient input gathered was that it was not a population-based survey. The submissions did not suggest that the responses were representative of the entire hypercholesterolemia population; however, all participants (with or without the experience of using evolocumab) were overwhelmingly positive about evolocumab being made available as an alternative for managing high cholesterol. All participants indicated that they were either not concerned or only somewhat concerned about administering an injection. The FH-CPN indicated that there is no doubt that evolocumab is the treatment of choice for patients who have had challenges in lowering their cholesterol levels with other therapies, who have had serious adverse reactions to statins or statin combinations, or who have FH.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	July 29, 2015
Alerts:	Weekly search updates until January 20, 2016
Study Types:	No search filters were applied
Limits:	No language or date limits Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
#	**Searches**
1	(Repatha* or evolocumab* or AMG 145 or AMG145 or LKC0U3A8NJ or UNIILKC0U3A8NJ).ti,ot,ab,sh,hw,rn,nm,kw.
2	(1256937-27-5 or "1256937275" or "125693727 5" or 1256937 275).rn,nm.
3	1 or 2
4	3 use pmez
5	*evolocumab/
6	(Repatha* or evolocumab* or AMG 145 or AMG145 or LKC0U3A8NJ or UNIILKC0U3A8NJ).ti,ab,kw.
7	5 or 6
8	7 use oemezd
9	4 or 8
10	exp animals/
11	exp animal experimentation/ or exp animal experiment/
12	exp models animal/
13	nonhuman/
14	exp vertebrate/ or exp vertebrates/
15	animal.po.
16	or/10-15
17	exp humans/
18	exp human experimentation/ or exp human experiment/
19	human.po.
20	or/17-19
21	16 not 20
22	9 not 21
23	22 not conference abstract.pt.
24	remove duplicates from 23

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	July 23, 2015
Keywords:	Drug name, Indication
Limits:	No language or date limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Rhainds and Tardif[26]	Review
Robinson et al.[27]	Protocol
Sabatine et al.[23]	Open label
Interim Clinical Study Report: 20110110[28]	Open label
Interim Clinical Study Report: 20120138[29]	Open label
Koren et al.[30]	Phase 2
Desai et al.[31]	Phase 2
Hirayama et al.[32]	Phase 2
Koren et al.[33]	Phase 2
Desai et al.[34]	Phase 2
Raal et al.[35]	Homozygous familial hypercholesterolemia
Clinical Study Report: 20110233[36]	Homozygous familial hypercholesterolemia

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 31: OTHER OUTCOMES, LAPLACE-2 — HIGH-INTENSITY, ATORVASTATIN 80 MG

	EVO 140 mg q.2w.	EVO 420 mg q.m.	EZE/ PLA q.2w.	EZE/PLA q.m.	PLA q.2w.	PLA q.m.
Apo B, % Change						
Mean (SD) day 1	79.9 (25.1)	77.9 (21.5)	85.3 (23.1)	78.7 (16.9)	81.1 (22.1)	80.1 (21.4)
LSM (SE) % change, weeks 10/12	–49.14 (2.13)	–53.26 (2.02)	–14.22 (2.98)	–13.62 (2.87)	10.20 (3.02)	5.48 (2.83)
Treatment difference (95% CI)	**Versus EZE** **EVO 140 mg:** –34.92 (–42.09 to –27.75), *P* < 0.001 **EVO 420 mg:** –39.64 (–46.57 to –32.71), *P* < 0.001			**Versus placebo** **EVO 140 mg:** –59.34 (–66.61 to –52.07), *P* < 0.001 **EVO 420 mg:** –58.74 (–65.56 to –51.93), *P* < 0.001		
LSM (SE) % change, week 12	–49.77 (2.28)	–46.47 (2.31)	–12.31 (3.20)	–12.16 (3.24)	11.64 (3.28)	6.54 (3.22)
Treatment difference (95% CI)	**Versus EZE** **EVO 140 mg:** –37.45 (–45.17 to –29.74), *P* < 0.001 **EVO 420 mg:** –34.31 (–42.15 to –26.47), *P* < 0.001			**Versus placebo** **EVO 140 mg:** –61.40 (–69.27 to –53.54), *P* < 0.001 **EVO 420 mg:** –53.01 (–60.77 to –45.25), *P* < 0.001		
Lp(a), % Change						
Mean (SD) day 1	80.8 (103.3)	75.1 (111.0)	81.1 (108.3)	95.3 (91.6)	102.9 (108.4)	93.3 (106.7)
LSM (SE) % change, weeks 10/12	–23.97 (2.10)	–27.46 (2.39)	8.05 (2.94)	9.96 (3.40)	–3.45 (2.99)	1.51 (3.35)
Treatment difference (95% CI)	**Versus EZE** **EVO 140 mg:** –32.02 (–39.11 to –24.93), *P* < 0.001 **EVO 420 mg:** –37.42 (–45.61 to –29.23), *P* < 0.001			**Versus placebo** **EVO 140 mg:** –20.52 (–27.71 to –13.33), *P* < 0.001 **EVO 420 mg:** –28.96 (–37.01 to –20.92), *P* < 0.001		
LSM (SE) % change, week 12	–24.61 (2.31)	–24.68 (2.53)	8.01 (3.26)	10.20 (3.57)	–2.23 (3.35)	3.41 (3.54)
Treatment difference (95% CI)	**Versus EZE** **EVO 140 mg:** –36.482 (–43.95 to –29.02), *P* < 0.001 **EVO 420 mg:** –34.88 (–43.52 to –26.25), *P* < 0.001			**Versus placebo** **EVO 140 mg:** –22.38 (–30.39 to –14.36), *P* < 0.001 **EVO 420 mg:** –28.10 (–36.62 to –19.58), *P* < 0.001		
Non-HDL-C, % Change						
Mean (SD) day 1	120.2 (42.3)	117.2 (36.3)	124.8 (35.4)	118.4 (25.5)	124.2 (39.3)	116.5 (35.7)
LSM (SE) % change, weeks 10/12	–54.44 (2.49)	–56.31 (2.23)	–16.19 (3.49)	–18.79 (3.16)	10.74 (3.59)	8.45 (3.13)
Treatment difference (95% CI)	**Versus EZE** **EVO 140 mg:** –38.25 (–46.68 to –29.81) **EVO 420 mg:** –37.52 (–45.15 to –29.90)			**Versus placebo** **EVO 140 mg:** –65.17 (–73.78 to –56.56) **EVO 420 mg:** –64.76 (–72.32 to –57.19)		
LSM (SE) % change, week 12	–54.84 (2.66)	–50.05 (2.50)	–14.34 (3.75)	–17.26 (3.52)	11.79 (3.87)	9.95 (3.51)
Treatment difference (95% CI)	**Versus EZE** **EVO 140 mg:** –40.51 (–49.55 to –31.47), *P* < 0.001 **EVO 420 mg:** –32.79 (–41.30 to –24.28), *P* < 0.001			**Versus placebo** **EVO 140 mg:** –66.64 (–75.88 to –57.39), *P* < 0.001 **EVO 420 mg:** –60.01 (–68.49 to –51.52), *P* < 0.001		

	EVO 140 mg q.2w.	EVO 420 mg q.m.	EZE/ PLA q.2w.	EZE/PLA q.m.	PLA q.2w.	PLA q.m.
Triglycerides, % Change						
Mean (SD) day 1	130.1 (74.5)	117.4 (54.7)	130.0 (55.6)	130.5 (65.8)	119.8 (56.0)	109.3 (45.2)
LSM (SE) % change, weeks 10/12	–9.27 (2.80)	–6.36 (3.11)	–8.10 (3.92)	–4.86 (4.39)	6.16 (4.02)	8.05 (4.35)
Treatment difference (95% CI)	**Versus EZE** **EVO 140 mg:** –1.17 (–10.63 to 8.30), *P* = 0.81 **EVO 420 mg:** –1.51 (–12.12 to 9.11), *P* = 0.78			**Versus placebo** **EVO 140 mg:** –15.43 (–25.06 to –5.79), *P* = 0.002 **EVO 420 mg:** –14.41 (–24.90 to –3.92), *P* = 0.007		
LSM (SE) % change, week 12	–10.07 (3.05)	–1.10 (3.74)	–7.40 (4.32)	–3.11 (5.23)	6.65 (4.45)	8.22 (5.22)
Treatment difference (95% CI)	**Versus EZE** **EVO 140 mg:** –2.67 (–13.05 to 7.72), *P* = 0.61 **EVO 420 mg:** 2.02 (–10.66 to 14.69), *P* = 0.75			**Versus placebo** **EVO 140 mg:** –16.72 (–27.34 to –6.10), *P* = 0.002 **EVO 420 mg:** –9.31 (–21.92 to 3.29), *P* = 0.15		
VLDL-C, % Change						
Mean (SD) day 1	26.0 (14.9)	23.4 (11.0)	26.0 (11.1)	26.1 (13.2)	23.9 (11.2)	21.8 (9.1)
LSM (SE) % change, weeks 10/12	–8.96 (2.82)	–6.38 (3.05)	–8.52 (3.93)	–6.13 (4.31)	6.24 (4.03)	8.31 (4.26)
Treatment difference (95% CI)	**Versus EZE** **EVO 140 mg:** –0.44 (–9.94 to 9.05), *P* = 0.93 **EVO 420 mg:** –0.25 (–10.66 to 10.16), *P* = 0.96			**Versus placebo** **EVO 140 mg:** –15.21 (–24.88 to –5.54), *P* = 0.002 **EVO 420 mg:** –14.69 (–24.97 to –4.42), *P* = 0.005		
LSM (SE) % change, week 12	–9.69 (3.05)	–1.06 (3.58)	–7.92 (4.32)	–6.00 (5.04)	6.73 (4.45)	8.54 (5.00)
Treatment difference (95% CI)	**Versus EZE** **EVO 140 mg:** –1.78 (–12.16 to 8.61), *P* = 0.74 **EVO 420 mg:** 4.94 (–7.25 to 17.14), *P* = 0.43			**Versus placebo** **EVO 140 mg:** –16.42 (–27.05 to –5.80), *P* = 0.003 **EVO 420 mg:** –9.60 (–21.68 to 2.48), *P* = 0.12		

Apo = apolipoprotein; CI = confidence interval; EVO = evolocumab; EZE = ezetimibe; HDL-C = high-density–lipoprotein cholesterol; Lp(a) = lipoprotein (a); LSM = least squares mean; PLA = placebo; q.2w. = every two weeks; q.m. = once monthly; SD = standard deviation; SE = standard error; VLDL-C = very–low-density–lipoprotein cholesterol.
Source: Clinical Study Report for LAPLACE-2.[7]

TABLE 32: OTHER OUTCOMES, LAPLACE-2 — HIGH-INTENSITY, ROSUVASTATIN 40 MG

	EVO 140 mg q.2w. N = 111	EVO 420 mg q.m. N = 112	PLA q.2w. N = 56	PLA q.m. N = 55
Apo B, % Change				
Mean (SD) day 1				
LSM (SE) % change, weeks 10/12	–47.07 (1.76)	–52.95 (1.76)	3.71 (2.46)	1.98 (2.57)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –50.78 (–56.72 to –44.83), *P* < 0.001 **EVO 420 mg:** –54.94 (–61.11 to –48.76), *P* < 0.001			
LSM (SE) % change, week 12	–45.61 (1.93)	–43.71 (2.13)	4.91 (2.71)	3.24 (3.13)

	EVO 140 mg q.2w. N = 111	EVO 420 mg q.m. N = 112	PLA q.2w. N = 56	PLA q.m. N = 55
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –50.52 (–57.06 to –43.99), *P* < 0.001 **EVO 420 mg:** –46.95 (–54.43 to –39.47), *P* < 0.001			
Lp(a), % Change				
Mean (SD) day 1				
LSM (SE) % change, weeks 10/12	–24.96 (2.12)	–25.93 (2.46)	8.59 (2.98)	6.26 (3.59)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –33.56 (–40.74 to –26.37), *P* < 0.001 **EVO 420 mg:** –32.19 (–40.80 to –23.58), *P* < 0.001			
LSM (SE) % change, week 12	–26.11 (2.21)	–21.97 (2.97)	10.38 (3.09)	10.21 (4.36)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –36.48 (–43.95 to –29.02), *P* < 0.001 **EVO 420 mg:** –32.17 (–42.61 to –21.74, *P* < 0.001			
Non-HDL-C, % Change				
Mean (SD) day 1				
LSM (SE) % change, weeks 10/12	–52.08 (1.88)	–55.72 (2.01)	6.19 (2.61)	1.58 (2.90)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –58.27 (–64.60 to –51.94), *P* < 0.001 **EVO 420 mg:** –57.31 (–64.29 to –50.32), *P* < 0.001			
LSM (SE) % change, week 12	–26.11 (2.21)	–21.97 (2.97)	10.38 (3.09)	10.21 (4.36)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –36.48 (–43.95 to –29.02), *P* < 0.001 **EVO 420 mg:** –32.17 (–42.61 to –21.74), *P* < 0.001			
Triglycerides, % Change				
Mean (SD) day 1				
LSM (SE) % change, weeks 10/12	–9.15 (2.70)	–15.43 (2.77)	8.44 (3.76)	10.75 (3.98)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –17.59 (–26.71 to –8.46), *P* < 0.001 **EVO 420 mg:** –26.18 (–35.76 to –16.59), *P* < 0.001			
LSM (SE) % change, week 12	–5.58 (3.34)	–10.51 (3.04)	10.97 (4.66)	10.00 (4.38)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –16.55 (–27.84 to –5.26), *P* = 0.004 **EVO 420 mg:** –20.51 (–31.04 to –9.98), *P* < 0.001			
VLDL-C, % Change				
Mean (SD) day 1				
LSM (SE) % change, weeks 10/12	–9.09 (2.71)	–15.05 (2.58)	7.06 (3.76)	8.13 (3.72)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –16.15 (–25.27 to –7.03), *P* < 0.001 **EVO 420 mg:** –23.18 (–32.11 to –14.25), *P* < 0.001			

	EVO 140 mg q.2w. N = 111	EVO 420 mg q.m. N = 112	PLA q.2w. N = 56	PLA q.m. N = 55
LSM (SE) % change, week 12	–6.10 (3.33)	–9.95 (3.03)	10.09 (4.65)	8.59 (4.37)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –16.19 (–27.46 to –4.92), *P* = 0.005 **EVO 420 mg:** –18.54 (–29.04 to –8.05), *P* < 0.001			

Apo = apolipoprotein; CI = confidence interval; EVO = evolocumab; HDL-C = high-density–lipoprotein cholesterol; Lp(a) = lipoprotein (a); LSM = least squares mean; PLA = placebo; q.2w. = every two weeks; q.m. = once monthly; SD = standard deviation; SE = standard error; VLDL-C = very–low-density–lipoprotein cholesterol.
Source: Clinical Study Report for LAPLACE-2.[7]

TABLE 33: OTHER OUTCOMES, LAPLACE-2 — MODERATE-INTENSITY, ROSUVASTATIN 5 MG

	EVO 140 mg q.2w. N = 111	EVO 420 mg q.m. N = 112	PLA q.2w. N = 56	PLA q.m. N = 55
Apo B, % Change				
Mean (SD) day 1				
LSM (SE) % change, weeks 10/12	–49.79 (1.46)	–53.59 (1.32)	5.07 (1.97)	2.54 (1.89)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –54.86 (–59.66 to –50.05), *P* < 0.001 **EVO 420 mg:** –56.14 (–60.66 to –51.61), *P* < 0.001			
LSM (SE) % change, week 12	–50.15 (1.54)	–48.58 (1.49)	6.35 (2.10)	4.63 (2.11)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –56.50 (–61.60 to –51.40), *P* < 0.001 **EVO 420 mg:** –53.21 (–58.29 to –48.13), *P* < 0.001			
Lp(a), % Change				
Mean (SD) day 1				
LSM (SE) % change, weeks 10/12	–24.26 (2.21)	–23.16 (2.50)	11.41 (3.00)	3.65 (3.56)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –35.66 (–42.94 to –28.38), *P* < 0.001 **EVO 420 mg:** –26.81 (–35.36 to –18.27), *P* < 0.001			
LSM (SE) % change, week 12	–25.09 (2.47)	–20.85 (2.59)	11.40 (3.37)	4.49 (3.68)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –36.50 (–44.69 to –28.30), *P* < 0.001 **EVO 420 mg:** –25.34 (–34.19 to –16.49), *P* < 0.001			
Non-HDL-C, % Change				
Mean (SD) day 1				
LSM (SE) % change, weeks 10/12	–52.59 (1.54)	–55.47 (1.64)	7.02 (2.11)	3.73 (2.32)
Treatment difference versus placebo	**EVO 140 mg:** –59.61 (–64.73 to –54.48), *P* < 0.001			

	EVO 140 mg q.2w. N = 111	EVO 420 mg q.m. N = 112	PLA q.2w. N = 56	PLA q.m. N = 55
(95% CI)	**EVO 420 mg:** –59.20 (–64.80 to –53.60), *P* < 0.001			
LSM (SE) % change, week 12	–52.04 (1.74)	–51.57 (1.72)	7.92 (2.40)	5.85 (2.42)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –59.96 (–65.78 to –54.13), *P* < 0.001 **EVO 420 mg:** –57.42 (–63.27 to –51.57), *P* < 0.001			
Triglycerides, % Change				
Mean (SD) day 1				
LSM (SE) % change, weeks 10/12	–10.28 (3.04)	–7.26 (3.29)	12.43 (4.19)	12.26 (4.67)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –22.72 (–32.90 to –12.54), *P* < 0.001 **EVO 420 mg:** –19.52 (–30.76 to –8.28), *P* < 0.001			
LSM (SE) % change, week 12	–4.46 (4.16)	–6.88 (3.80)	13.57 (5.76)	12.96 (5.32)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –18.03 (–32.03 to –4.04), *P* = 0.012 **EVO 420 mg:** –19.83 (–32.71 to –6.96), *P* = 0.003			
VLDL-C, % Change				
Mean (SD) day 1				
LSM (SE) % change, weeks 10/12	–12.22 (2.86)	–7.25 (3.23)	12.86 (3.95)	12.54 (4.58)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –25.07 (–34.64 to –15.50), *P* < 0.001 **EVO 420 mg:** –19.79 (–30.81 to –8.77), *P* < 0.001			
LSM (SE) % change, week 12	–8.20 (3.64)	–6.28 (3.78)	13.79 (5.05)	12.47 (5.31)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –21.98 (–34.24 to –9.73), *P* < 0.001 **EVO 420 mg:** –18.75 (–31.60 to –5.90), *P* = 0.004			

Apo = apolipoprotein; CI = confidence interval; EVO = evolocumab; HDL-C = high-density–lipoprotein cholesterol; Lp(a) = lipoprotein (a); LSM = least squares mean; PLA = placebo; q.2w. = every two weeks; q.m. = once monthly; SD = standard deviation; SE = standard error; VLDL-C = very–low-density–lipoprotein cholesterol.
Source: Clinical Study Report for LAPLACE-2.[7]

TABLE 34: OTHER OUTCOMES, LAPLACE-2 — MODERATE-INTENSITY, SIMVASTATIN 40 MG

	EVO 140 mg q.2w. N = 111	EVO 420 mg q.m. N = 112	PLA q.2w. N = 56	PLA q.m. N = 55
Apo B, % Change				
Mean (SD) day 1				
LSM (SE) % change, weeks 10/12	–55.65 (2.63)	–54.37 (3.93)	–0.31 (3.02)	2.49 (4.67)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –55.34 (–59.94 to –50.74), *P* < 0.001 **EVO 420 mg:** –56.87 (–63.27 to –50.46), *P* < 0.001			
LSM (SE) % change, week 12	–55.95 (2.72)	–49.16 (3.97)	0.35 (3.17)	3.57 (4.74)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –56.30 (–61.47 to –51.14), *P* < 0.001 **EVO 420 mg:** –52.73 (–59.40 to –46.06), *P* < 0.001			
Lp(a), % Change				
Mean (SD) day 1				
LSM (SE) % change, weeks 10/12	–38.64 (3.92)	–32.16 (4.50)	–10.57 (4.49)	–4.99 (5.37)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –28.07 (–34.91 to –21.23), *P* < 0.001 **EVO 420 mg:** –27.16 (–34.59 to –19.73), *P* < 0.001			
LSM (SE) % change, week 12	–38.06 (3.96)	–29.23 (4.68)	–6.81 (4.57)	–1.06 (5.67)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –31.25 (–38.40 to –24.10), *P* < 0.001 **EVO 420 mg:** –28.17 (–36.79 to –19.55), *P* < 0.001			
Non-HDL-C, % Change				
Mean (SD) day 1				
LSM (SE) % change, weeks 10/12	–59.33 (2.79)	–56.01 (3.49)	0.74 (3.23)	6.81 (4.35)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –60.06 (–65.18 to –54.94), *P* < 0.001 **EVO 420 mg:** –62.82 (–70.22 to –55.42), *P* < 0.001			
LSM (SE) % change, week 12	–59.02 (2.87)	–50.96 (3.60)	1.89 (3.38)	5.66 (4.53)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –60.91 (–66.57 to –55.24), *P* < 0.001 **EVO 420 mg:** –56.63 (–64.63 to –48.62), *P* < 0.001			
Triglycerides, % Change				
Mean (SD) day 1				
LSM (SE) % change, weeks 10/12	–11.67 (5.97)	–15.93 (6.15)	9.29 (6.97)	13.78 (7.44)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –20.97 (–32.38 to –9.55), *P* < 0.001 **EVO 420 mg:** –29.71 (–40.84 to –18.57), *P* < 0.001			
LSM (SE) % change, week 12	–13.71 (5.91)	–14.65 (6.39)	8.07 (6.88)	16.72 (7.88)

	EVO 140 mg q.2w. N = 111	EVO 420 mg q.m. N = 112	PLA q.2w. N = 56	PLA q.m. N = 55
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –21.78 (–32.88 to –10.68), *P* < 0.001 **EVO 420 mg:** –31.36 (–44.10 to –18.62), *P* < 0.001			
VLDL-C, % Change				
Mean (SD) day 1				
LSM (SE) % change, weeks 10/12	–14.57 (5.17)	–16.50 (5.87)	8.64 (6.01)	16.37 (7.15)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –23.21 (–33.00 to –13.43), *P* < 0.001 **EVO 420 mg:** –32.87 (–43.60 to –22.14), *P* < 0.001			
LSM (SE) % change, week 12	–14.83 (5.30)	–15.86 (6.09)	7.63 (6.26)	20.97 (7.53)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –22.45 (–33.09 to –11.81), *P* < 0.001 **EVO 420 mg:** –36.83 (–48.96 to –24.70), *P* < 0.001			

Apo = apolipoprotein; CI = confidence interval; EVO = evolocumab; HDL-C = high-density–lipoprotein cholesterol; Lp(a) = lipoprotein (a); LSM = least squares mean; PLA = placebo; q.2w. = every two weeks; q.m. = once monthly; SD = standard deviation; SE = standard error; VLDL-C = very–low-density–lipoprotein cholesterol.
Source: Clinical Study Report for LAPLACE-2.[7]

TABLE 35: OTHER OUTCOMES, LAPLACE-2 — MODERATE-INTENSITY, ATORVASTATIN 10 MG

	EVO 140 mg q.2w.	EVO 420 mg q.m.	EZE/ PLA q.2w.	EZE/PLA q.m.	PLA q.2w.	PLA q.m.
Apo B, % Change						
Mean (SD) day 1	99.7 (26.4)	97.3 (28.9)	101.3 (31.2)	94.6 (20.4)	95.3 (26.0)	95.3 (29.6)
LSM % change (weeks 10/12)	–40.44 (1.26)	–42.45 (1.48)	–14.39 (1.83)	–10.86 (2.08)	5.96 (1.76)	2.24 (2.11)
Treatment difference (95% CI)	**Versus EZE** **EVO 140 mg:** –26.06 (–30.36 to –21.75), *P* < 0.001 **EVO 420 mg:** –31.59 (–36.61 to –26.57), *P* < 0.001			**Versus placebo** **EVO 140 mg:** –46.41 (–50.66 to –42.15), *P* < 0.001 **EVO 420 mg:** –44.69 (–49.75 to –39.63), *P* < 0.001		
LSM (SE) % change (week 12)	–40.74 (1.45)	–40.07 (1.63)	–12.14 (2.10)	–9.85 (2.28)	6.09 (2.02)	2.80 (2.31)
Treatment difference (95% CI)	**Versus EZE** **EVO 140 mg:** –28.60 (–33.56 to –23.65), *P* < 0.001 **EVO 420 mg:** –30.22 (–35.74 to –24.70), *P* < 0.001			**Versus placebo** **EVO 140 mg:** –46.83 (–51.73 to –41.94), *P* < 0.001 **EVO 420 mg:** –42.86 (–48.43 to –37.30), *P* < 0.001		
Lp(a), % Change						
Mean (SD) day 1	80.9 (107.2)	89.3 (95.0)	99.1 (103.9)	92.9 (113.9)	61.7 (71.3)	89.2 (109.1)
LSM % change (weeks 10/12)	–26.01 (2.08)	–22.64 (2.27)	1.44 (3.02)	6.85 (3.29)	6.07 (2.86)	–0.77 (3.28)
Treatment difference (95% CI)	**Versus EZE** **EVO 140 mg:** –27.45 (–34.53 to –20.38), *P* < 0.001			**Versus placebo** **EVO 140 mg:** –32.08 (–39.06 to –25.11), *P* < 0.001		

	EVO 140 mg q.2w.	EVO 420 mg q.m.	EZE/ PLA q.2w.	EZE/PLA q.m.	PLA q.2w.	PLA q.m.
	EVO 420 mg: –29.49 (–37.36 to –21.62), *P* < 0.001			**EVO 420 mg:** –21.86 (–29.70 to –14.03), *P* < 0.001		
LSM (SE) % change (week 12)	–25.87 (2.26)	–20.25 (2.36)	3.29 (3.28)	7.18 (3.38)	7.34 (3.13)	–0.43 (3.38)
Treatment difference (95% CI)	**Versus EZE** **EVO 140 mg:** –29.16 (–36.87 to –21.44), *P* < 0.001 **EVO 420 mg:** –27.44 (–35.56 to –19.32), *P* < 0.001			**Versus placebo** **EVO 140 mg:** –33.20 (–40.81 to –25.60), *P* < 0.001 **EVO 420 mg:** –19.82 (–27.92 to –11.72), *P* < 0.001		
Non-HDL-C, % Change						
Mean (SD) day 1	152.3 (45.6)	154.3 (53.1)	153.8 (53.2)	148.3 (36.8)	149.1 (46.9)	147.7 (51.4)
LSM % change (weeks 10/12)	–53.48 (1.48)	–56.09 (1.71)	–20.71 (2.15)	–16.56 (2.41)	6.80 (2.07)	1.28 (2.44)
Treatment difference (95% CI)	**Versus EZE** **EVO 140 mg:** –32.77 (–37.84 to –27.70), *P* < 0.001 **EVO 420 mg:** –39.53 (–45.34 to –33.71), *P* < 0.001			**Versus placebo** **EVO 140 mg:** –60.28 (–65.29 to –55.27), *P* < 0.001 **EVO 420 mg:** –57.37 (–63.23 to –51.51), *P* < 0.001		
LSM (SE) % change, week 12	–53.39 (1.66)	–52.50 (1.90)	–18.27 (2.40)	–14.78 (2.65)	8.25 (2.32)	2.43 (2.69)
Treatment difference (95% CI)	**Versus EZE** **EVO 140 mg:** –35.11 (–40.79 to –29.44), *P* < 0.001 **EVO 420 mg:** –37.72 (–44.15 to –31.30), *P* < 0.001			**Versus placebo** **EVO 140 mg:** –61.64 (–67.25 to –56.03), *P* < 0.001 **EVO 420 mg:** –54.93 (–61.40 to –48.46), *P* < 0.001		
Triglycerides, % Change						
Mean (SD) day 1	140.3 (56.2)	141.8 (105.9)	138.2 (75.1)	146.9 (103.9)	130.4 (64.3)	120.4 (52.1)
LSM % change (weeks 10/12)	–5.61 (2.81)	–13.38 (3.08)	–3.16 (4.10)	1.57 (4.35)	6.49 (3.94)	9.17 (4.41)
Treatment difference (95% CI)	**Versus EZE** **EVO 140 mg:** –2.45 (–12.09 to 7.19), *P* = 0.62 **EVO 420 mg:** –14.95 (–25.46 to –4.44), *P* = 0.006			**Versus placebo** **EVO 140 mg:** –12.10 (–21.63 to –2.58), *P* = 0.013 **EVO 420 mg:** –22.55 (–33.13 to –11.97), *P* < 0.001		
LSM (SE) % change (week 12)	–3.79 (3.72)	–13.26 (4.17)	–0.43 (5.39)	4.88 (5.84)	8.27 (5.23)	14.35 (5.92)
Treatment difference (95% CI)	**Versus EZE** **EVO 140 mg:** –3.37 (–16.16 to 9.43), *P* = 0.60 **EVO 420 mg:** –18.13 (–32.28 to –3.99), 0.012			**Versus placebo** **EVO 140 mg:** –12.06 (–24.69 to 0.57) *P* = 0.061 **EVO 420 mg:** –27.60 (–41.86 to –13.35), *P* < 0.001		
VLDL-C, % Change						
Mean (SD) day 1	28.1 (11.3)	26.5 (13.4)	26.7 (10.7)	27.2 (13.4)	26.1 (12.8)	24.1 (10.4)
LSM % change (weeks 10/12)	–6.85 (2.56)	–11.77 (3.11)	–5.35 (3.74)	1.77 (4.41)	6.51 (3.56)	9.53 (4.45)
Treatment difference (95% CI)	**Versus EZE** **EVO 140 mg:** –1.50 (–10.27 to 7.27), *P* = 0.74 **EVO 420 mg:** –13.54 (–24.17 to –2.91), *P* = 0.013			**Versus placebo** **EVO 140 mg:** –13.36 (–21.99 to –4.74), *P* = 0.003 **EVO 420 mg:** –21.31 (–31.98 to –10.64), *P* <0.001		
LSM (SE) % change (week 12)	–6.16 (2.88)	–11.73 (4.16)	–4.61 (4.19)	3.45 (5.89)	8.32 (4.00)	14.74 (5.91)

	EVO 140 mg q.2w.	EVO 420 mg q.m.	EZE/ PLA q.2w.	EZE/PLA q.m.	PLA q.2w.	PLA q.m.
Treatment difference (95% CI)	**Versus EZE** **EVO 140 mg:** –1.54 (–11.41 to 8.32), *P* = 0.76 **EVO 420 mg:** –15.19 (–29.40 to –0.97), *P* = 0.036			**Versus placebo** **EVO 140 mg:** –14.47 (–24.16 to –4.78), *P* = 0.004 **EVO 420 mg:** –26.47 (–40.71 to –12.24), *P* <0.001		

Apo = apolipoprotein; CI = confidence interval; EVO = evolocumab; EZE = ezetimibe; HDL-C = high-density–lipoprotein cholesterol; Lp(a) = lipoprotein (a); LSM = least squares mean; PLA = placebo; q.2w. = every two weeks; q.m. = once monthly; SD = standard deviation; SE = standard error; VLDL-C = very–low-density–lipoprotein cholesterol.
Source: Clinical Study Report for LAPLACE-2.[7]

TABLE 36: OTHER OUTCOMES, RUTHERFORD-2

	RUTHERFORD-2			
Apo B, % Change from baseline	**EVO 140 mg q.2w. N = 110**	**EVO 420 mg q.m. N = 110**	**PLA q.2w. N = 54**	**PLA q.m. N = 55**
Mean (SD) baseline, (g/L)	1.19 (0.31)	1.15 (0.26)	1.14 (0.30)	1.10 (0.22)
LSM[a] (SE), weeks 10 and 12	–49.58 (1.48)	–52.76 (1.36)	–0.19 (2.10)	2.21 (1.97)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –49.39 (–54.32 to –44.46), *P* < 0.001 **EVO 420 mg:** –54.98 (–59.58 to –50.38), *P* < 0.001			
LSM[a] (SE), week 12	–49.75 (1.63)	–44.81 (1.80)	–0.67 (2.32)	4.60 (2.70)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –49.09 (–54.55 to –43.63), *P* < 0.001 **EVO 420 mg:** –49.41 (–55.73 to –43.10), *P* < 0.001			
Lp(a), % Change from baseline				
Mean (SD) baseline, nmol/L	129.4 (125.0)	110.9 (127.9)	84.2 (92.7)	135.7 (120.4)
LSM[a] (SE), weeks 10 and 12	–24.03 (2.09)	–25.65 (2.07)	7.34 (2.97)	5.35 (2.95)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –31.37 (–38.33 to –24.41), *P* < 0.001 **EVO 420 mg:** –31.00 (–37.91 to –24.09), *P* < 0.001			
LSM[a] (SE), week 12	–22.89 (2.31)	–21.55 (2.17)	8.68 (3.27)	6.69 (3.16)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –31.57 (–39.28 to –23.87), *P* < 0.001 **EVO 420 mg:** –28.24 (–35.61 to –20.88), *P* < 0.001			
Non-HDL-C, % Change from baseline				
Mean (SD) baseline, mmol/L	4.85 (1.47)	4.62 (1.19)	4.54 (1.14)	4.54 (1.19)
LSM[a] (SE), weeks 10 and 12	–55.79 (1.63)	–57.28 (1.56)	0.21 (2.29)	2.72 (2.21)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –56.00 (–61.41 to –50.59), *P* < 0.001 **EVO 420 mg:** –60.01 (–65.24 to –54.77), *P* < 0.001			
LSM[a] (SE), week 12	–56.19 (1.71)	–49.67 (2.04)	–1.39 (2.40)	5.29 (2.94)

	RUTHERFORD-2			
Apo B, % Change from baseline	**EVO 140 mg q.2w. N = 110**	**EVO 420 mg q.m. N = 110**	**PLA q.2w. N = 54**	**PLA q.m. N = 55**
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –54.79 (–60.47 to –49.12), *P* < 0.001 **EVO 420 mg:** –54.95 (–61.95 to –47.96), *P* < 0.001			
TG, % Change from baseline				
Mean (SD) baseline, mmol/L	1.47 (0.68)	1.40 (0.66)	1.39 (1.03)	1.35 (0.59)
LSM[a] (SE), weeks 10 and 12	–13.27 (2.14)	–9.25 (2.27)	9.09 (3.02)	7.49 (3.26)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –22.36 (–29.48 to –15.24), *P* < 0.001 **EVO 420 mg:** –16.74 (–24.43 to –9.05), *P* < 0.001			
LSM[a] (SE), week 12	–16.09 (2.49)	–5.13 (2.84)	3.50 (3.51)	6.43 (4.15)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –19.59 (–27.92 to –11.26), *P* < 0.001 **EVO 420 mg:** –11.56 (–21.38 to –1.74), *P* = 0.021			
VLDL-C, % Change from baseline				
Mean (SD) baseline, mmol/L	0.67 (0.31)	0.64 (0.30)	0.60 (0.28)	0.62 (0.27)
LSM[a] (SE), weeks 10 and 12	–13.97 (2.06)	–9.20 (2.27)	8.66 (2.90)	6.34 (3.27)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –22.63 (–29.46 to –15.81), *P* < 0.001 **EVO 420 mg:** –15.54 (–23.25 to –7.84), *P* < 0.001			
LSM[a] (SE), week 12	–17.25 (2.48)	–5.06 (2.84)	3.73 (3.50)	4.10 (4.17)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –20.97 (–29.29 to –12.66), *P* < 0.001 **EVO 420 mg:** –9.17 (–19.01 to 0.68), *P* = 0.068			

Apo = apolipoprotein; CI = confidence interval; EVO = evolocumab; HDL-C = high-density–lipoprotein cholesterol; Lp(a) = lipoprotein (a); LSM = least squares mean; PLA = placebo; q.2w. = every two weeks; q.m. = once monthly; SD = standard deviation; SE = standard error; VLDL-C = very–low-density–lipoprotein cholesterol.

[a] LSM is from the repeated measures model, which includes treatment group, stratification factors (from IVRS), scheduled visit, and the interaction of treatment with scheduled visit as covariates.

Source: Clinical Study Report for RUTHERFORD-2.[8]

TABLE 37: OTHER OUTCOMES, DESCARTES

	DESCARTES	
	EVO 420 mg q.m. N = 599	**PLA q.m. N = 302**
Apo B, % Change from baseline		
Mean (SD) baseline, g/L	0.9 (0.2)	0.9 (0.2)
LSM [a] (SE)	–41.26 (1.02)	2.94 (1.41)
Treatment difference versus placebo (95% CI)	–44.21 (–47.56 to –40.85), *P* < 0.001 [b]	
Lp(a), % Change from baseline		
Mean (SD) baseline, nmol/L	84.0 (98.5)	89.3 (108.6)
LSM [a] (SE)	–27.72 (1.19)	–5.37 (1.62)
Treatment difference versus placebo (95% CI)	–22.35 (–26.15 to –18.55), *P* < 0.001 [b]	
Non-HDL-C, % Change from baseline	N = 515	N = 263
Mean (SD) baseline, mmol/L	3.2 (0.7)	3.2 (0.7)
LSM [a] (SE)	–41.82 (1.21)	8.44 (1.68)
Treatment difference versus placebo (95% CI)	–50.27 (–54.25 to –46.28), *P* < 0.001 [b]	
Triglycerides, % Change from baseline	N = 515	N = 263
Mean (SD) baseline, mmol/L	1.4 (0.7)	1.4 (0.7)
LSM [a] (SE)	–2.55 (1.72)	8.99 (2.39)
Treatment difference versus placebo (95% CI)	–11.54 (–17.21 to –5.86), *P* < 0.001 [b]	
VLDL-C, % Change from baseline	N = 511	N = 261
Mean (SD) baseline, mmol/L	0.5 (0.3)	0.6 (0.3)
LSM [a] (SE)	2.74 (3.36)	31.89 (4.69)
Treatment difference versus placebo (95% CI)	–29.15 (–40.23 to –18.08), *P* < 0.001 [b]	

Apo = apolipoprotein; CI = confidence interval; EVO = evolocumab; HDL-C = high-density–lipoprotein cholesterol; Lp(a) = lipoprotein (a); LSM = least squares mean; PLA = placebo; q.m. = once monthly; SD = standard deviation; SE = standard error; VLDL-C = very–low-density–lipoprotein cholesterol.

[a] LSM is from the repeated measures model, which includes treatment group, stratification factor(s) (from IVRS), scheduled visit, and the interaction of treatment with scheduled visit as covariates.

[b] Adjusted *P* value is based on a combination of sequential testing, the Hochberg procedure, the fallback procedure to control the overall significance level for all primary and secondary end points. Each individual adjusted *P* value is compared with 0.05 to determine statistical significance.

Source: Clinical Study Report for DESCARTES.[9]

TABLE 38: OTHER OUTCOMES, GAUSS-2

	GAUSS-2			
	EVO 140 mg q.2w. N = 103	EVO 420 mg q.m. N = 102	EZE/ PLA q.2w. N = 51	EZE/PLA q.m. N = 51
Apo B, % Change from baseline				
Mean (SD) baseline, g/L	1.40 (0.32)	1.33 (0.32)	1.40 (0.37)	1.40 (0.31)
LSM [a] (SE)	–45.88 (1.68)	–46.01 (1.65)	–13.67 (2.15)	–11.02 (2.21)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –32.20 (–36.92 to –27.49), *P* < 0.001 **EVO 420 mg:** –34.99 (–39.59 to –30.39), *P* < 0.001			
Lp(a), % Change from baseline				
Mean (SD) baseline, nmol/L	66.2 (72.5)	70.9 (99.9)	106.3 (101.0)	76.6 (96.7)
LSM [a] (SE)	–26.20 (2.64)	–23.72 (2.97)	–2.30 (3.36)	1.55 (4.01)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –23.90 (–31.27 to –16.54), *P* < 0.001 **EVO 420 mg:** –25.26 (–33.75 to –16.77), *P* < 0.001			
Non-HDL-C, % Change from baseline				
Mean (SD) baseline, mmol/L	5.90 (1.47)	5.75 (1.64)	5.99 (1.71)	6.03 (1.48)
LSM [a] (SE)	–48.72 (1.64)	–49.13 (1.40)	–17.18 (2.15)	–14.54 (1.86)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –31.53 (–36.34 to –26.73), *P* < 0.001 **EVO 420 mg:** –34.58 (–38.63 to –30.54), *P* < 0.001			
Triglycerides, % Change from baseline				
Mean (SD) baseline, mmol/L	2.03 (0.90)	1.69 (0.71)	2.07 (0.90)	2.11 (0.92)
LSM [a] (SE)	–6.32 (2.94)	–6.73 (3.44)	–3.74 (3.88)	–0.32 (4.65)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –2.59 (–11.38 to 6.20), *P* = 0.56 **EVO 420 mg:** –6.42 (–16.55 to 3.71), *P* = 0.21			
VLDL-C, % Change from baseline				
Mean (SD) baseline, mmol/L	0.91 (0.38)	0.77 (0.33)	0.95 (0.41)	0.96 (0.41)
LSM [a] (SE)	–7.60 (2.89)	–6.46 (3.21)	–5.76 (3.80)	–2.93 (4.41)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –1.84 (–10.43 to 6.75), *P* = 0.67 **EVO 420 mg:** –3.53 (–13.12 to 6.06), *P* = 0.47			

Apo = apolipoprotein; CI = confidence interval; EVO = evolocumab; EZE = ezetimibe; HDL-C = high-density–lipoprotein cholesterol; Lp(a) = lipoprotein (a); LSM = least squares mean; PLA = placebo; q.2w. = every two weeks; q.m. = once monthly; SD = standard deviation; SE = standard error; VLDL-C = very–low-density–lipoprotein cholesterol.

[a] LSM is from the repeated measures model, which includes treatment group, stratification factors (from IVRS), scheduled visit, and the interaction of treatment with scheduled visit as covariates.

Source: Clinical Study Report for GAUSS-2.[10]

TABLE 39: SUBGROUP ANALYSES, LAPLACE-2 — HIGH-INTENSITY, ATORVASTATIN 80 MG

	LAPLACE-2					
	EVO 140 mg q.2w.	**EVO 420 mg q.m.**	**EZE/PLA q.2w.**	**EZE/PLA q.m.**	**PLA q.2w.**	**PLA q.m.**
LDL-C at Baseline						
< Baseline Median (260.0 mg/dL)						
Mean (SD) day 1						
LSM [a] (SE) % (weeks 10 and 12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference (95% CI)	[redacted]			[redacted]		
LSM [a] (SE) % change (week 12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference (95% CI)	[redacted]			[redacted]		
≥ Baseline Median (260.0 mg/dL)						
Mean (SD) day 1						
LSM [a] (SE) % weeks 10 and 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference versus placebo (95% CI)	[redacted]			[redacted]		
Interaction *P* value	[redacted]			[redacted]		
LSM [a] (SE) % change (week 12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference versus placebo (95% CI)	[redacted]			[redacted]		
Interaction *P* value	[redacted]			[redacted]		
Baseline CHD Risk Factors						
Baseline CHD Risk Factors < 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LSM [a] (SE) % (weeks 10 and 12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference (95% CI)	[redacted]			[redacted]		

	LAPLACE-2					
	EVO 140 mg q.2w.	**EVO 420 mg q.m.**	**EZE/PLA q.2w.**	**EZE/PLA q.m.**	**PLA q.2w.**	**PLA q.m.**
	[redacted]			[redacted]		
LSM [a] (SE) % change (week 12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference (95% CI)	[redacted]			[redacted]		
Baseline CHD Risk Factors ≥ 2						
LSM [a] (SE) % (weeks 10 and 12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference (95% CI)	[redacted]			[redacted]		
LSM [a] (SE) % change (week 12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference (95% CI)	[redacted]			[redacted]		
Interaction *P* value (10/12 weeks)	[redacted]			[redacted]		
Interaction *P* value (12 weeks)	[redacted]			[redacted]		

CI = confidence interval; EVO = evolocumab; EZE = ezetimibe; HDL-C = high-density–lipoprotein cholesterol; Lp(a) = lipoprotein (a); LSM = least squares mean; PLA = placebo; q.2w. = every two weeks; q.m. = once monthly; SD = standard deviation; SE = standard error.

[a] LSM is from the repeated measures model, which includes treatment group, stratification factor (from IVRS), scheduled visit, and the interaction of treatment with scheduled visit as covariates.

Source: Clinical Study Report for LAPLACE-2.[7]

TABLE 40: SUBGROUP ANALYSES, LAPLACE-2 — ATORVASTATIN 10 MG

	LAPLACE-2					
	EVO 140 mg q.2w.	**EVO 420 mg q.m.**	**EZE/PLA q.2w.**	**EZE/PLA q.m.**	**PLA q.2w.**	**PLA q.m.**
LDL-C Baseline						
LDL-C <Baseline Median (260.0 mg/dL)						
Mean (SD) day 1						
LSM [a] (SE) % change (weeks 10 and 12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference versus placebo (95% CI)	[redacted]			[redacted]		
LSM [a] (SE) % change (week 12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference versus placebo (95% CI)	[redacted]			[redacted]		
LDL-C ≥ Baseline Median (260.0 mg/dL)						
Mean (SD) day 1						
LSM [a] (SE) % change (weeks 10 and 12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference versus placebo (95% CI)	[redacted]			[redacted]		
Interaction *P* value	[redacted]			[redacted]		
LSM [a] (SE) % change (week 12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference versus placebo (95% CI)	[redacted]			[redacted]		
Interaction *P* value	[redacted]			[redacted]		
Baseline CHD Risk Factors						
Baseline CHD Risk Factors < 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LSM [a] (SE) % change (weeks 10 and 12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference (95% CI)	[redacted]			[redacted]		

	LAPLACE-2					
	EVO 140 mg q.2w.	**EVO 420 mg q.m.**	**EZE/PLA q.2w.**	**EZE/PLA q.m.**	**PLA q.2w.**	**PLA q.m.**
	[redacted]			[redacted]		
LSM [a] (SE) % change (week 12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference (95% CI)	[redacted]			[redacted]		
Baseline CHD Risk Factors ≥ 2						
LSM [a] (SE) % change (weeks 10 and 12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference (95% CI)	[redacted]			[redacted]		
LSM [a] (SE) % change (week 12)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference (95% CI)	[redacted]			[redacted]		
Interaction *P* value (weeks 10/12)	[redacted]			[redacted]		
Interaction *P* value (week 12)	[redacted]			[redacted]		

CHD = coronary heart disease; CI = confidence interval; EVO = evolocumab; EZE = ezetimibe; LDL-C = low-density–lipoprotein cholesterol; LSM = least squares mean; PLA = placebo; q.2w. = every two weeks; q.m. = once monthly; SD = standard deviation; SE = standard error.

[a] LSM is from the repeated measures model, which includes treatment group, stratification factor (from IVRS), scheduled visit, and the interaction of treatment with scheduled visit as covariates.

Source: Clinical Study Report for LAPLACE-2.[7]

TABLE 41: SUBGROUP ANALYSES, LAPLACE-2 — MODERATE-INTENSITY, ROSUVASTATIN 5MG

	EVO 140 mg q.2w. N = 111	EVO 420 mg q.m. N = 112	PLA q.2w. N = 56	PLA q.m. N = 55
LDL-C < Baseline Median (260.0 mg/dL)				
Mean (SD) day 1				
LSM (SE) % change (weeks 10 and 12)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference versus placebo (95% CI)	[redacted]			

	EVO 140 mg q.2w. N = 111	EVO 420 mg q.m. N = 112	PLA q.2w. N = 56	PLA q.m. N = 55
LSM (SE) % change (week 12)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference versus placebo (95% CI)	[redacted]			
LDL-C ≥ Baseline Median (260.0 mg/dL)				
Mean (SD) day 1				
LSM (SE) % change (weeks 10 and 12)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference versus placebo (95% CI)	[redacted]			
Interaction *P* value	[redacted]			
LSM (SE) % change (week 12)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference versus placebo (95% CI)	[redacted]			
Interaction *P* value	[redacted]			
Baseline CHD Risk Factors				
Baseline CHD Risk Factors < 2	[redacted]	[redacted]	[redacted]	[redacted]
LSM (SE) % change (weeks 10 and 12)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference (95% CI)	[redacted]			
LSM (SE) % change (week 12)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference (95% CI)	[redacted]			
Baseline CHD Risk Factors ≥ 2	[redacted]	[redacted]	[redacted]	[redacted]
LSM (SE) % change (weeks 10 and 12)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference (95% CI)	[redacted]			
LSM (SE) % change (week 12)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference (95% CI)	[redacted]			
Interaction *P* value (weeks 10/12)	[redacted]			
Interaction *P* value (week 12)	[redacted]			

CHD = coronary heart disease; CI = confidence interval; EVO = evolocumab; LDL-C = low-density–lipoprotein cholesterol; LSM = least squares mean; PLA = placebo; q.2w. = every two weeks; q.m. = once monthly; SD = standard deviation; SE = standard error.
Source: Clinical Study Report for LAPLACE-2.[7]

TABLE 42: SUBGROUP ANALYSES, LAPLACE-2 — HIGH-INTENSITY, ROSUVASTATIN 40 MG

	EVO 140 mg q.2w. N = 111	EVO 420 mg q.m. N = 112	PLA q.2w. N = 56	PLA q.m. N = 55
LDL-C < Baseline Median (260.0 mg/dL)				
Mean (SD) day 1				
LSM % change (weeks 10 and 12), mean (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference versus placebo (95% CI)	[redacted]			
LSM % change (week 12), mean (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference versus placebo (95% CI)	[redacted]			
LDL-C ≥ Baseline Median (260.0 mg/dL)				
Mean (SD) day 1				
LSM % change (weeks 10 and 12), mean (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference versus placebo (95% CI)	[redacted]			
Interaction *P* value	[redacted]			
LSM % change (week 12), mean (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference versus placebo (95% CI)	[redacted]			
Interaction *P* value	[redacted]			
Baseline CHD Risk Factors				
Baseline CHD Risk Factors < 2	[redacted]	[redacted]	[redacted]	[redacted]
LSM (SE) % change (weeks 10 and 12)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference (95% CI)	[redacted]			
LSM (SE) % change (week 12)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference (95% CI)	[redacted]			

	EVO 140 mg q.2w. N = 111	EVO 420 mg q.m. N = 112	PLA q.2w. N = 56	PLA q.m. N = 55
Baseline CHD Risk Factors ≥ 2	[redacted]	[redacted]	[redacted]	[redacted]
LSM (SE) % change (weeks 10 and 12)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference (95% CI)	[redacted]			
LSM (SE) % change (week 12)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference (95% CI)	[redacted]			
Interaction *P* value (weeks 10/12)	[redacted]			
Interaction *P* value (week 12)	[redacted]			

CHD = coronary heart disease; CI = confidence interval; EVO = evolocumab; LDL-C = low-density–lipoprotein cholesterol; LSM = least squares mean; PLA = placebo; q.2w. = every two weeks; q.m. = once monthly; SD = standard deviation; SE = standard error.
Source: Clinical Study Report for LAPLACE-2.[7]

TABLE 43: SUBGROUP ANALYSES, LAPLACE-2 — MODERATE-INTENSITY, SIMVASTATIN 40 MG

	EVO 140 mg q.2w. N = 111	EVO 420 mg q.m. N = 112	PLA q.2w. N = 56	PLA q.m. N = 55
LDL-C < Baseline Median (260.0 mg/dL)				
Mean (SD) day 1				
LSM (SE) % change (weeks 10 and 12)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference versus placebo (95% CI)	[redacted]			
LSM (SE) % change (week 12)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference versus placebo (95% CI)	[redacted]			
LDL-C ≥ Baseline Median (260.0 mg/dL)				
Mean (SD) day 1				
LSM (SE) % change (weeks 10 and 12)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference versus placebo (95% CI)	[redacted]			

	EVO 140 mg q.2w. N = 111	EVO 420 mg q.m. N = 112	PLA q.2w. N = 56	PLA q.m. N = 55
Interaction *P* value	[redacted]			
LSM (SE) % change (week 12)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference versus placebo (95% CI)	[redacted]			
Baseline CHD Risk Factors				
Baseline CHD Risk Factors < 2	[redacted]	[redacted]	[redacted]	[redacted]
LSM (SE) % change (weeks 10 and 12)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference (95% CI)	[redacted]			
LSM (SE) % change (week 12)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference (95% CI)	[redacted]			
Baseline CHD Risk Factors ≥ 2	[redacted]	[redacted]	[redacted]	[redacted]
LSM (SE) % change (weeks 10 and 12)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference (95% CI)	[redacted]			
LSM (SE) % change (week 12)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference (95% CI)	[redacted]			
Interaction *P* value (weeks 10/12)	[redacted]			
Interaction *P* value (week 12)	[redacted]			

CHD = coronary heart disease; CI = confidence interval; EVO = evolocumab; LDL-C = low-density–lipoprotein cholesterol; LSM = least squares mean; q.2w. = every two weeks; q.m. = once monthly; SD = standard deviation; SE = standard error.
Source: Clinical Study Report for LAPLACE-2.[7]

TABLE 44: SUBGROUP ANALYSES, RUTHERFORD-2

	RUTHERFORD-2			
	EVO 140 mg q.2w. N = 110	**EVO 420 mg q.m. N = 110**	**PLA q.2w. N = 54**	**PLA q.m. N = 55**
Screening LDL-C value (< 160 mg/dL, ≥ 160 mg/dL)				
LDL-C ≤ 160 mg/dL	N = 69	N = 67	N = 35	N = 34
LSM [a] (SE) % change, weeks 10 and 12	–62.06 (2.30)	–66.35 (2.00)	1.57 (3.23)	4.52 (2.88)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –63.62 (–71.49 to –55.76), P < 0.001 **EVO 420 mg:** –70.87 (–77.84 to –63.91), P < 0.001			
	N = 66	N = 65	N = 34	N = 28
LSM [a] (SE) % change, week 12	–62.25 (2.32)	–59.18 (2.77)	1.25 (3.26)	6.88 (4.07)
Treatment difference versus placebo (95% CI)	**EVO 140 mg:** –63.50 (–71.44 to –55.57), P < 0.001 **EVO 420 mg:** –66.06 (–75.82 to –56.29), P < 0.001			
LDL-C ≥ 160 mg/dL	N = 40	N = 40	N = 18	N = 20
LSM [a] (SE)	–58.40 (2.08)	–59.81 (2.75)	–4.80 (3.09)	–3.69 (3.97)
Treatment difference versus placebo [b] (95% CI)	**EVO 140 mg:** –53.60(–61.06 to –46.14), P < 0.001 **EVO 420 mg:** –56.12(–65.78 to –46.45), P < 0.001			
	N = 38	N = 38	N = 17	N = –18
LSM [a] (SE) % change, week 12	–58.15 (2.37)	–51.71 (3.57)	–7.02 (3.54)	1.13 (5.13)
Treatment difference versus placebo [b] (95% CI)	**EVO 140 mg:** –51.12 (–59.67 to –42.58), P < 0.001 **EVO 420 mg:** –52.84 (–65.36 to –40.33), P < 0.001			
Interaction *P* value (10/12 weeks)	0.067	0.015		
Interaction *P* value (12 weeks)	0.036	0.099		
Baseline CHD Risk Factors				
Baseline CHD Risk Factors < 2	[redacted]	[redacted]	[redacted]	[redacted]
LSM [a] (SE) % change, weeks 10 and 12	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference versus placebo [b] (95% CI)	[redacted]			
	[redacted]	[redacted]	[redacted]	[redacted]
LSM [a] (SE) % change, week 12	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference versus placebo [b] (95% CI)	[redacted]			

	RUTHERFORD-2			
	EVO 140 mg q.2w. N = 110	**EVO 420 mg q.m. N = 110**	**PLA q.2w. N = 54**	**PLA q.m. N = 55**
Baseline CHD Risk Factors ≥ 2	[redacted]	[redacted]	[redacted]	[redacted]
LSM [a] (SE) % change, weeks 10 and 12	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference versus placebo[b] (95% CI)	[redacted]			
	[redacted]	[redacted]	[redacted]	[redacted]
LSM [a] (SE) % change, week 12	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference versus placebo[b] (95% CI)	[redacted]			
Interaction *P* value (weeks 10/12)	[redacted]	[redacted]		
Interaction *P* value (week 12)	[redacted]	[redacted]		

CHD = coronary heart disease; CI = confidence interval; EVO = evolocumab; LDL-C = low-density–lipoprotein cholesterol; LSM = least squares mean; q.2w. = every two weeks; q.m. = once monthly; SE = standard error.

[a] LSM is from the repeated measures model within each subgroup, which includes treatment group, scheduled visit, and the interaction of treatment with scheduled visit as covariates.

[b] Treatment differences are within each dose frequency group using placebo in the same group as the reference.

Source: Clinical Study Report for RUTHERFORD-2.[8]

TABLE 45: SUBGROUP ANALYSES, DESCARTES

	DESCARTES	
Screening LDL-C value < Baseline Median (100.5 mg/dL)	**EVO 420 mg q.m. N = 599**	**PLA q.m. N = 302**
LDL-C < Baseline Median (100.5 mg/dL)	[redacted]	[redacted]
LSM[a] (SE) % change, week 52	[redacted]	[redacted]
Treatment difference versus placebo (95% CI)	[redacted]	
LDL-C ≥ Baseline Median (100.5 mg/dL)	[redacted]	[redacted]
LSM[a] (SE) % change, week 52	[redacted]	[redacted]
Treatment difference versus placebo (95% CI)	[redacted]	
Interaction P value	[redacted]	
Baseline CHD Risk Factors		
Baseline CHD Risk Factors <2	[redacted]	[redacted]
LSM[a] (SE) % change, week 52	[redacted]	[redacted]
Treatment difference versus placebo (95% CI)	[redacted]	
Baseline CHD Risk Factors ≥ 2	[redacted]	[redacted]
LSM[a] (SE) % change, week 52	[redacted]	[redacted]
Treatment difference versus placebo (95% CI)	[redacted]	
Interaction *P* value	[redacted]	
Background therapy		
Diet Only		
LSM[a] (SE) % change, week 52	[redacted]	[redacted]
Treatment difference versus placebo (95% CI)	[redacted]	
Diet + Atorvastatin 10 mg		
	[redacted]	[redacted]
LSM[a] (SE) % change, week 52	[redacted]	[redacted]
Treatment difference versus placebo (95% CI)	[redacted]	
Diet + Atorvastatin 80 mg		
	[redacted]	[redacted]
LSM[a] (SE) % change, week 52	[redacted]	[redacted]
Treatment difference versus placebo (95% CI)	[redacted]	

	DESCARTES	
Screening LDL-C value < Baseline Median (100.5 mg/dL)	**EVO 420 mg q.m. N = 599**	**PLA q.m. N = 302**
Diet + Atorvastatin 80 mg + Ezetimibe 10 mg		
	[redacted]	[redacted]
LSM[a] (SE) % change, week 52	[redacted]	[redacted]
Treatment difference versus placebo (95% CI)	[redacted]	
Interaction *P* value	[redacted]	

CHD = coronary heart disease; CI = confidence interval; EVO = evolocumab; LDL-C = low-density–lipoprotein cholesterol; LSM = least squares mean; q.m. = once monthly; SE = standard error.

[a] Within each subgroup, the LSM is from the repeated measures model, which includes treatment group, stratification factor(s) (from IVRS), scheduled visit, and the interaction of treatment with scheduled visit as covariates.

Source: Clinical Study Report for DESCARTES.[9]

TABLE 46: SUBGROUP ANALYSES, GAUSS-2

	GAUSS-2			
	EVO 140 mg q.2w. N = 103	**EVO 420 mg q.m. N = 102**	**EZE/PLA q.2w. N = 51**	**EZE/ q.m. N = 51**
Screening LDL-C value				
LDL-C < 180 mg/dL	[redacted]	[redacted]	[redacted]	[redacted]
LSM (SE) % change, weeks 10 and 12	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference versus placebo (95% CI)	[redacted]			
	[redacted]	[redacted]	[redacted]	[redacted]
LSM (SE) % change, week 12	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference versus placebo (95% CI)	[redacted]			
LDL-C ≥ 180 mg/dL	[redacted]	[redacted]	[redacted]	[redacted]
LSM (SE) % change, weeks 10 and 12	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference versus placebo (95% CI)	[redacted]			
	[redacted]	[redacted]	[redacted]	[redacted]
LSM (SE) % change, week 12	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference versus placebo (95% CI)	[redacted]			
Interaction P value (weeks 10/12)	[redacted]	[redacted]		
Interaction P value (week 12)	[redacted]	[redacted]		
Baseline CHD Risk Factors				
Baseline CHD Risk Factors <2	[redacted]	[redacted]	[redacted]	[redacted]
LSM (SE) % change, weeks 10 and 12	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference versus placebo (95% CI)	[redacted]			
	[redacted]	[redacted]	[redacted]	[redacted]
LSM (SE) % change, week 12	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference versus placebo (95% CI)	[redacted]			
Baseline CHD Risk Factors ≥ 2	[redacted]	[redacted]	[redacted]	[redacted]
LSM (SE) % change, weeks 10 and 12	[redacted]	[redacted]	[redacted]	[redacted]

	GAUSS-2			
	EVO 140 mg q.2w. N = 103	**EVO 420 mg q.m. N = 102**	**EZE/PLA q.2w. N = 51**	**EZE/ q.m. N = 51**
Treatment difference versus placebo (95% CI)				
LSM (SE) % change, week 12				
Treatment difference versus placebo (95% CI)				
Interaction P value (weeks 10/12)				
Interaction P value (week 12)				
Baseline Statin Use				
No Baseline Statin Use				
LSM (SE) % change, weeks 10 and 12				
Treatment difference versus placebo (95% CI)				
LSM (SE) % change, week 12				
Treatment difference versus placebo (95% CI)				
Baseline Statin Use				
LSM (SE) % change, weeks 10 and 12				
Treatment difference versus placebo (95% CI)				
LSM (SE) % change, week 12				
Treatment difference versus placebo (95% CI)				
Interaction P value (weeks 10/12)				
Interaction P value (week 12)				

CHD = coronary heart disease; CI = confidence interval; EVO = evolocumab; EZE = ezetimibe; LDL-C = low-density–lipoprotein cholesterol; LSM = least squares mean; q.2w. = every two weeks; q.m. = once monthly; SE = standard error.
Source: Clinical Study Report for GAUSS-2.[10]

APPENDIX 5: SUMMARY OF OTHER STUDIES — OSLER-2

Objectives

The objective of this section is to summarize the one-year interim analysis of the two-year open-label extension study OSLER-2.[29]

Summary

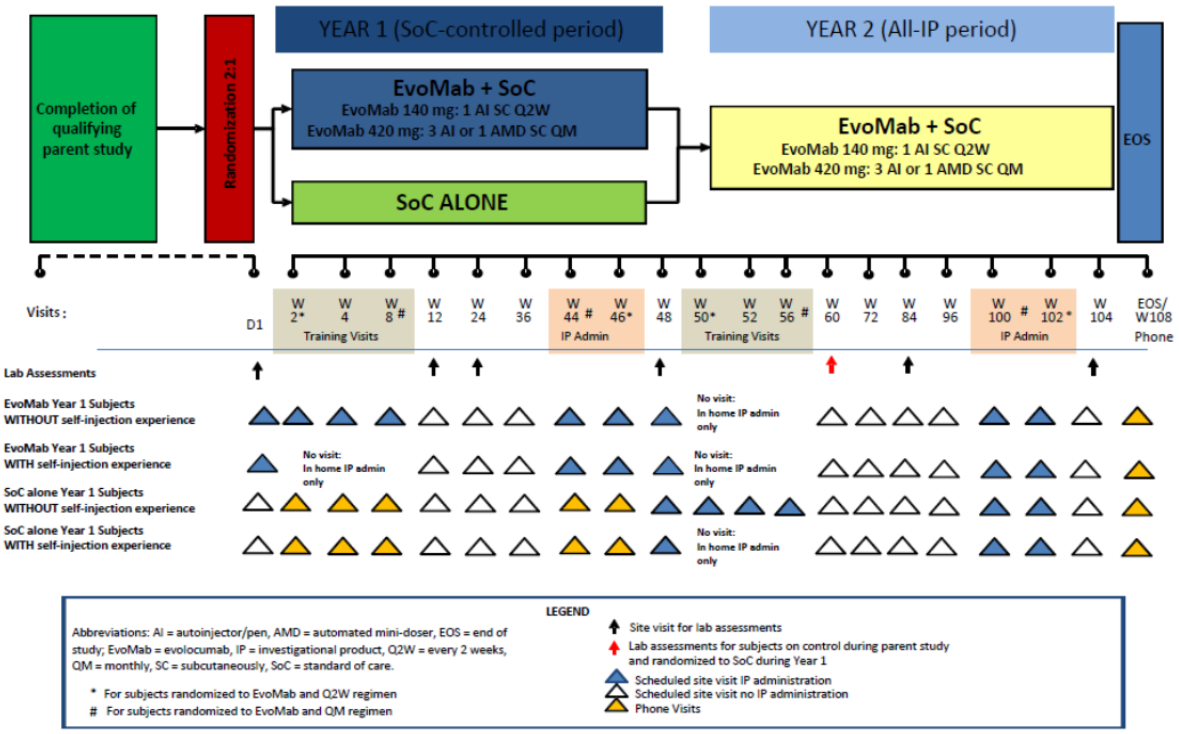
Study Design

The primary objective of study OSLER -2 was to characterize the safety and tolerability of long-term treatment with evolocumab. The overall study design is presented in Figure 6. It was a phase 3, multi-centre, randomized controlled open-label extension study designed to assess the long-term safety (at two years) and efficacy of evolocumab in patients with primary hyperlipidemia and mixed dyslipidemia. All patients had completed one of seven phase 2 or 3 studies (known as the "parent study") of evolocumab before enrolling in this study. Eligible patients were randomized 2:1 to receive subcutaneous evolocumab plus standard of care (one of two dose regimens in the evolocumab group or standard of care alone the control group) for the first 48 weeks of the study (also referred as year 1). Evolocumab was administered either 140 mg every two weeks or 420 mg once monthly. After week 48 (year 1), all patients entered the evolocumab treatment period (referred to as year 2), in which they received open-label evolocumab either 140 mg every two weeks or 420 mg once monthly for approximately one year or until the investigator recommended discontinuation. The primary outcome of this study was the patient's incidence of adverse events. The efficacy data (such as reduction in low-density–lipoprotein cholesterol), in terms of change from the study baseline (i.e., the end of the parent study) to the one-year cut-off, were not reported. Efficacy data were reported only for weeks 12 and 24 in the extension period. Statistical analyses in this open-label extension study were descriptive in nature.

Baseline Characteristics and Patient Disposition

At the time of the data cut-off for this interim report, 3,121 patients were randomized. However, only [redacted] (Table 47). [redacted] (Table 48).

FIGURE 6: STUDY DESIGN AND TREATMENT SCHEMA FOR OPEN-LABEL EXTENSION (STUDY 20120138)



AI = auto-injector; AMD = please define; EOS = end of study; EvoMab = evolocumab; IP = please define; Q2W = every two weeks; QM = once monthly; SC = subcutaneous; SoC = standard of care; W = week.
Source: Clinical Study Report for Study 20120138.[29]

TABLE 47: BASELINE AND DEMOGRAPHICS (INTERIM STANDARD-OF-CARE–CONTROLLED PERIOD ANALYSIS SET)

	Control in Parent Study		Evo in Parent Study		All		
	SoC (N = 352)	**Evo + SoC (N = 704)**	**SoC (N = 625)**	**Evo + SoC (N = 1,247)**	**SoC (N = 977)**	**Evo + SoC (N = 1,951)**	**Total (N = 2,928)**
Sex, n (%)							
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race, n (%)							
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Black or African American	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Native Hawaiian or Other Pacific Islander	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Caucasian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Region, n (%)							
North America	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Europe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asia Pacific	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age (years)							
n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Min–Max	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Evo = Evolocumab; SoC = standard of care.

[a] Parent study indicated the study the patient participated before enrolling in OSLER-2 open-label study.

Source: Clinical Study Report for OSLER-2, p. 161–4.

TABLE 48: PATIENT DISPOSITION (STANDARD-OF-CARE–CONTROLLED PERIOD, ALL RANDOMIZED PATIENTS)

	Control in Parent Study		Evo in Parent Study		All		
	SoC (N = 375) n (%)	Evo + SoC (N = 749) n (%)	SoC (N = 666) n (%)	Evo + SoC (N = 1,331) n (%)	SoC (N = 1,041) n (%)	Evo + SoC (N = 2,080) n (%)	Total (N = 3,121) n (%)
Patients screened							[redacted]
Patients included	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient who never received Evo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients who received Evo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients who completed SoC period	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients continuing SoC period	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients who discontinued study during the SoC period	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal of consent from study	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decision by sponsor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Evo = evolocumab; SoC = standard of care.
[a] Parent study indicated the study the patient participated before enrolling in OSLER-2 open-label study.
Source: Clinical Study Report for OSLER-2, p. 156.

Results

The adverse events profile is presented in Table 49 and Table 50. [redacted]

TABLE 49: SUMMARY OF OVERALL ADVERSE EVENTS (INTERIM STANDARD-OF-CARE–CONTROLLED PERIOD ANALYSIS SET)

	Control in Parent Study		Evo in Parent Study		All	
	SoC (N = 352) n (%)	Evo + SoC (N = 704) n (%)	SoC (N = 625) n (%)	Evo + SoC (N = 1,247) n (%)	SoC (N = 977) n (%)	Evo + SoC (N = 1,951) n (%)
All adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events leading to discontinuation of Evo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injection-related adverse events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Evo = evolocumab; SoC = standard of care.
[a] Parent study indicated the study the patient participated before enrolling in OSLER-2 open-label study.
Source: Clinical Study Report for OSLER-2, p. 92.

TABLE 50: ADVERSE EVENTS OCCURRING IN AT LEAST 1% OF PATIENTS (INTERIM STANDARD-OF-CARE–CONTROLLED PERIOD ANALYSIS SET)

	Control in Parent Study		Evo in Parent Study		All	
Preferred Term	SoC (N = 352) n (%)	Evo + SoC (N = 704) n (%)	SoC (N = 625) n (%)	Evo + SoC (N = 1,247) n (%)	SoC (N = 977) n (%)	Evo + SoC (N = 1,951) n (%)
Patients with AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infection						
Myalgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sinusitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Back Pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Control in Parent Study		Evo in Parent Study		All	
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Osteoarthritis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Influenza	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Muscle spasms	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injection-site erythema	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Musculoskeletal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injection-site pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asthma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; Evo = evolocumab; SoC = standard of care.
[a] Parent study indicated the study the patient participated before enrolling to OSLER-2 open-label study.
Source: Clinical Study Report for OSLER-2, p. 94.

Limitation of Study

The study is limited by its open-label nature. Participants were from seven previous phase 2 or phase 3 studies in which the inclusion criteria such as baseline severity may have varied. Concomitant medications allowed in the parent studies may also have been different. The interim analysis was done only at year 1 for the randomization period; there were no safety data for the two-year period. The efficacy data (such as reduction in low-density–lipoprotein cholesterol), in terms of change from the study baseline (i.e., the end of the parent study) to the one-year cut-off were not reported. Furthermore, the statistical analyses were descriptive in nature.

Conclusions

[redacted]

REFERENCES

1. Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J [Internet]. 2013 Dec [cited 2015 Sep 10];34(45):3478-90a. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3844152
2. Sniderman AD, Tsimikas S, Fazio S. The severe hypercholesterolemia phenotype: clinical diagnosis, management, and emerging therapies. J Am Coll Cardiol. 2014 May 20;63(19):1935-47.
3. Genest J, Hegele RA, Bergeron J, Brophy J, Carpentier A, Couture P, et al. Canadian Cardiovascular Society position statement on familial hypercholesterolemia: supplemental material. Can J Cardiol [Internet]. 2014 Sep 30 [cited 2015 Sep 10]. Available from: http://www.onlinecjc.ca/cms/attachment/2019041156/2039290283/mmc1.pdf
4. Sullivan D, Watts G, Craig IH, Cardiovascular Genetic Diseases Writing Group. Guidelines for the diagnosis and management of familial hypercholesterolaemia [Internet]. Sydney: Cardiac Society of Australia and New Zealand; 2013 Nov 30. [cited 2015 Sep 10]. Available from: http://www.csanz.edu.au/wp-content/uploads/2013/12/Familial_Hypercholesterolemia_2013.pdf
5. Marbach JA, McKeon JL, Ross JL, Duffy D. Novel treatments for familial hypercholesterolemia: pharmacogenetics at work. Pharmacotherapy. 2014 Sep;34(9):961-72.
6. Primary Panel, Genest J, Hegele RA, Bergeron J, Brophy J, Carpentier A, et al. Canadian Cardiovascular Society position statement on familial hypercholesterolemia. Can J Cardiol. 2014 Dec;30(12):1471-81.
7. Clinical Study Report: 20110115. A double-blind, randomized, placebo and ezetimibe controlled, multicenter study to evaluate safety, tolerability and efficacy of AMG 145 on LDL-C in combination with statin therapy in subjects with primary hypercholesterolemia and mixed dyslipidemia [**CONFIDENTIAL** internal manufacturer's report]. Thousand Oaks (CA): Amgen Inc.; 2014 Apr 30.
8. Clinical Study Report: 20110117. A double-blind, randomized, placebo and ezetimibe controlled, multicenter study to evaluate safety, tolerability and efficacy of AMG 145 on LDL-C in subjects with heterozygous familial hypercholesterolemia (RUTHERFORD-2) [**CONFIDENTIAL** internal manufacturer's report]. Thousand Oaks (CA): Amgen Inc.; 2014 Apr 8.
9. Clinical Study Report: 20110109. A double-blind, randomized, placebo-controlled, multicenter study to evaluate long-term tolerability and durable efficacy of AMG 145 on LDL-C in hyperlipidimic subjects [**CONFIDENTIAL** internal manufacturer's report]. Thousand Oaks (CA): Amgen Inc.; 2014 Jun 19.
10. Clinical Study Report: 20110116. A double-blind, randomized, multicenter study to evaluate safety, tolerability and efficacy of AMG 145, compared with ezetimibe, in hypercholesterolemic subjects unable to tolerate an effective dose of a HMG-CoA reductase inhibitor [**CONFIDENTIAL** internal manufacturer's report]. Thousand Oaks (CA): Amgen Inc.; 2014 Apr 6.
11. Robinson JG, Nedergaard BS, Rogers WJ, Fialkow J, Neutel JM, Ramstad D, et al. Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. JAMA. 2014 May 14;311(18):1870-82.
12. Raal FJ, Stein EA, Dufour R, Turner T, Civeira F, Burgess L, et al. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. Lancet. 2015 Jan 24;385(9965):331-40.

13. CDR submission: Repatha, 140 mg in 1.0 mL (140 mg/mL), solution for subcutaneous injection. Company: Amgen Canada Inc. [**CONFIDENTIAL** manufacturer's submission]. Mississauga: Amgen Canada Inc.; 2015 Jun.
14. Health Canada reviewer's report: Repatha (evolocumab) [**CONFIDENTIAL** internal report]. Ottawa: Therapeutics Products Directorate, Health Canada; 2015.
15. Blom DJ, Hala T, Bolognese M, Lillestol MJ, Toth PD, Burgess L, et al. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. N Engl J Med. 2014 May 8;370(19):1809-19.
16. Stroes E, Colquhoun D, Sullivan D, Civeira F, Rosenson RS, Watts GF, et al. Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. J Am Coll Cardiol. 2014 Jun 17;63(23):2541-8.
17. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Statistical review(s) [Internet]. In: Repatha (evolocumab). Company: Amgen, Inc. Application no.:125522. Approval date: 27/08/2015. Rockville (MD): FDA; 2015 Aug 24. (FDA drug approval package). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125522Orig1s000TOC.cfm.
18. Mancini GB, Tashakkor AY, Baker S, Bergeron J, Fitchett D, Frohlich J, et al. Diagnosis, prevention, and management of statin adverse effects and intolerance: Canadian Working Group Consensus update. Can J Cardiol. 2013 Dec;29(12):1553-68.
19. Pirillo A, Catapano AL. Statin intolerance: diagnosis and remedies. Curr Cardiol Rep. 2015 May;17(5):27.
20. Zhang H, Plutzky J, Skentzos S, Morrison F, Mar P, Shubina M, et al. Discontinuation of statins in routine care settings: a cohort study. Ann Intern Med [Internet]. 2013 Apr 2 [cited 2015 Nov 2];158(7):526-34. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3692286
21. Stroes ES, Thompson PD, Corsini A, Vladutiu GD, Raal FJ, Ray KK, et al. Statin-associated muscle symptoms: impact on statin therapy—European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. Eur Heart J [Internet]. 2015 May [cited 2015 Nov 2];36(17):1012-22. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4416140/
22. Cohen JC, Boerwinkle E, Mosley TH, Jr., Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N Engl J Med. 2006 Mar 23;354(12):1264-72.
23. Sabatine MS, Giugliano RP, Wiviott SD, Raal FJ, Blom DJ, Robinson J, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015 Apr 16;372(16):1500-9.
24. Swiger KJ, Martin SS. PCSK9 inhibitors and neurocognitive adverse events: exploring the FDA directive and a proposal for N-of-1 trials. Drug Saf. 2015 Jun;38(6):519-26.
25. Labonte P, Begley S, Guevin C, Asselin MC, Nassoury N, Mayer G, et al. PCSK9 impedes hepatitis C virus infection in vitro and modulates liver CD81 expression. Hepatology. 2009 Jul;50(1):17-24.
26. Rhainds D, Tardif JC. Reduction of LDL-C levels with AMG-145, a monoclonal antibody against PCSK9, in heterozygous familial hypercholesterolemia: the RUTHERFORD study. Clinical Lipidology. 2013;8(5):513-7.
27. Robinson JG, Rogers WJ, Nedergaard BS, Fialkow J, Neutel JM, Ramstad D, et al. Rationale and design of LAPLACE-2: a phase 3, randomized, double-blind, placebo- and ezetimibe-controlled trial evaluating the efficacy and safety of evolocumab in subjects with hypercholesterolemia on background statin therapy. Clin Cardiol [Internet]. 2014 Apr [cited 2015 Aug 7];37(4):195-203. Available from: http://onlinelibrary.wiley.com/doi/10.1002/clc.22252/epdf

28. Interim Clinical Study Report: 20110110. A multicenter, controlled, open-label extension study to assess the long-term safety and efficacy of evolocumab [**CONFIDENTIAL** internal manufacturer's report]. Thousand Oaks (CA): Amgen Inc.; 2014 Jul 10.

29. Interim Clinical Study Report: 20120138. A multicenter, controlled, open-label extension (OLE) study to assess the long-term safety and efficacy of AMG 145 - 2 [**CONFIDENTIAL** internal manufacturer's report]. Thousand Oaks (CA): Amgen Inc.; 2014 Jul 7. OSLER 2.

30. Koren MJ, Lundqvist P, Bolognese M, Neutel JM, Monsalvo ML, Yang J, et al. Anti-PCSK9 monotherapy for hypercholesterolemia: the MENDEL-2 randomized, controlled phase III clinical trial of evolocumab. J Am Coll Cardiol. 2014 Jun 17;63(23):2531-40.

31. Desai NR, Giugliano RP, Zhou J, Kohli P, Somaratne R, Hoffman E, et al. AMG 145, a monoclonal antibody against PCSK9, facilitates achievement of national cholesterol education program-adult treatment panel III low-density lipoprotein cholesterol goals among high-risk patients: an analysis from the LAPLACE-TIMI 57 trial (LDL-C assessment with PCSK9 monoclonal antibody inhibition combined with statin thErapy-thrombolysis in myocardial infarction 57). J Am Coll Cardiol. 2014 Feb 11;63(5):430-3.

32. Hirayama A, Honarpour N, Yoshida M, Yamashita S, Huang F, Wasserman SM, et al. Effects of evolocumab (AMG 145), a monoclonal antibody to PCSK9, in hypercholesterolemic, statin-treated Japanese patients at high cardiovascular risk--primary results from the phase 2 YUKAWA study. Circ J [Internet]. 2014 [cited 2015 Aug 7];78(5):1073-82. Available from: https://www.jstage.jst.go.jp/article/circj/78/5/78_CJ-14-0130/_pdf

33. Koren MJ, Giugliano RP, Raal FJ, Sullivan D, Bolognese M, Langslet G, et al. Efficacy and safety of longer-term administration of evolocumab (AMG 145) in patients with hypercholesterolemia: 52-week results from the Open-Label Study of Long-Term Evaluation Against LDL-C (OSLER) randomized trial. Circulation [Internet]. 2014 Jan 14 [cited 2015 Aug 7];129(2):234-43. Available from: http://circ.ahajournals.org/content/129/2/234.full.pdf+html

34. Desai NR, Kohli P, Giugliano RP, O'Donoghue ML, Somaratne R, Zhou J, et al. AMG145, a monoclonal antibody against proprotein convertase subtilisin kexin type 9, significantly reduces lipoprotein(a) in hypercholesterolemic patients receiving statin therapy: an analysis from the LDL-C Assessment with Proprotein Convertase Subtilisin Kexin Type 9 Monoclonal Antibody Inhibition Combined with Statin Therapy (LAPLACE)-Thrombolysis in Myocardial Infarction (TIMI) 57 trial. Circulation [Internet]. 2013 Aug 27 [cited 2015 Aug 7];128(9):962-9. Available from: http://circ.ahajournals.org/content/128/9/962.full.pdf+html

35. Raal FJ, Honarpour N, Blom DJ, Hovingh GK, Xu F, Scott R, et al. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial. Lancet. 2015 Jan 24;385(9965):341-50.

36. Clinical Study Report: 20110233. A 2-part, phase 2/3 study to assess the safety, tolerability and efficacy of AMG 145 in subjects with homozygous familial hypercholesterolemia. Part A - Open-label, single-arm, multicenter pilot study to evaluate safety, tolerability and efficacy of AMG 145 in subjects with homozygous familial hypercholesterolemia. Part B - Double-blind, randomized, placebo-controlled, multicenter study to evaluate safety, tolerability and efficacy of AMG 145 in subjects with homozygous familial hypercholesterolemia [**CONFIDENTIAL** internal manufacturer's report]. Thousand Oaks (CA): Amgen Inc.; 2014 Jun 3.