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CADTH COMMON DRUG REVIEW

Clinical Review Report (Resubmission)

EVOLOCUMAB (REPATHA)

(Amgen Canada Inc.)

Indication: As an adjunct to diet and maximally tolerated statin therapy in adult patients with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low-density lipoprotein cholesterol (LDL-C)

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Abbreviations

AE	adverse event
AI	auto-injector (pen)
ApoB	apolipoprotein-B
ASCVD	atherosclerotic cardiovascular disease
CDR	CADTH Common Drug Review
CI	confidence interval
CK	creatinine kinase
CCS	Canadian Cardiovascular Society
CDEC	CADTH Canadian Drug Expert Committee
CEC	clinical events committee
CHFC	Cardiac Health Foundation of Canada
CK	creatinine kinase
CV	cardiovascular
CVD	cardiovascular disease
eCRF	electronic Case Report Form
FAS	full analysis set
HC	hypercholesterolemia
HDL-C	high-density lipoprotein cholesterol
HeFH	heterozygous familial hypercholesterolemia
IAS	intravascular ultrasound analysis set
ITC	indirect treatment comparison
IVRS	interactive voice response system
IWRS	the interactive Web response system
IVUS	intravascular ultrasound
LDL-C	low-density lipoprotein cholesterol
LP-a	lipoprotein-a
LSM	least squares mean
MCID	minimal clinically important difference
MI	myocardial infarction
NMA	network meta-analysis
PAD	peripheral artery disease
PAV	per cent atheroma volume
PCSK9	pro-protein convertase subtilisin/kexin type 9
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
TAV	total atheroma volume

Drug	Evolocumab (Repatha).
Indication	As an adjunct to diet and maximally tolerated statin therapy in adult patients with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD) who require additional lowering of low-density lipoprotein cholesterol (LDL-C)
Reimbursement Request	For the treatment of patients as an adjunct to diet and maximally tolerated statin therapy in adult patients with clinical ASCVD who require additional lowering of LDL-C
Dosage Form	Solution for subcutaneous injection
NOC Date	10-09-2015
Manufacturer	Amgen Canada Inc.

Executive Summary

Introduction

Primary hypercholesterolemia is a key risk factor for various cardiovascular (CV) events, including myocardial infarction (MI), stroke, and death due to cardiovascular disease (CVD). Two key characteristics that tend to elevate the risk of developing CV events are familial hypercholesterolemia (heterozygous affects one in 500 Canadians; homozygous one in 1,000,000 Canadians)[1,2] and pre-existing clinical atherosclerotic cardiovascular disease (ASCVD).[3]

Modifications to diet and lifestyle are the recommended initial interventions for patients who do not have a compelling need for pharmacotherapy.[3] For many years, 3-hydroxy-3-methyl glutaryl co-enzyme A (HMG-CoA) reductase inhibitors (statins) have been the standard first-line pharmacotherapeutic intervention. The Canadian Cardiovascular Society (CCS) suggests targeting a low-density lipoprotein cholesterol (LDL-C) of < 2.0 mmol/L or a 50% reduction in LDL-C, with consideration to more aggressive targets of LDL-C < 1.8 mmol/L in patients with more recent acute coronary syndrome and established coronary disease.[3] The key limitation to the use of statins has been the development of myalgia, a relatively common tolerability issue that, in a much smaller number of patients, can progress to myositis or, rarely, rhabdomyolysis. After statins, the most commonly used therapeutic intervention is ezetimibe, a cholesterol absorption inhibitor that is typically combined with statins rather than used as monotherapy.[3]

Evolocumab is a fully human monoclonal antibody directed against pro-protein convertase subtilisin/kexin type 9 (PCSK9). PCSK9 is an enzyme that is involved in the processing of LDL-C receptors. PCSK9 facilitates the internalization and breakdown of LDL-C receptors; therefore, it is thought that inhibiting PCSK9 leads to an increase in LDL-C receptors, which in turn mobilizes LDL, removing it from the circulation. Evolocumab is administered as a subcutaneous injection, at either 420 mg once monthly or 140 mg twice monthly. It is indicated as an adjunct to diet and maximally tolerated statin therapy in adult patients with heterozygous familial hypercholesterolemia (HeFH) or clinical ASCVD who require additional lowering of LDL-C.

In February 2016, the CADTH Canadian Drug Expert Committee (CDEC) issued a recommendation that evolocumab be listed for patients with HeFH who require additional lowering of LDL-C as per the Health Canada approved indication. For patients with clinical ASCVD, CDEC recommended that evolocumab not be listed. The reasons cited for this decision were the short duration of the available clinical studies, which limited the ability to evaluate the clinical benefit of evolocumab in reducing clinical events, and an insufficient amount of clinical study evidence, specifically for patients who had experienced a prior CV event, as the manufacturer had requested listing criteria for high-risk patients who had experienced a prior CV event.[4] The focus of the resubmission was patients with ASCVD. The two new studies not available at the time of the original CADTH Common Drug Review (CDR) review are the Global Assessment of Plaque Regression with PCSK9 Antibody as Measured by Intravascular Ultrasound (GLAGOV), as well as the recently completed Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial. FOURIER was not part of the formal resubmission package from the manufacturer; however, results from FOURIER were recently published, and this study met the inclusion criteria for this systematic review.[5] Additionally, the manufacturer submitted data from a post hoc subgroup analysis of patients with ASCVD from the LDL-C Assessment with PCSK9 Monoclonal Antibody Inhibition Combined with Statin Therapy (LAPLACE-2) and Open-Label Study of Long-Term Evaluation Against LDL Cholesterol (OSLER-2) trials, and a network meta-analysis (NMA) comparing evolocumab to alirocumab and to ezetimibe in patients already taking statins.[5] With its large sample size (27,564 patients), high proportion of patients with established ASCVD (81% of patients had had a prior MI, for example), and focus on clinical events, the FOURIER trial is the most important element of the manufacturer's resubmission.

The objective of the current report was to perform a systematic review of the beneficial and harmful effects of evolocumab for the treatment of HeFH or clinical ASCVD as an adjunct to diet and maximally tolerated statin therapy in adult patients who require additional lowering of LDL-C. This current report is an update of the previous CDR review of evolocumab for this indication. The difference between the protocol for this review and the protocol for the previous submission to CDR is the removal of statins from the list of comparators and addition of alirocumab to the list of comparators. These changes were in line with the indication for evolocumab and its appropriate comparators.

Results and Interpretation

Included Studies

Two double-blind, randomized controlled trials (RCTs), both comparing evolocumab with placebo in patients with ASCVD not at the LDL-C target despite maximized statin therapy, met the inclusion criteria for this systematic review. FOURIER required patients to have clinically evident ASCVD (prior MI, stroke, or symptomatic peripheral artery disease). For example, 81% of the 27,546 patients had a previous MI, while in GLAGOV, only 35% of the 970 patients had a prior MI. FOURIER was an event-driven study, randomizing patients on stable statin doses in a 1:1 manner either to evolocumab or to placebo with a median follow-up of 26 months, while GLAGOV also randomized patients on a stable statin regimen to evolocumab or placebo over 78 weeks. FOURIER focused on various CV events for its primary and secondary outcomes, with the primary outcome being a composite of major CV events (CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization), and the key secondary outcome being a composite of CV death, MI, or stroke. Other secondary outcomes were all-cause mortality, as well as

individual components of the composite and other composites, such as CV death, hospitalization for worsening heart failure, and ischemic fatal or non-fatal stroke or transient ischemic attack. In GLAGOV, the primary outcome was the change in per cent atheroma volume from baseline to week 78; secondary outcomes included the nominal change in total atheroma volume to week 78 or patients with plaque regression at 78 weeks.

Key critical appraisal issues in GLAGOV included the lack of an established minimal clinically important difference for the primary outcome, making it challenging to place the 1% reduction in per cent atheroma volume into a clinical context. The GLAGOV study was also not powered to assess clinical outcomes such as mortality and CV mortality/morbidity. FOURIER was powered to assess clinical outcomes and was of sufficient size to assess uncommon harms such as neurocognitive events. Neither study was of sufficient duration to assess long-term safety, particularly since PCSK9 represents a novel pharmacologic target.

Efficacy

Evolocumab demonstrated superiority over placebo for both the primary and key secondary outcomes (CV death, MI, stroke) in FOURIER. Due to the fact that FOURIER was an event-driven study, the study end point for clinical events occurred at a median follow-up of 26 months rather than at a predetermined time point. 9.8% of evolocumab patients versus 11.3% of placebo patients had a primary outcome event; this difference between groups was statistically significant (hazard ratio 0.85, 95% confidence interval [CI], 0.79 to 0.92; $P < 0.001$). There was a smaller proportion of evolocumab- versus placebo-treated patients who reached the key secondary end point of CV death, MI, or stroke (5.9% versus 7.4% of patients); this difference was statistically significant (hazard ratio 0.80, 95% CI, 0.73 to 0.88, $P < 0.001$). There was no statistically significant difference in overall mortality (3.2% versus 3.1%) or CV mortality (1.8% versus 1.7%) between evolocumab and placebo. Patient input to CDR suggests that clinical events, most notably MI and stroke, are of importance to patients with ASCVD; these events, particularly MI, drove the results for the primary and key secondary composite outcomes. Where there was a lower proportion of evolocumab patients than placebo patients with an event, other secondary outcomes included MI (3.4% versus 4.6%, hazard ratio 0.73, 95% CI, 0.65 to 0.82, $P < 0.001$), stroke (1.5% versus 1.9%; hazard ratio 0.79, 95% CI, 0.66 to 0.95, $P = 0.01$), coronary revascularization (5.5% versus 7.0%; hazard ratio 0.78, 95% CI, 0.71 to 0.86, $P < 0.001$) and the composite of ischemic stroke or transient ischemic attack (1.7% versus 2.1%; hazard ratio 0.77, 95% CI, 0.65 to 0.92, $P = 0.003$). However, based on the manufacturer's statistical hierarchy, none of these should have been tested; thus, these analyses should be considered exploratory in nature.

FOURIER addressed two key limitations of the original CDR review by focusing on patients with established ASCVD and having sufficient power to focus on key clinical outcomes, such as overall mortality, CV mortality, and morbidity. FOURIER did not demonstrate a statistically significant benefit for evolocumab over placebo for overall mortality or for CV mortality; however, there was evidence of statistical superiority of evolocumab over placebo for major CV events and for the key secondary composite of CV death, MI, and stroke. The treatment effect for these composites, although statistically significant, was small (absolute difference of 1.5% between groups); therefore, the clinical significance of such a small difference is questionable. There was no evidence of heterogeneity in treatment effect from the subgroup analyses of FOURIER, suggesting that identifying a specific subpopulation for which evolocumab is better suited will be challenging. There

continues to be no direct evidence comparing evolocumab to alirocumab, the only other PCSK9 inhibitor marketed in Canada.

The manufacturer submitted an NMA by Toth et al. comparing evolocumab to alirocumab, ezetimibe, and placebo in patients with familial or non-familial hypercholesterolemia who were candidates for evolocumab or other lipid-lowering therapies as an add-on to statins (see Appendix 7 for the review).[6] Evolocumab lowered LDL-C to a greater extent than these comparators did; for example, at 12 weeks or more of follow-up, evolocumab evoked a mean per cent reduction in LDL-C of –19.65% (95% CI, –26.62 to –12.94) versus alirocumab 75 mg given biweekly, (–13.08%, 95% CI, –21.44 to –5.13) versus alirocumab 150 mg biweekly, (–45.97%, 95% CI, –52.88 to –39.21) versus ezetimibe, and a mean of –73.56% (95% CI, –78.67 to –65.87) versus placebo. These results would suggest an unusually large placebo response, perhaps calling into question the generalizability of the findings. Additional limitations of this NMA include the focus on patients with familial hypercholesterolemia versus patients with ASCVD; therefore, it may exclude patients that are relevant to the population in this resubmission. The NMA did not include results from either FOURIER or GLAGOV, nor did it include comparisons of clinical events or compare risk of harms. Therefore, it is not known what the potential clinical benefit of additional LDL-C lowering with evolocumab might be, or whether it would come at the expense of increased risk of adverse effects. There are a number of important limitations of such an analysis; however, the results do generate the hypothesis that the LDL-C lowering capability of the PCSK9 inhibitors may differ.

Harms

In FOURIER, the proportion of patients with an adverse event (AE) was similar between the evolocumab and placebo groups (77.4% in each) after a median follow-up of 26 months. After 78 weeks in GLAGOV, 76.9% of evolocumab-treated patients and 79.8% of placebo-treated patients experienced an AE. In FOURIER, the proportion of patients with a serious adverse event (SAE) was similar between the evolocumab (24.8%) and placebo (24.7%) groups. In GLAGOV, [redacted] of evolocumab-treated and [redacted] of placebo-treated patients experienced an SAE. The most serious AE in GLAGOV was [redacted], which occurred in [redacted] of evolocumab-treated and [redacted] of placebo-treated patients.

In GLAGOV, 3.3% of evolocumab patients and 2.3% of placebo patients withdrew due to an AE.

In FOURIER, the notable harms experienced after a median follow-up of 26 months for evolocumab versus placebo were as follows: neurocognitive AEs (1.6% of patients in the evolocumab group versus 1.5% in the placebo group), allergic reactions (3.1% versus 2.9%), muscle-related harms (5.0% versus 4.8%), and rhabdomyolysis (0.1% in each). Injection site reactions occurred in 2.1% of evolocumab-treated and 1.6% of placebo-treated patients. Adjudicated cases of new-onset diabetes were reported in 8.1% of evolocumab-treated and 7.7% of placebo-treated patients.

Findings from FOURIER addressed one of the key safety concerns associated with use of PCSK9 inhibitors, demonstrating no increased risk of neurocognitive events with evolocumab therapy over a median follow-up of 26 months. Since the original CDR review, new concerns have arisen over the development of neutralizing antibodies. The recent withdrawal of bococizumab due to a very high incidence of neutralizing antibodies has renewed focus on this issue across the class. Neutralizing antibodies were not detected in either FOURIER or GLAGOV. The length of follow-up in FOURIER was shorter than

originally planned (a median of 26 months versus approximately five years); therefore, a lack of long-term safety data remains a concern.

Conclusions

FOURIER addressed two key limitations of the original CDR submission, enrolling patients with established ASCVD and focusing on clinical end points. FOURIER demonstrated the superiority of evolocumab over placebo for the primary composite end point, as well as the key secondary composite of CV death, MI, or stroke, which was considered to be a meaningful outcome from a Health Technology Assessment perspective. The treatment effect was small for each of these end points, with an absolute difference between evolocumab and placebo of 1.5% for the primary and key secondary end points, and a hazard ratios of 0.85 (95% CI, 0.79 to 0.92; $P < 0.001$) for the primary end point and 0.80 (95% CI, 0.73, to 0.88, $P < 0.001$) for the key secondary end point. The clinical significance of such a difference is not clear.

The treatment effect appears to have been largely driven by an improvement in the risk of MI and stroke, and there was no difference in mortality (all-cause or CV) or hospitalizations for unstable angina between groups. The reduction in clinical events was less than what was anticipated based on the LDL reduction provided by evolocumab; however, this finding might have been due to the unexpectedly short follow-up in this trial (a median of 26 months versus the planned five years). GLAGOV was a much smaller study, and although it met its primary outcome, demonstrating the superiority of evolocumab over placebo for reduction in per cent atheroma volume, the clinical significance of this finding is less clear. An NMA provided by the manufacturer provides minimal value to assess comparative efficacy relative to that of the other available PCSK9 inhibitors or ezetimibe, as it did not evaluate clinical outcomes and did not include the results of FOURIER. There was no clear difference between evolocumab and placebo with respect to SAEs or AEs in either study. Notable harms, such as neurocognitive, muscle-related, and hepatic events, were also similar between evolocumab and placebo. There was a slight numerical increase in the risk of injection site reactions with evolocumab over placebo; this is not uncommon with monoclonal antibodies. The duration of follow-up (FOURIER: median of 26 months; GLAGOV: 78 weeks) is likely inadequate for assessing the long-term safety of PCSK9 inhibition. The relative efficacy and harms of evolocumab versus other available therapies such as alirocumab or ezetimibe, are currently unknown.

Table 1: Summary of Results

Outcome	FOURIER		GLAGOV	
	Evolocumab N = 13,784	Placebo N = 13,780	Evolocumab N = 484	Placebo N = 484
CV Death, MI, Stroke, Hospitalization For UA, or Coronary Revascularization (Primary Outcome in FOURIER)				
Participants, n (%)	1,344 (9.8)	1,563 (11.3)	NR	NR
HR [95% CI][a]	0.85 [0.79 to 0.92], *P* < 0.001[b]			
CV Death, MI, Stroke (Key Secondary)				
Participants, n (%)	816 (5.9)	1,013 (7.4)	NR	NR
HR [95% CI][a]	0.80 [0.73 to 0.88], *P* < 0.001[b]			
Other Secondary				
Mortality	444 (3.2)	426 (3.1)	3 (1)	4 (1)
HR [95% CI][a]	1.04 [0.91 to 1.19], *P* = 0.54			
CV death	251 (1.8)	240 (1.7)	[redacted]	[redacted]
HR [95% CI][a]	1.05 [0.88 to 1.25], *P* = 0.62			
Myocardial infarction	468 (3.4)	639 (4.6)	10 (2)	14 (3)
HR [95% CI][a]	0.73 [0.65 to 0.82], *P* < 0.001			
Hospitalization due to UA	236 (1.7)	239 (1.7)	3 (1)	4 (1)
HR [95% CI][a]	0.99 [0.82 to 1.18], *P* = 0.89			
Stroke	207 (1.5)	262 (1.9)	2 (< 1)	3 (1)
HR [95% CI][a]	0.79 [0.66 to 0.95], *P* = 0.01			
Coronary revascularization	759 (5.5)	965 (7.0)	NR	NR
HR [95% CI][a]	0.78 [0.71 to 0.86], *P* < 0.001			
Ischemic stroke or TIA	229 (1.7)	295 (2.1)		NR
HR [95% CI][a]	0.77 [0.65 to 0.92], *P* = 0.003			
CV death or hospitalization for worsening heart failure	402 (2.9)	408 (3.0)	NR	NR
HR [95% CI][a]	0.98 [0.86 to 1.13], *P* = 0.82			
LDL-C, % change				
Mean (SD) baseline, mmol/L	2.532 (0.748)	2.529 (0.703)	2.397 (0.712)	2.394 (0.696)
% Change from baseline to week 48 (FOURIER), week 78 (GLAGOV)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment difference[c] [95% CI] between groups, week 48	[redacted]		NR	
HARMS				
Serious Adverse Events				
Participants with > 0 SAEs, N (%)	3,410 (24.8)	3,404 (24.7)	[redacted]	[redacted]
Notable Harms				
Neurocognitive events	217 (1.6)	202 (1.5)	7 (1.4)	6 (1.2)
Injection site reaction	296 (2.1)	219 (1.6)	[redacted]	[redacted]
Allergic reaction	420 (3.1)	393 (2.9)	33 (6.8)	23 (4.8)
Muscle-related event	682 (5.0)	656 (4.8)	0	0
Rhabdomyolysis	8 (0.1)	11 (0.1)	0	0

Outcome	FOURIER		GLAGOV	
	Evolocumab N = 13,784	Placebo N = 13,780	Evolocumab N = 484	Placebo N = 484
Adjudicated case of new-onset diabetes	677 (8.1)	644 (7.7)	NR	NR
Aminotransferase level > 3 times ULN	240/13,543 (1.8)	242/13,523 (1.8)	NR	NR
Creatinine kinase level > 5 times ULN	95/13,543 (0.7)	99/13,523 (0.7)	NR	NR
Neutralizing antibodies	0	0	0	0
Binding antibodies	43 (0.3)	-	1 (0.2)	0

CI = confidence interval; CV = cardiovascular; HR = hazard ratio; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; NR = not reported; SAE = serious adverse event; SD = standard deviation; TIA = transient ischemic attack; UA = unstable angina; ULN = upper limit of normal.

[a] Hazard ratios and 95% confidence intervals were generated with the use of a Cox proportional-hazards model with stratification factors as covariates, and *P* values for time-to-event analyses were calculated with the use of log-rank tests.

[b] Statistically significant difference versus comparator; note *that P* values for mortality, MI, hospitalization due to UA, stroke, and coronary revascularization were reported, but should be considered exploratory according to the hierarchy for statistical testing.

[c] Least squares mean is from the repeated measures model, which includes treatment group, stratification factors (from interactive voice response system [IVRS]), scheduled visit, and the interaction of treatment with scheduled visit as covariates.

Source: Clinical Study Report for FOURIER[7] and GLAGOV.[8]

Introduction

Disease Prevalence and Incidence

Primary hypercholesterolemia is a key risk factor for various cardiovascular (CV) events, including myocardial infarction (MI), stroke, and death due to CV disease. Elevated cholesterol levels, most notably of low-density lipoprotein cholesterol (LDL-C), contribute to the development of atherosclerotic plaques, which damage the vascular endothelium and lead to vessel occlusion. Two key characteristics that tend to elevate the risk of developing CV events are familial hypercholesterolemia (heterozygous affects one in 500 Canadians; homozygous one in 1,000,000 Canadians)[1,2] and pre-existing atherosclerotic cardiovascular disease (ASCVD). ASCVD is much more common than the genetic forms of the disease.

Standards of Therapy

Modifications to diet and lifestyle are the recommended initial interventions for patients who do not have a compelling need for pharmacotherapy.[3] The standard first-line pharmacotherapeutic intervention for many years has been statins. The most recent Canadian Cancer Society (CCS) guidelines outline five high-risk conditions for which statin therapy is always indicated: clinical atherosclerosis, abdominal aortic aneurysm, diabetes mellitus, chronic kidney disease, and an LDL-C of 5 mmol/L or higher. CCS suggests targeting an LDL-C of < 2.0 mmol/L or a 50% reduction in LDL-C, with consideration of more aggressive targets of LDL-C < 1.8 mmol/L in patients with more recent acute coronary syndrome and established coronary disease.[3]

The key limitation to the use of statins has been the development of myalgia, a relatively common tolerability issue that, in a much smaller number of patients, can progress to myositis or, rarely, rhabdomyolysis. After statins, the most commonly used therapeutic intervention is ezetimibe, a cholesterol absorption inhibitor that is typically combined with statins rather than used as monotherapy. Additional lipid-lowering therapies, such as fibrates, bile acid binding resins, and niacin, are used infrequently.

Drug

Evolocumab is a fully human monoclonal antibody directed against pro-protein convertase subtilisin/kexin type 9 (PCSK9). PCSK9 is an enzyme that is involved in the processing of LDL-C receptors. PCSK9 facilitates the internalization and breakdown of LDL-C receptors. Therefore, it is thought that inhibiting PCSK9 leads to an increase in LDL-C receptors, which in turn mobilizes LDL, removing it from the circulation. Evolocumab is administered as a subcutaneous (SC) injection, either at 420 mg once monthly or 140 mg twice monthly. It is indicated as an adjunct to diet and maximally tolerated statin therapy in adult patients with heterozygous familial hypercholesterolemia (HeFH) or clinical ASCVD who require additional lowering of LDL-C. Evolocumab is also indicated as an adjunct to diet and other LDL-C lowering therapies (e.g., statins, ezetimibe, and LDL apheresis) in adults and adolescents ≥ 12 years of age with homozygous familial hypercholesterolemia who require additional lowering of LDL-C.

Table 2: Key Characteristics of PCSK9 Inhibitors, Statins, and Ezetimibe

	PCSK9 Inhibitors	Statins	Ezetimibe
Mechanism of Action	Inhibits PCSK9, increases LDL-C receptor density	Inhibits cholesterol synthesis via inhibition of HMG-CoA reductase	Reduces cholesterol absorption by inhibiting the intestinal Niemann–Pick Like1 transporter

Indication[a]	Evolocumab/alirocumab:
	As an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or clinical ASCVD who require additional lowering of LDL-C
	
	Evolocumab:
	As an adjunct to diet and other LDL-C lowering therapies (e.g., statins, ezetimibe, and LDL apheresis) in adults and adolescents ≥ 12 years of age with homozygous familial hypercholesterolemia who require additional lowering of LDL-C
		All:
		• Primary hypercholesterolemia
		• Mixed dyslipidemia
		• Various also indicated for:
		  ○ dysbetalipoproteinemia
		  ○ hypertriglyceridemia
		  ○ HeFH and HoFH
		  ○ HeFH in children
		
		Many statins also have cardiovascular indications, such as reducing the risk of coronary events in patients with/without clinically evident CHD, reducing the risk of major adverse cardiac events in patients with CHD who have undergone a PCI, and slowing progression of coronary atherosclerosis in patients with CHD.
			CAD

Route of Administration	Subcutaneous	Oral	Oral
Recommended Dose	Alirocumab: 75 mg every 2 weeks. If response is inadequate, can be increased to 150 mg every 2 weeks. Evolocumab: 140 mg every 2 weeks or 420 mg once monthly.	Various	10 mg once daily
Serious Side Effects/ Safety Issues	Hypersensitivity reactions	Contraindicated in active liver disease or unexplained, persistently abnormal transaminases. Warnings/precautions: elevated transaminases; myalgia; risk of hyperglycemia and type 2 diabetes	Contraindicated in active liver disease or unexplained, persistently elevated transaminases Warnings: hepatitis; pancreatitis; myopathy/ rhabdomyolysis/ myalgia
Other			

ASCVD = atherosclerotic cardiovascular disease; CAD = coronary artery disease; CHD = coronary heart disease; HeFH = heterozygous familial hypercholesterolemia; HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A; HoFH = homozygous familial hypercholesterolemia; LDL-C = Low-density lipoprotein cholesterol; PCSK9 = pro-protein convertase subtilisin/kexin type 9.

[a] Health Canada indication.

Source: Product monographs for evolocumab, alirocumab, statins, ezetimibe.[9]

Submission History

In February 2016, the CADTH Canadian Drug Expert Committee (CDEC) issued a recommendation that evolocumab be listed in patients with HeFH who require additional lowering of LDL-C as per the Health Canada approved indication. For patients with clinical ASCVD, CDEC recommended that evolocumab not be listed. The reasons cited for this decision were the lack of evidence that evolocumab reduces the risk of CV events and an insufficient amount of clinical study evidence, specifically for patients who had experienced a prior CV event.[4,5]

Four double-blind randomized controlled trials (RCTs) were included in the original CADTH Common Drug Review (CDR) review: LAPLACE-2, RUTHERFORD-2, DESCARTES, and GAUSS-2. DESCARTES was a 52-week study, while the other studies were 12 weeks in duration. The studies ranged in size from 307 to 1,899 patients; patients with established ASCVD made up < 35% of the population across the included studies. Across studies, patients were either on background statin therapy or ezetimibe. Evolocumab lowered LDL-C versus placebo or ezetimibe, with a per cent reduction versus ezetimibe of approximately 38% and a per cent reduction versus placebo of between 60% and 76% after 12 weeks. After 52 weeks in DESCARTES, LDL-C was reduced by 57% versus placebo. The studies were not powered to assess clinical outcomes; there were few CV events across studies; and there were no statistically significant differences between evolocumab and comparison groups for clinical outcomes in any study. At the submitted price, CDR's reanalysis of the manufacturer's pharmacoeconomic model suggested that evolocumab was cost-effective when combined with high-intensity statins in patients with HeFH who are unable to meet target LDL-C levels with currently available therapies (with an incremental cost-utility ratio of $23,822 to $68,813 per quality-adjusted life-year when compared with high-intensity statins alone or ezetimibe plus high-intensity statins). Therefore, CDEC recommended evolocumab in patients with HeFH who require additional lowering of LDL-C and who are receiving an optimally tolerated standard of care. However, due to the lack of data suggesting that evolocumab could reduce the risk of CV events in patients with clinical ASCVD, and the small proportion (< 35%) of patients with established ASCVD across the included studies, CDEC recommended that evolocumab not be listed in this population.

Basis of Resubmission

The focus of the resubmission is on the effects of evolocumab in patients with ASCVD, as measured either from studies not previously reviewed by CDR or from post hoc subgroup analyses of patients with ASCVD from studies completed at the time of the original CDR review of evolocumab.

The two new studies not available at the time of the original CDR review are the GLAGOV and the recently completed FOURIER trial. Both studies featured patients with ASCVD, although there appeared to be a higher proportion of patients with a prior CV event in FOURIER (for example, 81% had had a prior MI, versus 35% in GLAGOV). FOURIER was not part of the formal resubmission package from the manufacturer; however, results from FOURIER were recently published and this study met the inclusion criteria for this systematic review.[5]

Additionally, the manufacturer submitted data from a post hoc subgroup analysis of patients with ASCVD from the LAPLACE-2 and OSLER-2 trials. A network meta-analysis (NMA)

was also submitted comparing evolocumab with alirocumab and to ezetimibe in patients already taking statins.[5]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of evolocumab for the treatment of HeFH or clinical ASCVD, as an adjunct to diet and maximally tolerated statin therapy in adult patients who require additional lowering of LDL-C.

Methods

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

The difference between the protocol for this review and the protocol for the previous submission to CDR is the removal of statins from the list of comparators and the addition of alirocumab to the list of comparators. These changes were in line with the indication for evolocumab and its appropriate comparators.

Any studies included in the previous CDR review were excluded from the current review.

Table 3: Inclusion Criteria for the Systematic Review

Patient Population	Adults with clinical atherosclerotic CVD who require additional lowering of low-density lipoprotein cholesterol (LDL-C) Subgroups: • Baseline LDL-C • Established CVD at baseline • Concomitant use of anti-hyperlipidemics during study • Patients who are not candidates for or who are intolerant to statins • Ezetimibe use
Intervention	Evolocumab 140 mg SC every 2 weeks or 420 mg once monthly, as an adjunct to diet and maximally tolerated statin therapy
Comparators	Ezetimibe Alirocumab 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:
	  ○ ApoB
	  ○ LP-A
	  ○ Non–HDL-C
	  ○ TG
	  ○ VLDL-C
	
	Harms outcomes:
	AEs, SAEs, WDAEs
	Notable harms: immune reactions, injection site reactions, muscle symptoms, neurocognitive impairment, hepatitis C, elevated liver enzymes, and diabetes

Study Design	E.g., published and unpublished DB RCTs

AE = adverse event; ApoB = apolipoprotein-B; DB = double-blind; 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 and 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 Medical Subject Headings (MeSH), and keywords. The main search concept was Repatha (evolocumab).

No methodological filters were applied to limit retrieval. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. See Appendix 2 for the detailed search strategies.

The initial search was completed on March 20, 2017. Regular alerts were established to update the search until the CDEC meeting on July 19, 2017. 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 *Grey Matters* checklist (https://www.cadth.ca/grey-matters):

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

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 drug manufacturer 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; excluded studies (with reasons) are presented in Appendix 2: Literature Search Strategy.

Results

Findings from the Literature

A total of two studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4 and described in Included Studies. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

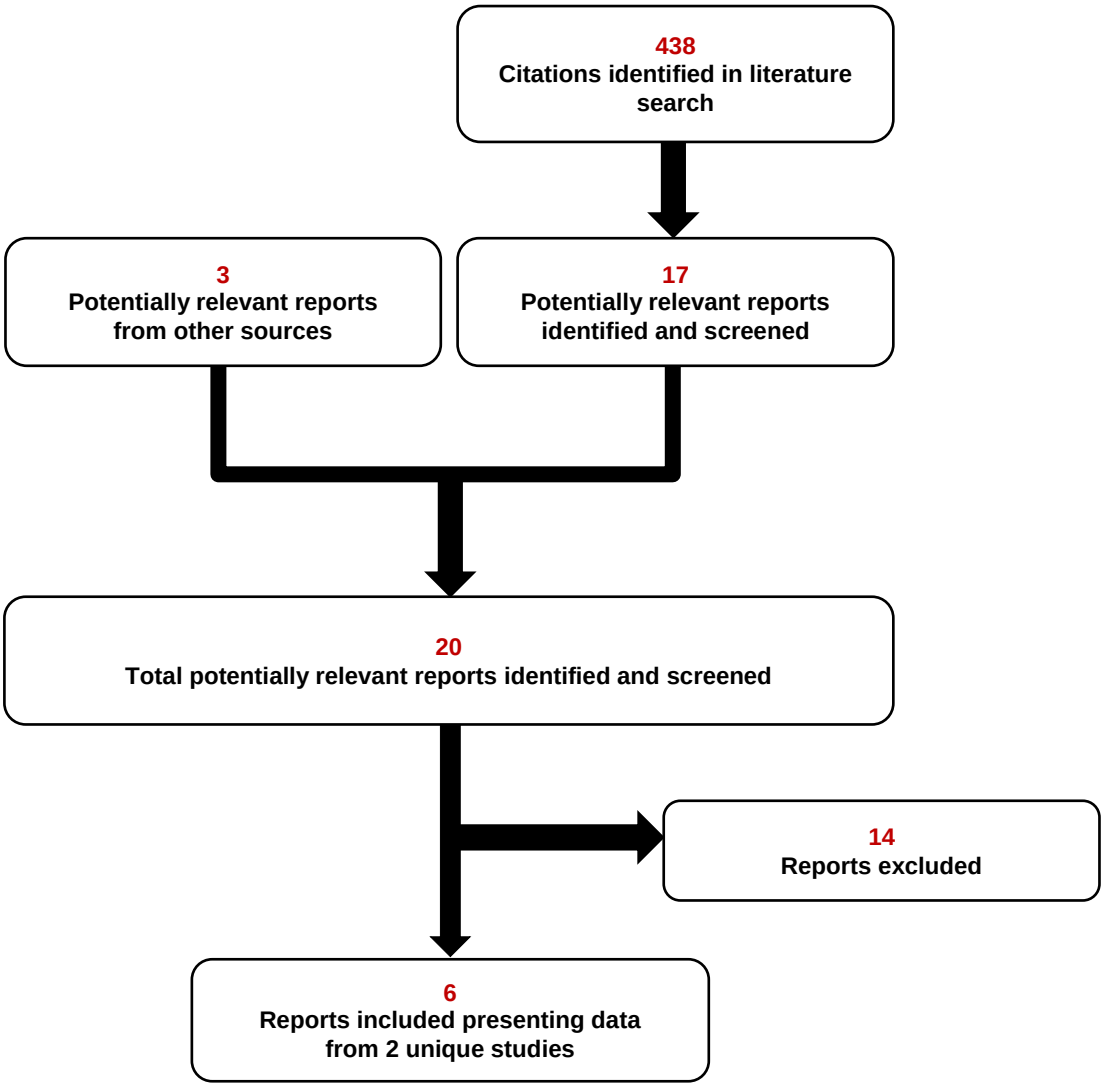


Table 4: Details of Included Studies

		FOURIER	GLAGOV
Designs & Populations	**Study Design**	DB RCT	DB RCT
	Locations	Canada, USA, Europe, South America, China, Australia, India, Israel, Korea, Japan, Malaysia, and South Africa	North America, Europe, South America, Asia, Australia, and South Africa
	Randomized (N)	27,564	970
	Inclusion Criteria	• Between 40 and 85 years of age. • Clinically evident atherosclerotic cardiovascular disease, defined as a history of myocardial infarction, non-hemorrhagic stroke, or symptomatic peripheral artery disease, as well as additional characteristics that placed them at higher cardiovascular risk. • Patients had to have a fasting LDL cholesterol level of ≥ 1.8 mmol/L or an HDL-C level of ≥ 2.6 mmol/L while they were taking an optimized regimen of lipid-lowering therapy, which was defined as preferably a high-intensity statin, but at least atorvastatin, at a dose of 20 mg daily or its equivalent, with or without ezetimibe. • Most recent fasting triglycerides ≤ 4.5 mmol/L by central laboratory before randomization.	• 18 years or older. • Demonstrated at least one epicardial coronary stenosis of ≥ 20% on clinically indicated coronary angiography and had a target vessel suitable for imaging, with 50% or less visual obstruction. • Patients were required to have been treated with a stable statin dose for ≥ 4 weeks and to have an LDL-C level of 2.07 mmol/L or higher or between 1.55 mmol/L and 2.07 mmol/L with one major or three minor cardiovascular risk factors. Major risk factors included non-coronary atherosclerotic vascular disease, myocardial infarction, hospitalization for unstable angina in the preceding 2 years, or type 2 diabetes mellitus. • Minor risk factors included current cigarette smoking, hypertension, low levels of high-density lipoprotein cholesterol, family history of premature coronary heart disease, high-sensitivity • C-reactive protein (hsCRP) level of 19.05 mmol/L or higher, or being age 50 years or older for men and 55 years or older for women. • By design, patients with an entry LDL-C level between 1.55 and 2.07 mmol/L were limited to 25% of the total patient cohort. • A 4-week lipid stabilization period was included for patients not currently taking lipid-modifying therapy at screening. Inclusion of patients intolerant to statins was limited to 10% of the total cohort.
	Exclusion Criteria	• Within 4 weeks of their most recent MI or stroke. • New York Heart Association class III or IV or last known left ventricular ejection fraction < 30%. • Estimated glomerular filtration rate < 20 mL/min/1.73m2. • Aspartate aminotransferase or alanine aminotransferase > 3 × upper limit of normal. • Known hemorrhagic stroke at any time. • Uncontrolled or recurrent ventricular tachycardia. • Planned or expected cardiac surgery or revascularization within 3 months after randomization. • Uncontrolled hypertension, defined as a sitting systolic blood pressure > 180 mm hg or a diastolic blood pressure > 110 mm hg.	• Uncontrolled diabetes or hypertension, heart failure, renal dysfunction, or liver disease. • Coronary artery bypass graft surgery < 6 weeks prior to the qualifying intravascular ultrasound. • Uncontrolled cardiac arrhythmia, defined as recurrent and highly symptomatic ventricular tachycardia, atrial fibrillation with rapid ventricular response, or supraventricular tachycardia not controlled by medications in the 3 months prior to randomization.

		FOURIER	GLAGOV
		• Use of cholesteryl ester transfer protein inhibition treatment, mipomersen, or lomitapide within 12 months prior to randomization. Fenofibrate therapy must be stable for at least 6 weeks prior to final screening at a dose that is appropriate for the duration of the study in the judgment of the investigator. Other fibrate therapy (and derivatives) are prohibited.	
DRUGS	**Intervention**	Evolocumab (either 140 mg every 2 weeks or 420 mg SC every month, according to patient preference)	Evolocumab 420 mg SC once monthly
	Comparator(s)	Placebo (matching)	Placebo SC once monthly
DURATION	**Phase**		
	Run-in	4 weeks to 12 weeks	2 weeks placebo run-in/screening 2 to 4 weeks: lipid stabilization period
	Double-blind	Study ends when 1,630 patients have reached the key secondary end point (median follow-up: 26 months).	78 weeks
	Follow-up	-	2 weeks
OUTCOMES	**Primary End Point**	Major CV events, defined as the composite of CV death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization	Nominal change in per cent atheroma volume from baseline to 78 weeks post-randomization, as determined by intravascular ultrasound (IVUS)
	Other End Points	The key secondary efficacy end point was the composite of CV death, myocardial infarction, or stroke. Other secondary outcomes included: • time to CV death • time to death by any cause • time to first myocardial infarction (fatal or non-fatal) • time to first stroke • time to first coronary revascularization • time to CV death or first hospitalization for worsening heart failure, whichever occurs first • time to ischemic fatal or non-fatal stroke or TIA, whichever occurs first. Exploratory end points included: • time to coronary death • total number of events from the components of the primary end point (myocardial infarction, hospitalization for unstable angina, stroke, coronary revascularization, and CV death) • LDL-C response (LDL-C <1.8 mmol/L]) at each scheduled assessment • change and per cent change from baseline at each scheduled assessment in each of the following parameters: LDL-C, total cholesterol, non-HDL-C, ApoB, total cholesterol/HDL-C ratio, ApoB/ApoA1 ratio, triglycerides, VLDL-C, HDL-C, ApoA1, LP-a • change from baseline in PCSK9 at each	Secondary end points included: • nominal change in normalized total atheroma volume from baseline to 78 weeks • percentage of patients showing plaque regression (any reduction from baseline in PAV and TAV) Exploratory end points included: • change in lipid parameters, such as LDL-C • incidence of adjudicated events (all-cause mortality, CV death, MI, hospitalization for unstable angina, coronary revascularization, stroke, TIA, and hospitalization for heart failure) Additional exploratory post hoc analyses included comparison of the change in PAV and percentage of patients undergoing regression of PAV in those with LDL-C ≤ 1.8 mmol/L at baseline. Safety: • treatment-emergent AE, laboratory values, and vital signs • ECG parameters • anti-evolocumab antibodies

		FOURIER	GLAGOV
		scheduled assessment • hemoglobin A1C at each scheduled assessment • hsCRP at each scheduled assessment AEs and central laboratory testing	
NOTES	**Publications**	Sabatine 2017[10]	Nicholls 2016[11]

AE = adverse events; Apo = apolipoprotein; CV = cardiovascular; DB = double-blind; ECG = electrocardiogram; HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; LP-a = lipoprotein-a; MI = myocardial infarction; PAV = per cent atheroma volume; PCSK9 = pro-protein convertase subtilisin/kexin type 9; RCT = randomized controlled trial; SC = subcutaneous; TAV = total atheroma volume; TIA = transient ischemic attack; VLDL-C = very low-density lipoprotein cholesterol.

Note: Three additional reports were included (manufacturer's resubmission[5], Clinical Study Report[7,8]).

Source: Clinical Study Report for FOURIER;[7] Clinical Study Report for GLAGOV.[8]

Included Studies

Description of Studies

Two manufacturer–sponsored, multi-centre, double-blind randomized controlled trials (RCTs) met the inclusion criteria for this review, both featuring patients who had failed to reach their target LDL-C on statin therapy. FOURIER randomized 27,564 patients in a 1:1 manner to either evolocumab or placebo, while GLAGOV randomized 970 patients in a 1:1 manner either to evolocumab or to placebo over a 78-week treatment course. FOURIER required patients to have clinically evident ASCVD (prior MI, stroke, or symptomatic peripheral artery disease), and the majority of patients in FOURIER (81%) had a prior MI, while in GLAGOV, only 35% of patients had a prior MI. In FOURIER, patients were allowed to choose which dosage regimen of evolocumab they would receive (420 mg monthly or 140 mg twice monthly), and were also allowed to switch back to the other regimen during the study. In GLAGOV, patients were on the monthly dosage regimen. FOURIER was an event-driven study and was designed to end when a total of 1,630 patients had reached the key secondary end point, which occurred earlier than the original estimate (five years), for a median follow-up of 26 months. The primary outcome of FOURIER was a composite of major CV events (CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization), while the primary outcome of GLAGOV was to assess the nominal change in per cent atheroma volume through vascular imaging after 78 weeks. The key secondary outcome in FOURIER was a composite of CV death, MI, or stroke, and other secondary outcomes included components of the composite outcome, such as all-cause and CV death, MI, stroke, hospitalization for unstable angina, and coronary revascularization. In GLAGOV, the key secondary outcome was nominal change in total atheroma volume, and other secondary outcomes included the proportion of patients with plaque regression. In both studies, enrolled patients were on a background of lipid-lowering therapy (a statin), were to undergo a lipid stabilization period (four weeks), and once stabilized, were to remain on that dose throughout the study.

Randomization/Blinding

All patients who entered into the screening period for FOURIER received a unique patient identification number before any study procedures were performed, assigned by the interactive voice response system (IVRS) or interactive Web response system (IWRS). This number was used to identify the patient throughout the clinical study and was to be used on all study documentation related to that patient. Assignment to the two treatment arms was based on a computer-generated randomization schedule prepared by the manufacturer before the start of the study. Randomization was stratified by the most recent screening LDL-C level (< 2.2 mmol/L versus ≥ 2.2 mmol/L) and by geographical region. Once eligibility into the study was confirmed, a site representative made the randomization call to the IVRS or IWRS to assign a randomization number to the patient. Individual patient treatment assignments were to be maintained by the IVRS, and members of the manufacturer's study team were not to have access to unblinded data until the study was unblinded for the final analysis. Any unplanned unblinding occurring during the study period was documented and reported in the final clinical study report. The independent Data Monitoring Committee members and Independent Biostatistical Group had access to treatment assignments and patient-level data from the clinical trial database. Central laboratory results were blinded post-treatment until unblinding of the clinical database and were not reported to the investigator post-screening. The procedures for randomization in GLAGOV were similar to FOURIER, although stratified by region only.

Populations

Inclusion and Exclusion Criteria

Participants in FOURIER were to have clinically evident ASCVD, defined as a history of MI, non-hemorrhagic stroke, or symptomatic peripheral artery disease, as well as additional characteristics that placed them at higher CV risk (e.g., smoking history or diabetes mellitus). Patients were to have a fasting LDL-C of at least 1.8 mmol/L or a non– high-density lipoprotein cholesterol (non–HDL-C) of at least 2.6 mmol/L. Both studies required patients to be on a stable statin dose, defined as at least four weeks on the same dose. To be enrolled in GLAGOV, patients were to have an LDL-C of 2.07 mmol/L or higher or an LDL-C between 1.55 mmol/L and 2.07 mmol/L with either one major or three minor CV risk factors. Major risk factors included non-coronary ASCVD, MI, hospitalization for unstable angina in the preceding two years, or type 2 diabetes mellitus.

Baseline Characteristics

Participants in both studies were predominantly male (FOURIER: 75% male; GLAGOV: 72% male) and Caucasian (FOURIER: 85%; GLAGOV: 94%), and they were around 60 years of age (mean ages: FOURIER: 62.5 years; GLAGOV: 59.8 years) (Table 5, Table 6). In FOURIER, all patients had a history of ASCVD, with the most common previous diagnosis being MI (81%) followed by ischemic stroke (19%). In GLAGOV, the majority (93%) had a diagnosis of coronary artery disease (CAD), although only 35% had had a prior MI and only 2% had had a prior stroke. The majority of patients were on a high-intensity statin at baseline in both FOURIER (69%) and GLAGOV (59%). There were no clear differences in key baseline characteristics between groups within FOURIER and GLAGOV.

Table 5: Summary of Baseline Characteristics: FOURIER

	FOURIER	
	Evolocumab (n = 3,784)	Placebo (n = 13,780)
Mean (SD) age, years	62.5 (9.1)	62.5 (8.9)
Male, n (%)	10,397 (75.4)	10,398 (75.5)
Caucasian, n (%)	11,748 (85.2)	11,710 (85.0)
LDL-C at baseline, mmol/L, mean (SD)	2.53 (0.75)	2.53 (0.70)
Region		
North America	2,287 (16.6)	2,284 (16.6)
Europe	8,666 (62.9)	8,669 (62.9)
Latin America	913 (6.6)	910 (6.6)
Asia Pacific	1,918 (13.9)	1,917 (13.9)
Smokers, n (%)	3,854 (28.0)	3,923 (28.5)
Participants with diabetes, n (%)	5,054 (36.7)	5,027 (36.5)
Participants with hypertension, n (%)	11,045 (80.1)	11,039 (80.1)
Participants with previous PCI, n (%)		
Participants with previous MI, n (%)	11,145 (80.9)	11,206 (81.3)
Participants with non-hemorrhagic stroke, n (%)	2,686 (19.5)	2,651 (19.2)
Participants with MI alone, n (%)	[redacted]	[redacted]
Participants with non-hemorrhagic stroke alone n (%)	[redacted]	[redacted]
CV events (1 or more), n (%)	[redacted]	[redacted]
CV events (2), n (%)	[redacted]	[redacted]
CV events (3)	[redacted]	[redacted]
Baseline statin use in patients, n (%)		
High-intensity	9,585 (69.5)	9,518 (69.1)
Moderate-intensity	4,161 (30.2)	4,231 (30.7)
Low-intensity	38 (< 1)	31 (< 1)
Ezetimibe use in patients, n (%)	726 (5.3)	714 (5.2)
Cardiovascular Risk Factors		
Major, n (%)		
Symptomatic PAD, if enrolled with history of MI or stroke	[redacted]	[redacted]
MI or non-hemorrhagic stroke within 6 months of screening	[redacted]	[redacted]
Additional prior MI/stroke (in addition to qualifying event)	[redacted]	[redacted]
Type 1 or 2 diabetes mellitus	5,054 (36.7)	5,027 (36.5)
Current cigarette use	3,854 (28.0)	3,923 (28.5)
Age ≥ 65 years & ≤ 85 years	[redacted]	[redacted]
Minor		
History of non–MI-related coronary revascularization	[redacted]	[redacted]
Residual CAD (≥ 40% stenosis in ≥ 2 large vessels)	[redacted]	[redacted]
HDL-C < 1.03 mmol/L (male) or < 1.29 mmol/L (fem)	[redacted]	[redacted]
High-sensitivity CRP > 2 mg/L	[redacted]	[redacted]
LDL-C ≥ 3.36 mmol/L or non–HDL-C ≥ 4.14 mmol/L	[redacted]	[redacted]
Metabolic syndrome	[redacted]	[redacted]
Use of Other CV Medications		
Beta-blocker	10,441 (75.8)	10,374 (75.4)
ACEi	[redacted]	[redacted]
ARB	[redacted]	[redacted]

	FOURIER	
	Evolocumab (n = 3,784)	Placebo (n = 13,780)
Antiplatelet therapy	[redacted]	[redacted]
MRA	[redacted]	[redacted]
ACEi or ARB, MRA, or both	10,803 (78.4)	10,730 (77.9)

ACEi = Angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; CAD = coronary artery disease; CRP = C-reactive protein; CV = cardiovascular; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; SD = standard deviation.

Source: Clinical Study Report for FOURIER[7], Sabatine 2017.[10]

Table 6: Summary of Baseline Characteristics: GLAGOV

	GLAGOV	
	Evolocumab (n = 84)	Placebo (n = 84)
Mean (SD) age, years	59.8 (9.6)	59.8 (8.8)
Male, n (%)	349 (72.1)	350 (72.3)
Caucasian, n (%)	456 (94.2)	452 (93.4)
LDL-C at baseline, mmol/L, mean [95% CI]	2.40 (2.33 to 2.46)	2.39 (2.33 to 2.46)
Region		
North America	[redacted]	[redacted]
Europe	[redacted]	[redacted]
Latin America	[redacted]	[redacted]
Asia Pacific	[redacted]	[redacted]
Smokers, n (%)	124 (25.6)	113 (23.3)
Participants with diabetes, n (%)	98 (20.2)	104 (21.5)
Participants with hypertension, n (%)	398 (82.2)	405 (83.7)
Participants with previous PCI, n (%)	189 (39.0)	188 (38.8)
Participants with previous MI, n (%)	169 (35.3)	171 (34.9)
Baseline statin use in patients, n (%)		
High-intensity	280 (57.9)	290 (59.9)
Moderate-intensity	196 (40.5)	185 (38.2)
Low-intensity	2 (0.4)	1 (0.2)
Ezetimibe use in patients, n (%)	9 (1.9)	9 (1.9)
History of CAD diagnosis, n (%)	[redacted]	[redacted]
CAD	[redacted]	[redacted]
Angina due to ASCVD	[redacted]	[redacted]
MI	[redacted]	[redacted]
Coronary artery bypass graft	[redacted]	[redacted]
PCI	[redacted]	[redacted]
Cerebrovascular disease or PAD by history, (%)	[redacted]	[redacted]
TIA	[redacted]	[redacted]
Stroke or cerebral infarction	[redacted]	[redacted]
Carotid or vertebral artery disease	[redacted]	[redacted]
Cardiovascular risk factors		
Major, n (%)		
Peripheral artery disease	[redacted]	[redacted]

	GLAGOV	
	Evolocumab (n = 84)	Placebo (n = 84)
Abdominal aortic aneurysm	[redacted]	[redacted]
Cerebrovascular disease	[redacted]	[redacted]
MI or hospitalization for UA in past 2 yrs	[redacted]	[redacted]
Type 2 diabetes mellitus	[redacted]	[redacted]
Minor		
Current cigarette use	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]
Low LDL-C	[redacted]	[redacted]
Family history of premature CAD	[redacted]	[redacted]
Age (men ≥ 50yrs, women ≥ 55 yrs)	[redacted]	[redacted]
High-sensitivity CRP ≥ 2 mg/L	[redacted]	[redacted]
Participants with ≥ 3 minor risk factors	[redacted]	[redacted]
Use of other CV medications		
Beta-blocker	362 (74.8)	370 (76.4)
ACEi	260 (53.7)	264 (54.5)
ARB	87 (18.0)	92 (19.0)
Antiplatelet therapy	454 (93.8)	465 (96.1)

ACEi = angiotensin converting enzyme inhibitor; ASCVD = atherosclerotic cardiovascular disease; ARB = angiotensin receptor blocker; CAD = coronary artery disease; CI = confidence interval; CRP = C-reactive protein; CV = cardiovascular; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; SD = standard deviation; TIA = transient ischemic attack; UA = unstable angina; yrs = years.

Source: Clinical Study Report for GLAGOV.[8]

Interventions

FOURIER

In FOURIER, baseline statin intensity (high, moderate, low) was defined for each statin, using daily doses, as follows:

- atorvastatin: High: ≥ 40 mg; moderate: 10 to < 40 mg; low: < 10 mg
- rosuvastatin: High: ≥ 20 mg; moderate: 5 to < 20 mg; low: < 5mg
- simvastatin: High: 80 mg; moderate: 20 to < 80 mg; low: < 20 mg
- pravastatin, lovastatin, fluvastatin, and pitavastatin did not report a high-intensity dose; the cut-offs for moderate versus low-intensity were 40 mg, 40 mg, 80 mg, and 2 mg, respectively.

FOURIER featured a lipid stabilization period of up to 12 weeks, where patients received lipid-lowering therapy with a maximally tolerated dosage of atorvastatin at between 20 mg to 80 mg daily with a recommended dose of 80 mg, if tolerated. A dose of 20 mg daily was considered acceptable if it was documented that the LDL-C or non–HDL goals were achieved or that there was an intolerance to a higher dose. If a patient was receiving ezetimibe when entering screening, ezetimibe could be continued. Furthermore, if the investigator recommended additional therapy beyond statin use for patients in order to achieve their LDL-C or non–HDL-C goals, ezetimibe could be added during the lipid stabilization period. The dose of maximally tolerated atorvastatin and, if applicable, ezetimibe had to be stable during the last four weeks of the lipid stabilization period and could not be changed for the duration of the trial. After at least four weeks of stable run-in

therapy, fasting LDL-C and non–HDL-C were evaluated for eligibility determination. If plasma LDL-C was ≥ 1.8 mmol/L or non–HDL-C was ≥ 2.6 mmol/L, and all other eligibility criteria were met, patients were randomized to receive either evolocumab or the placebo.

Evolocumab was administered at either 140 mg in 1.0 mL (one administration by pre-filled auto-injector [AI] pen) or at 420 mg in 3.0 mL or 3.5 mL (three administrations by pre-filled AI pen or one administration by personal injector) once monthly, and the placebo was administered either at 1.0 mL (one administration by pre-filled AI pen) or at 3.0 mL or 3.5 mL (three administrations by pre-filled AI pen or one administration by personal injector) once monthly. The three injections for the monthly administration, if applicable, could be administered into different injection sites. The subcutaneous (SC) injections were to be administered in a consecutive fashion, with all injections completed within 30 minutes. Participants chose whether to start their investigational product (IP) administration at a frequency of every two weeks or monthly, and had an opportunity every 12 weeks to switch between the different frequencies, provided that the required approvals and supply of product were available at the study site.

GLAGOV

In GLAGOV, all patients were required to be on optimal background statin therapy before randomization. Optimal background statin therapy was defined as an effective statin dosage of at least atorvastatin 20 mg daily or the equivalent titrated to achieve the target LDL-C (change or goal), as defined by regional guidelines. Where locally approved, highly effective statin therapy, defined as at least atorvastatin 40 at mg daily or equivalent, was recommended. Participants who were not on optimal background lipid-lowering therapy at screening, but who were otherwise eligible, could enter the study after a lipid stabilization period of two to four weeks. During this period, the patient could either initiate or titrate statin therapy with a maximum of one up-titration step. Statin-intolerant patients (not to exceed ~10% of planned patient enrolment) had to meet the statin intolerance entry criteria defined in the protocol, meeting both of the following conditions:

a) Tried at least two statins and was unable to tolerate any dose or increase statin dose above the total weekly maximum doses due to intolerable myopathy; i.e., myalgia (muscle pain, ache, or weakness without creatinine kinase [CK] elevation), myositis (muscle symptoms with increased CK levels), or rhabdomyolysis (muscle symptoms with marked CK elevation);

b) Experienced resolved or improved symptoms when the statin dose was decreased or discontinued.

In GLAGOV, patients received evolocumab 420 mg monthly SC injections or placebo monthly SC injections using three pre-filled AI pens that were identical in appearance. Investigators were informed if triglycerides were > 11.3 mmol/L so that appropriate patient follow-up could be initiated. The central laboratory also compared LDL-C concentrations for each patient with their last assessed LDL-C. If the LDL-C increased by 0.39 mmol/L (for LDL-C < 2.59 mmol/L) or increased more than 15% (for LDL-C > 2.59 mmol/L), the study centre was notified by an automated system, without unblinding them, to instruct the patient on compliance (study drug, statin, and diet). In order to maintain the blind, the same reminder was provided to additional patients in each treatment arm, using an appropriate algorithm to balance the frequency of alerts for both treatment groups.

Outcomes

FOURIER

The primary outcome in FOURIER was a composite of major CV events (CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization), while the key secondary outcome was a composite of CV death, MI, or stroke. The manufacturer chose this combined end point on the basis of the anticipated event rate as well as the modifiability of the associated event rate in response to LDL-C reduction. According to the manufacturer, this end point (or very similar) has been utilized in multiple large CV outcomes studies using different modalities for lipid reduction, although no references were provided. Events that occurred after randomization and up to the completed end-of-study visit and were potential end points were to be reported as potential end points by the investigator. These events were to be recorded within 24 hours of knowledge of the event. Information regarding dates of onset and resolution, severity, action taken, and investigator assessment of relatedness and seriousness was to be collected. The data monitoring committee followed the occurrence of these events to see if specific action was indicated during the course of the study. If a reported potential end point was negatively adjudicated (i.e., it did not meet the definitions of an end point), the event was to be reclassified as an adverse event (AE) or an SAE and reported to regulatory agencies as required, if applicable.

All deaths and components of primary and secondary end points were adjudicated by an independent external clinical events committee (CEC) (Thrombolysis in Myocardial Infarction [TIMI] Study Group, Boston, Massachusetts, US) using standardized definitions based on the "Standardized Definitions for Cardiovascular and Stroke End Point Events in Clinical Trials and the Third Universal Definition of Myocardial Infarction" (Hicks et al. 2012). They include the events occurring between the patient randomization date and the patient's last confirmed survival status date, inclusive. The censoring date for patients without an event was the patient's last non-fatal potential end point collection date.

Fasting (at least nine hours) blood samples were shipped to a central laboratory for analysis of complete lipid profiles. Standard laboratory procedures were used for lipid assessments. For all analyses related to LDL-C, unless specified otherwise, a reflexive approach was used, where the calculated LDL-C based on the Friedewald equation was employed unless the calculated LDL-C was < 1.0 mmol/L or triglycerides were > 4.5 mmol/L, in which case preparative ultracentrifugation LDL-C was determined and utilized.

GLAGOV

The primary end point in GLAGOV was the nominal change in per cent atheroma volume (PAV) from baseline to 78 weeks post-randomization, as determined by intravascular ultrasound (IVUS). The PAV was calculated as the total atheroma volume divided by the total vessel volume. Total atheroma volume in a ≥ 40 mm segment of the targeted coronary artery was the average plaque area over the *n* images that were evaluated by IVUS multiplied by a constant factor. CDR conducted a search for evidence regarding the validity of this outcome, and no minimal clinically important difference (MCID) was found.

Secondary end points included the nominal change in normalized total atheroma volume (TAV) from baseline to 78 weeks and the percentage of patients showing plaque regression (any reduction from baseline in PAV and TAV).

Exploratory end points included the change in lipid parameters, such as LDL-C, and the incidence of adjudicated events (all-cause mortality, CV death, MI, hospitalization for unstable angina, coronary revascularization, stroke, TIA, and hospitalization for heart failure). Adjudication occurred through an independent CEC. Blood draw for fasting lipids occurred on day one and weeks 12, 24, 52, 64, 76, and 78. Additional exploratory post hoc analyses included comparison of the change in PAV and the percentage of patients undergoing regression of PAV in those with LDL-C ≤ 1.8 mmol/L at baseline. Safety and tolerability were also evaluated. Safety end points included the patient incidence of treatment-emergent AEs, safety laboratory values, and vital signs at each scheduled visit, and the incidence of anti-evolocumab antibody (binding and neutralizing) formation.

Statistical Analysis

FOURIER

The calculation of sample size in FOURIER was based on the key secondary end point in this study (a triple composite of CV death, MI, or stroke) and assumed a placebo event rate of approximately 2% per year, a 26-month enrolment period, and a total 3% of loss to follow-up rate over the study duration of approximately 56 months. The hazard ratio for the triple composite end point in this study design was assumed to be 0.8, an estimate based on the recent Cholesterol Treatment Trialists' (CTT) Collaboration (2010) meta-analysis, which assessed the relationship between LDL-C reduction and CV events and concluded that the relative risk decreases by 1% for every 0.05 mmol/L reduction in LDL-C. However, it was assumed that attenuation of treatment effect would occur because of a three-month treatment lag at the beginning of the trial and non-compliance of 10% per year during the course of the study. The overall type I error was controlled at a 0.05 significance level. After accounting for these factors, and based on a two-sided log-rank test demonstrating the superiority of evolocumab over placebo, a total sample size of 27,500 patients, with approximately 1,630 patients experiencing a key secondary end point event, was required to ensure approximately 90% power. Assuming an annualized event rate of approximately 4.5% and a hazard ratio of 0.8 for the primary end point, at the time of the 1,630 key secondary events observed among a total of 27,500 patients, there would be approximately 3,550 primary events observed, which would ensure a power of 99.8% to demonstrate the superiority of evolocumab over placebo in the primary end point.

The full analysis set (FAS) was used as the analysis set for the primary analysis of the primary and secondary efficacy end points. The primary analysis of all time-to-event end points (including the primary and secondary end points) used a log-rank test stratified by the randomization stratification factors to compare the survival functions of each treatment group. Kaplan–Meier curves were estimated and Kaplan–Meier estimates (95% CI) were calculated. In addition, a hazard ratio and 95% CI were estimated from a Cox model stratified by the randomization stratification factors. For each patient, the date of randomization was used as the starting point for all time-to-event calculations. For each event, the onset date adjudicated by CEC was used as the event onset date for time-to-event calculations. Primary analyses of the primary and secondary efficacy end points included the events from the patient randomization date to the patient end-of-study date. For patients who discontinued the study early (due to consent withdrawal or loss to follow-up), vital status data were collected during the end-of-study visit period and prior to the overall trial study end date, as permitted by local law. All adjudicated death cases collected up to the study end date were included in the analysis based on the CEC adjudicated results (CV deaths, non-CV deaths, and undetermined deaths). Analysis of the primary end

point was repeated 1) using the start date of the end-of-study visit period instead of the individual last potential end point collection date for censoring, 2) using the on-treatment period for each subject, 3) using last confirmed survival status date for censoring, 4) stratifying the model by the stratification factor information captured in the electronic case report form (eCRF) (as opposed to the IVRS information), if the discrepancy in stratum assignment between IVRS and eCRF occurred in more than 5% of subjects, and 5) using the per-protocol set if more than 5% of subjects experienced an important protocol deviation.

In order to preserve the overall type I error rate at 0.05 in the final analysis of the primary and secondary end points, the following multiplicity adjustment approach was applied. The primary end point (quintuple composite of CV death, MI, stroke, hospitalization for unstable angina, and coronary revascularization) was to be compared by the treatment groups at a significance level of 0.05. If the primary end point reached statistical significance at the 0.05 level, the key secondary end point (a triple composite of CV death, MI, and stroke) was tested at a significance level of 0.05. If the key secondary end point reached a statistical significance level of 0.05, then the end point of CV death was to be tested at a significance level of 0.05. If the end point of CV death reached a statistical significance level of 0.05, then the following testing was to be conducted in parallel under the Bonferroni split:

- The end point of all-cause death was to be tested at a significance level of 0.04.
- Other remaining secondary end points (time to first MI, time to first stroke, time to first coronary revascularization, time to CV death or first hospitalization for worsening heart failure, and time to fatal or non-fatal ischemic stroke or TIA) were to be tested at an overall significance level of 0.01 applying the Hochberg method. No multiplicity adjustment was used for exploratory or sensitivity analyses. Therefore, in FOURIER, once statistical significance was not reached for the end point of CV death as above, statistical testing should have been halted.

Missing data for clinical events was not imputed.

Subgroups:

The following baseline characteristics were used for covariate analyses:

- Stratification factors:
  - final screening LDL-C level (< 2.2 mmol/L or ≥ 2.2 mmol/L)
  - geographical region (Europe, North America [US and Canada], Latin America, Asia Pacific, and South Africa)
- age at study enrolment (< 65 years, ≥ 65 years)
- sex
- race (white, non-white)
- prior MI: (No, < 1 year, 1 to < 2 years, ≥ 2 years)
- baseline PCSK9 level
- baseline LDL-C
- ezetimibe use at baseline (yes, no)

In addition to the baseline covariates listed above, the following were also used for subgroup analyses of the primary and key secondary efficacy end points:

- prior non-hemorrhagic stroke (yes, no)
- symptomatic peripheral artery disease (PAD) (yes, no)
- baseline HDL-C by quartiles (Q1, median, Q3)
- baseline triglycerides by quartiles (Q1, median, Q3)
- baseline high-sensitivity C-reactive protein (< 2 mg/L, ≥ 2 mg/L)
- ACC/AHA high-intensity statin therapy at baseline (yes, no)
- history of type 2 diabetes (yes, no)

Of the above subgroups, the ones that are of interest for this review include baseline LDL-C, prior MI, ezetimibe use, prior stroke, and statin therapy at baseline.

GLAGOV

The planned total sample size was 950 patients (475 randomized to each group). The assumptions in the sample size calculation were based on the study of coronary atheroma by IVUS in a trial evaluating the effects of rosuvastatin versus those of atorvastatin (SATURN). For this study, the assumed treatment effect was a change of at least 0.706 in PAV at week 78, which was approximated from an expected treatment effect of > 0.8 mmol/L reduction in LDL-C from baseline to week 78. Assuming 25% of randomized patients were not included in the primary analysis, a sample size of 950 patients provided approximately 712 patients in the primary analysis and ensured 90% power to test the study hypothesis. The sample size calculation was performed using a two-sided t-test with a 0.05 significance level.

To assess the primary end point of nominal change in PAV from baseline to week 78, an analysis of covariance (ANCOVA) model was used on the IVUS analysis set (IAS), including terms for the treatment group, stratification factor (region), and baseline PAV as covariates. Least-square means and corresponding 95% CIs were provided for each treatment (evolocumab and placebo) and for the difference between the treatment groups.

The key sensitivity analysis was conducted using a regression-based multiple imputation procedure to impute the missing primary end point in the FAS. The imputation model included treatment group, background therapy intensity, stratification factor, baseline LDL, baseline PAV, age, and sex as covariates. Five imputations were conducted, and each complete data set after imputation was analyzed using the same ANCOVA model as the primary analysis.

The secondary IVUS efficacy end point of change in TAV from baseline to week 78 was analyzed using a method similar to that used for the primary end point, but adjusting for baseline TAV. The secondary efficacy end point of regression in either PAV or TAV was analyzed using the Cochran–Mantel Hansel (CMH) test with adjustment for the stratification factor. The percentage of patients demonstrating regression in PAV or TAV was summarized by treatment group.

For multiplicity adjustment, in order to preserve the family wise type I error rate at 0.05 for testing the primary and secondary end points, the primary analysis of primary end point was tested first. If the treatment effect from the primary analysis of the primary end point was significant at a significance level of 0.05, hierarchical statistical testing of the secondary end points was carried out at a significance level of 0.05 in the following order:

1. Change in PAV
2. Change in TAV
3. Regression in PAV
4. Regression in TAV

Pre-defined subgroups included stratification factor region (North America, Europe, Latin America, and Asia Pacific) and baseline covariates, such as age (< median, ≥ median; < 65, ≥ 65), sex, race (white, non-white), PAV (< median, ≥ median), TAV (< median, ≥ median), LDL-C (< median, ≥ median), non–HDL-C (< median, ≥ median), PCSK9 (< median, ≥ median), family history of premature coronary heart disease (yes, no), prior MI (yes, no), type 2 diabetes mellitus (yes, no), prior statin use (yes, no), American College of Cardiology/American Heart Association high-intensity statin background therapy at baseline (yes, no), Systematic COronary Risk Evaluation (SCORE) risk classification (low, moderate, high, very high), and current cigarette use (yes, no). The subgroups identified in the review protocol included LDL-C, established CVD at baseline, concomitant use of anti-hyperlipidemics during study, and patients who were not candidates for (or who were intolerant to) statins.

Analysis Populations

FOURIER

The primary analysis set in this study comprised the FAS, which was defined as all randomized patients. Efficacy analyses were performed on the FAS. All patients were analyzed according to their randomized treatment assignment.

Safety analyses were performed on the safety analysis set, which was defined as all randomized patients who received at least one dose of investigational product. For safety analyses, patients were grouped according to their randomized treatment group assignment with the following exception: if a patient received treatment throughout the study that was different from the randomized treatment group assignment, then the patient was grouped by the actual treatment group.

The per-protocol analysis set was composed of patients who received at least one dose of investigational product and did not have any pre-specified selected important protocol deviations thought to impact the efficacy analyses.

GLAGOV

The FAS included all randomized patients who received at least one dose of investigational product. It was used for all analyses except for IVUS-related efficacy end points. 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 IAS included patients in the FAS with a baseline IVUS and an IVUS measurement conducted after week 52. The core IVUS laboratory (i.e., the Cleveland Clinic) selected week 52 as the time point that would be sufficient for observing a treatment effect. The IAS was used for the analysis of IVUS-related end points.

The lipid stabilization analysis set included all patients who received at least one dose of statin during the lipid stabilization period. The lipid stabilization analysis set was used in safety analyses during the lipid stabilization period.

The complete analysis set included patients in the IAS who adhered to the scheduled investigational product (i.e., the investigational product completion box was checked on the eCRF) and had an observed value for the primary end point.

Patient Disposition

Less than 1% of patients withdrew from FOURIER, with no clear difference in the proportion of withdrawals between evolocumab (0.7%) and placebo groups (0.9%). There was a relatively small proportion of patients who withdrew from GLAGOV, and no differences in proportion of withdrawals between groups (Table 7, Table 8).

Table 7: Patient Disposition: FOURIER

	FOURIER	
	Evolocumab	**Placebo**
Screened, N	44,664	
Excluded prior to randomization	[redacted]	
Did not meet the inclusion criteria – n (%):		
Screening LDL-C < 1.8mmol/L/non-HDL-C < 2.6mmol/L	[redacted]	
No major risk factors and < 2 minor risk factors	[redacted]	
Screening triglycerides > 4.5mmol/L	[redacted]	
No history of clinically evident cardiovascular disease	[redacted]	
No informed consent	[redacted]	
< 40 or > 85 years of age	[redacted]	
Met the exclusion criteria – n (%)		
Unavailable for study visits or procedures	[redacted]	
Randomized, N (%)	13,784	13,780
Randomized and treated	13,769	13,756
Discontinued treatment, N (%)	1,682 (12.2)	1,746 (12.7)
Adverse event	628 (4.6)	581 (4.2)
Patient request	786 (5.7)	881 (6.4)
Physician decision	34 (0.2)	47 (0.3)
Protocol-specified criteria	14 (0.1)	11 (0.1)
Study closure/decision by sponsor	22 (0.2)	37 (0.3)
Other	198 (1.4)	189 (1.4)
Died during follow-up, N (%)	444 (3.2)	426 (3.1)
Withdrew consent	88 (0.6)	105 (0.8)
Vital status known	58 (0.4)	86 (0.6)
Vital status searched and not listed as dead in registry	3 (< 0.1)	1 (< 0.1)
Vital status unknown	27 (0.2)	18 (0.1)
Lost to follow-up	5 (< 0.1)	13 (0.1)
Discontinued study	93 (0.7)	118 (0.9)
Full consent withdrawn	88 (0.6)	105 (0.8)

	FOURIER	
Lost to follow-up	5 (< 0.1)	13 (< 0.1)
Primary analysis, N	13,784 (100)	13,780 (100)
Safety, N	13,769 (99.9)	13,756 (99.8)
Per-protocol, N	[redacted]	[redacted]

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

Source: Clinical Study Report for FOURIER.[7]

Table 8: Patient Disposition: GLAGOV

	GLAGOV	
	Evolocumab	Placebo
Screened, N	2,682	
Enrolled	1,246	
Enrolled but not randomized	[redacted]	
Adverse event	[redacted]	
Death	[redacted]	
Participant request	32 (2.6)	
Lost to follow-up	[redacted]	
Protocol-specified criteria	235 (18.9)	
Randomized, N (%)	484	486
Randomized and treated	484	484
Discontinued treatment, N (%)	38 (7.9)	35 (7.2)
Adverse event	18 (3.7)	11 (2.3)
Death	1 (0.2)	0
Patient preference	12 (2.5)	19 (3.9)
Lost to follow-up	3 (0.6)	2 (0.4)
Physician decision	1 (0.2)	1 (0.2)
Other	3 (0.6)	2 (0.4)
Discontinued study, N (%)	[redacted]	[redacted]
Death	[redacted]	[redacted]
Withdrew consent	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]
Sponsor decision	[redacted]	[redacted]
Protocol-specified criteria	[redacted]	[redacted]
Did not complete end point assessment	61 (12.6)	61 (12.6)
Died before IVUS obtained	3 (0.6)	1 (0.2)
Final IVUS not obtained	43 (8.9)	44 (9.1)
Final IVUS not analyzable	15 (3.1)	16 (3.3)
Primary analysis	423 (87)	423 (87)
Completer, N	411 (85)	416 (86)
Safety, N	484 (100)	484 (100)

IVUS = intravascular ultrasound.

Source: Clinical Study Report for GLAGOV.[8]

Exposure to Study Treatments

The mean ± SD duration of exposure in FOURIER was [redacted] months in the evolocumab group and [redacted] months with placebo. The median duration of exposure was [redacted] months, with a range of [redacted] months to [redacted] months. The primary end point was obtained for 99.5% of potential patient-years follow-up. Compliance data regarding missing doses does not appear to have been reported. The mean ± SD duration of exposure was similar in GLAGOV between evolocumab ([redacted] months) and the placebo ([redacted] months). The mean ± SD number of doses received was also similar between evolocumab ([redacted]) and the placebo ([redacted]).

Critical Appraisal

Internal Validity

Allocation concealment appears to have been facilitated throughout the randomization process through use of an IVRS/IWRS and a computer-generated randomization schedule prepared before the trial.

Blinding was facilitated using a matched placebo injection. An external committee adjudicated clinical events that the investigators had identified, applying a standardized definition for such events. It is not clear how many clinical events identified by the investigators were negatively adjudicated by this committee, nor is it clear if the reasons for these decisions were recorded. Injection site reactions and hypersensitivity reactions are known complications of monoclonal antibody therapy, and such reactions could have potentially resulted in an unblinding of the study drug. There were numerical differences in the proportion of patients with reactions associated with monoclonal antibodies in both studies; however, the proportion of patients experiencing these reactions was low. Therefore, the impact on blinding was likely minimal.

In order to maintain consistency in dosages, patients who performed injections on themselves received training. Otherwise, trained staff performed the injections. It is not clear whether any follow-up was provided after training was complete to ensure that patients were using the correct procedure when injecting themselves. Participants were provided reminders regarding compliance if their LDL-C levels increased by an unusually large amount from one visit to the next, and these reminders were carried out in a way that reduced the risk of compromising the blind. However, compliance data do not appear to have been reported.

The manufacturer accounted for multiple comparisons using a hierarchical statistical testing protocol in GLAGOV and a mix of a hierarchical design and a Bonferroni split/Hochberg method in FOURIER. The hierarchical testing procedure was followed in GLAGOV. In FOURIER, statistical testing should have stopped after CV death failed to reach statistical significance; however, it continued, with the manufacturer describing these further tests as exploratory. Additionally, it is not clear whether the manufacturer adjusted for testing of individual components of the composite end points.

A relatively large proportion (~13% of the randomized population) of data were missing for the analysis of the primary outcome in GLAGOV. Although the reasons for the missing data were clear in some cases (death, not analyzable, etc.), the largest proportion of missing data (9% of the total randomized) was attributed to an IVUS not being obtained. It is not clear why these data were not obtained, although the proportion of missing data between groups was similar (9% in each). Several sensitivity analyses were performed using various methods for imputation, and all supported the findings of the primary analysis.

External Validity

The study population appeared to reflect what one would expect to see in terms of patients receiving evolocumab for the indication under review, according to the clinical expert. The expert did note that inclusion criteria in FOURIER appeared to enhance the chance of clinical events by including patients with additional CV risk factors, such as smoking history and diabetes mellitus. This may have led to the higher-than-anticipated event rate in FOURIER, which resulted in the study ending earlier than originally planned.

The primary outcome in GLAGOV was a surrogate outcome of change in PAV, while FOURIER was designed to assess clinical outcomes that are more directly relevant to the indication under study. There does not appear to be an established MCID for change in atheroma volume, based on a literature search performed by CDR. According to the clinical expert, any reduction in atheroma volume is clinically significant; however, with the advent of event-driven studies such as FOURIER, there is far less focus on vascular imaging as an outcome. In FOURIER, the expert believed the key secondary outcome (CV death, stroke, MI) to be a more meaningful outcome than the primary composite outcome; however, both appear relevant and generalizable to clinical practice. The manufacturer noted that numerous major CV trials have used the same primary end point, but did not provide any references.

The length of follow-up of both included studies was likely too short to assess the long-term harms associated with the use of evolocumab. PCSK9 represents a novel therapeutic target, and the consequences of chronic therapy with a PCSK9 inhibitor are unknown. Additionally, the consequences of reducing LDL-C to very low levels are also unknown. FOURIER was originally estimated to be a five-year study, but due to a higher-than-expected event rate, the median follow-up ended up being just 26 months. Therefore, although there are no clear safety signals at present, the risk of long-term use of evolocumab is unknown.

Efficacy

Only those efficacy outcomes identified in the review protocol are reported below. See Appendix 4 for detailed efficacy data.

Mortality

There was no statistically significant difference in mortality between evolocumab and placebo groups in FOURIER after a median follow-up of 26 months (Table 9) or GLAGOV after 78 weeks (Table 10).

Major Adverse Cardiovascular Events

The primary outcome of FOURIER was a composite of patients experiencing CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization. After a median follow-up of 26 months, 9.8% of evolocumab patients reached this primary outcome versus 11.3% of placebo patients; this difference between groups was statistically significant (hazard ratio 0.85; 95% CI, 0.79 to 0.92; $P < 0.001$) (Table 9). Therefore, evolocumab demonstrated superiority over placebo for the primary outcome of FOURIER, and the clinical expert believed this difference to be of clinical significance. Subgroup analyses were provided for the primary outcome, and no statistically significant interactions were reported for subgroups based on the types of disease (i.e., MI versus stroke, PAD, or

polyvascular disease), statin intensity ("high" versus "not high"), ezetimibe use, or baseline LDL-C (< 2.07 versus 2.07 to < 2.38 versus 2.38 to 2.82 versus > 2.82 mmol/L) (Table 14).

The key secondary outcomes in FOURIER of CV death, MI, or stroke occurred in a lower proportion of evolocumab versus placebo patients (5.9% versus 7.4%); this difference was statistically significant (hazard ratio 0.80; 95% CI, 0.73 to 0.88; *P* < 0.001) (Table 9). The median follow-up at this time was 26 months. Therefore, evolocumab demonstrated superiority over placebo for the key secondary outcome of FOURIER, and the clinical expert believed this to be a clinically significant difference. Subgroup analyses were provided for the key secondary outcome, and no statistically significant interactions were reported for subgroups based on types of disease (i.e., MI versus stroke, PAD, or polyvascular disease), statin intensity ("high" versus "not high"), ezetimibe use, or baseline LDL-C (< 2.07 versus 2.07 to < 2.38 versus 2.38 to 2.82 versus > 2.82 mmol/L) (Table 14).

CV Mortality

There was no statistically significant difference between evolocumab and placebo patients in CV deaths in FOURIER after a median follow-up of 26 months (Table 9) or after 78 weeks in GLAGOV (Table 10).

CV Morbidity

In FOURIER, where there was a lower proportion of evolocumab patients with an event after a median follow-up of 26 months when compared with placebo patients, other secondary outcomes included MI (3.4% versus 4.6%; hazard ratio 0.73; 95% CI, 0.65 to 0.82; *P* < 0.001), stroke (1.5% versus 1.9%; hazard ratio of 0.79; 95% CI, 0.66 to 0.95; *P* = 0.01), coronary revascularization (5.5% versus 7.0%; hazard ratio of 0.78; 95% CI, 0.71 to 0.86; *P* < 0.001), and the composite of ischemic stroke or transient ischemic attack (1.7% versus 2.1%; hazard ratio 0.77, 95% CI, 0.65 to 0.92; *P* = 0.003) (Table 9). Note that all of these outcomes were tested outside of the statistical hierarchy; therefore, the analyses provided and *P* values should be considered exploratory. Cardiovascular morbidity, reported as adjudicated CV events, was also reported in GLAGOV; however, this was an exploratory outcome, and no statistical analyses were planned (Table 10).

Changes in LDL-C

In FOURIER, there was a larger proportion of patients reaching an LDL-C target of <1.8 mmol/L in the evolocumab group versus the placebo group after 48 weeks (86.5% versus 16.7% of patients, respectively); this difference between groups was statistically significant, with a difference between groups of 69.9% (95% CI, 69.0 to 70.7; *P* < 0.0001) (Table 9). After 48 weeks, the least squares mean (LSM) per cent reduction in LDL-C was larger for evolocumab versus placebo; this difference was statistically significant, with an LSM treatment difference between groups of –59.02% (95% CI, –59.74 to –58.31; *P* < 0.0001). The 48-week time point was where the maximum number of study patients had available LDL-C data.

Change in LDL-C was an exploratory outcome in GLAGOV. No statistical tests were reported (Table 10).

Other Efficacy Outcomes

In FOURIER, other lipid parameters were reported as exploratory outcomes. The LSM difference (95% CI) between evolocumab and placebo were statistically significant for per

cent reductions in non–HDL-C (−51.59; −52.24 to −50.95, *P* < 0.0001), apolipoprotein-B (−48.72; −49.38 to −48.06, *P* < 0.0001); VLDL-C (−26.86; −27.84 to −25.88, *P* < 0.0001), triglycerides (−15.88; −16.90 to −14.86, *P* < 0.0001), and lipoprotein-a (−35.48; −35.96 to −35.01, *P* < 0.0001).

The primary outcome of GLAGOV was the change from baseline in PAV. Evolocumab reduced PAV after 78 weeks by 1% versus placebo, and this difference was statistically significant, with an LSM difference of −1.01% (95% CI,−1.4 to −0.64, *P* < 0.0001). No MCID was found for change in PAV; however, the clinical expert believed any regression achieved was a clinically significant finding. Change from baseline to week 78 in TAV was a key secondary outcome of GLAGOV, and evolocumab reduced TAV versus placebo; this difference was statistically significant (−4.89 mm; 95% CI, −7.25 to −2.53, *P* < 0.0001). There was a larger proportion of patients in the evolocumab versus the placebo group that had regression in PAV, with a difference between groups of 17.0% (95% CI, 10.3 to 23.5, *P* < 0.0001) and in TAV, with a difference between groups 12.5% (95% CI, 5.8 to 19.1, *P* = 0.0002) (Table 13). Subgroup analyses were reported for the primary outcome, and no statistically significant interactions were reported for subgroups based on prior MI ("yes" versus "no"), statin intensity ("high" versus "other"), prior statin use ("yes" versus "no"), and LDL-C ("above" versus "below" the median) (Table 14).

Table 9: Key Efficacy Outcomes: FOURIER

	FOURIER		
	Evolocumab N = 13,784	**Placebo N = 13,780**	**HR [95% CI][a]**
CV death, MI, stroke, hospitalization for UA, or coronary revascularization (primary outcome)			
Participants, n (%)	1,344 (9.8)	1,563 (11.3)	0.85 [0.79 to 0.92], *P* < 0.001[b]
CV death, MI, stroke (key secondary)			
Participants, n (%)	816 (5.9)	1,013 (7.4)	0.80 [0.73 to 0.88], *P* < 0.001[b]
Mortality	444 (3.2)	426 (3.1)	1.04 [0.91 to 1.19], *P* = 0.54
CV death	251 (1.8)	240 (1.7)	1.05 [0.88 to 1.25], *P* = 0.62
Due to acute myocardial infarction	25 (0.2)	30 (0.2)	0.84 [0.49 to 1.42]
Due to stroke	31 (0.2)	33 (0.2)	0.94 [0.58 to 1.54]
Other cardiovascular death	195 (1.4)	177 (1.3)	1.10 [0.90 to 1.35]
Myocardial Infarction	468 (3.4)	639 (4.6)	0.73 [0.65 to 0.82], *P* < 0.001
Hospitalization due to UA	236 (1.7)	239 (1.7)	0.99 [0.82 to 1.18], *P* = 0.89
Stroke	207 (1.5)	262 (1.9)	0.79 [0.66 to 0.95], *P* = 0.01
Ischemic	171 (1.2)	226 (1.6)	0.75 [0.62 to 0.92]
Hemorrhagic	29 (0.2)	25 (0.2)	1.16 [0.68 to 1.98]
Unknown	13 (0.1)	14 (0.1)	0.93 [0.44 to 1.97]
Coronary revascularization	759 (5.5)	965 (7.0)	0.78 [0.71 to 0.86]to *P* < 0.001
Urgent	403 (2.9)	547 (4.0)	0.73 [0.64 to 0.83]
Elective	420 (3.0)	504 (3.7)	0.83 [0.73 to 0.95]
CV death or hospitalization for worsening heart failure	402 (2.9)	408 (3.0)	0.98 [0.86 to 1.13], *P* = 0.82
Ischemic stroke or TIA	229 (1.7)	295 (2.1)	0.77 [0.65 to 0.92], *P* = 0.003
CTTC composite end point	1,271 (9.2)	1,512 (11.0)	0.83 [0.77 to 0.90], *P* < 0.001
LDL-C – change from baseline			**Treatment difference [95% CI]**

	FOURIER		
	Evolocumab N = 13,784	Placebo N = 13,780	HR [95% CI][a]
Mean (SD) baseline, mmol/L	2.532 (0.748)	2.529 (0.703)	
Change from baseline to week 48, mmol/L	[redacted]	[redacted]	
Mean (SD) % change to week 48	[redacted]	[redacted]	
LSM[c] (SE) % change to week 48	[redacted]	[redacted]	[redacted]
Patients with LDL-C < 1.8 mmol/L			
Baseline, n (%)	[redacted]	[redacted]	
Week 48, n (%)	[redacted]	[redacted]	[redacted]

CI = confidence interval; CTTC = Cholesterol Treatment Trialists' Collaboration; CV = cardiovascular HR = hazard ratio; LDL-C = low-density lipoprotein cholesterol; LSM = least squares mean; MI = myocardial infarction; NR = not reported; TIA = transient ischemic attack; UA = unstable angina.

[a] Hazard ratios and 95% confidence intervals were generated with the use of a Cox proportional-hazards model with stratification factors as covariates, and *P* values for time-to-event analyses were calculated with the use of log-rank tests.

[b] Statistically significant difference versus comparator. Note that *P* values for mortality, MI, hospitalization due to UA, stroke, coronary revascularization, CV death, or hospitalization for worsening heart failure were reported, but should be considered exploratory, according to the hierarchy for statistical testing.

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

Source: Clinical Study Report for FOURIER.[7]

Table 10: Key Efficacy Outcomes: GLAGOV

	GLAGOV	
	Evolocumab N = 484	Placebo N = 484
% Atheroma volume (primary outcome)		
% atheroma volume (PAV), mean baseline (95% CI)	36.4 (35.6 to 37.2)	37.2 (36.4 to 38.0)
LSM[a] [95% CI] change from baseline to week 78 (IVUS population-primary analysis)	−0.95 (−1.33 to −0.58) N = 423	0.05 (−0.32 to 0.42) N = 423
Between-group differences, LSM [95% CI]	−1.01 (−1.4 to −0.64)	
P value	*P* < 0.0001	
LDL-C		
Baseline, mean (SD) mmol/L	2.397 (0.712)	2.394 (0.696)
Mean (SD) Change from baseline to week 78, mmol/L	[redacted]	[redacted]
Mean (SD) % change from baseline to week 78	[redacted]	[redacted]
Clinical events, n (%) (adjudicated), by week 78		
Deaths, n (%)	3 (1)	4 (1)
CV deaths, n (%)	[redacted]	[redacted]
MI, n (%)	10 (2)	14 (3)
Fatal MI	0	0
Hospitalization for UA, n (%)	3 (1)	4 (1)
Coronary revascularization, n (%)	50 (10)	66 (14)
PCI	[redacted]	[redacted]
Surgery	[redacted]	[redacted]
Cerebrovascular event, n (%)	[redacted]	[redacted]
Stroke	2 (< 1)	3 (1)
Heart failure, n (%)	[redacted]	[redacted]

	GLAGOV	
	Evolocumab N = 484	Placebo N = 484
Hospitalization for heart failure	[redacted]	[redacted]

CI = confidence interval; CV = cardiovascular; IVUS = intravascular ultrasound; LDL-C = low-density lipoprotein cholesterol; LSM = least squares mean; MI = myocardial infarction; PAV = per cent atheroma volume; PCI = percutaneous coronary intervention; SD = standard deviation; UA = unstable angina.

[a] The LSM is from the general linear ANCOVA model, which includes terms for the treatment group, the geographic region stratification factor, and baseline PAV.

Source: Clinical Study Report for GLAGOV.[8]

Harms

Only those harms identified in the review protocol are reported below (see Objectives and Methods section).

Adverse Events

In FOURIER, the proportion of patients with an AE was similar between the evolocumab and placebo groups (77.4% in each) after a median follow-up of 26 months (Table 11). In GLAGOV, 76.9% of evolocumab-treated patients and 79.8% of placebo-treated patients experienced at least one AE over the 78-week study (Table 11).

Serious Adverse Events

In FOURIER, the proportion of patients with an SAE was 24.8% with evolocumab and 24.7% with placebo after a median follow-up of 26 months (Table 11). The most common SAEs were unstable angina, which occurred in 1.7% of evolocumab-treated and 2.0% of placebo-treated patients, and angina pectoris, which occurred in 1.5% of evolocumab and 1.6% of placebo patients. In GLAGOV, over 78 weeks, [redacted] of evolocumab-treated and [redacted] of placebo-treated patients experienced an SAE. The most common SAE was [redacted], which occurred in [redacted] of evolocumab-treated and [redacted] of placebo-treated patients (Table 11).

Withdrawals Due to Adverse Events

In FOURIER, [redacted] of patients in the evolocumab groups and [redacted] of patients in the placebo group withdrew due to an AE after a median of 26 months of therapy, with the most common reason being myalgia ([redacted] of patients in each group). In GLAGOV, [redacted] of evolocumab patients and [redacted] of placebo patients withdrew due to an AE over the course of 78 weeks (Table 11). Myalgia was also the most common reason for a withdrawal due to an AE in GLAGOV; [redacted] of evolocumab and [redacted] of placebo patients withdrew for this reason.

Notable Harms

After a median follow-up of 26 months in FOURIER, patients experienced the following notable harms: neurocognitive AE (1.6% in the evolocumab group versus 1.5% in the placebo group), allergic reaction ([redacted] versus [redacted]), muscle-related ([redacted] versus [redacted] rhabdomyolysis ([redacted] in each). Injection site reactions occurred in 2.1% of evolocumab-treated and 1.6% of placebo-treated patients. Adjudicated cases of new-onset diabetes were reported in 8.1% of evolocumab-treated and 7.7% of placebo-treated patients in FOURIER (Table 11), while this was not specifically reported in GLAGOV. After 78 weeks in GLAGOV, patients experienced the following notable harms: neurocognitive AE (1.4%

versus 1.2%), allergic reaction (6.8% versus 4.8%), and injection site reactions occurred (2.9% versus 1.9%) of evolocumab versus placebo-treated patients, respectively. No muscle-related events were reported in GLAGOV.

Table 11: Harms

	FOURIER		GLAGOV	
Adverse Events	**Evolocumab N = 13,769**	**Placebo N = 13,756**	**Evolocumab N = 484**	**Placebo N = 484**
Participants with > 0 AEs, N (%)	10,664 (77.4)	10,644 (77.4)	372 (76.9)	386 (79.8)
Most common (> 5% in one group)				
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]
Angina pectoris	[redacted]	[redacted]	[redacted]	[redacted]
Chest pain	[redacted]	[redacted]	[redacted]	[redacted]
Non-cardiac chest pain	[redacted]	[redacted]	[redacted]	[redacted]
Myalgia	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]
Serious Adverse Events				
Participants with > 0 SAEs, N (%)	3,410 (24.8)	3,404 (24.7)	135 (27.9)	142 (29.3)
Most common (1% in either group)				
Angina unstable	[redacted]	[redacted]	[redacted]	[redacted]
Angina pectoris	[redacted]	[redacted]	[redacted]	[redacted]
Atrial fibrillation	[redacted]	[redacted]	[redacted]	[redacted]
Non-cardiac chest pain	[redacted]	[redacted]	[redacted]	[redacted]
Coronary artery disease	[redacted]	[redacted]	[redacted]	[redacted]
WDAEs				
WDAEs, N (%)	[redacted]	[redacted]	[redacted]	[redacted]
Most common reasons				
Myalgia	[redacted]	[redacted]	[redacted]	[redacted]
Notable Harms				
Neurocognitive events	217 (1.6)	202 (1.5)	7 (1.4)	6 (1.2)
Delirium	[redacted]	[redacted]	[redacted]	[redacted]
Hallucination	[redacted]	[redacted]	[redacted]	[redacted]
Mental impairment disorder	[redacted]	[redacted]	[redacted]	[redacted]
Amnesia	[redacted]	[redacted]	[redacted]	[redacted]
Cognitive disorder	[redacted]	[redacted]	[redacted]	[redacted]
Dementia	[redacted]	[redacted]	[redacted]	[redacted]
Disturbance in attention	[redacted]	[redacted]	[redacted]	[redacted]
Memory impairment	[redacted]	[redacted]	[redacted]	[redacted]
Injection site reaction	296 (2.1)	219 (1.6)	14 (2.9)	9 (1.9)
Allergic reaction	[redacted]	[redacted]	33 (6.8)	23 (4.8)
Muscle-related event	[redacted]	[redacted]	0	0
Rhabdomyolysis	[redacted]	[redacted]	0	0

Adverse Events	FOURIER		GLAGOV	
	Evolocumab N = 13,769	Placebo N = 13,756	Evolocumab N = 484	Placebo N = 484
Adjudicated case of new-onset diabetes	677 (8.1)	644 (7.7)	NR	NR
Potential cases of hepatitis C	[redacted]	[redacted]	[redacted]	[redacted]
Aminotransferase level > 3 times ULN	240/13,543 (1.8)	242/13,523 (1.8)	NR	NR
Transaminase elevations/hepatic disorders	[redacted]	[redacted]	[redacted]	[redacted]
Creatine kinase level > 5 times ULN	95/13,543 (0.7)	99/13,523 (0.7)	NR	NR
Neutralizing antibodies	0	0	0	0
Binding antibodies	43 (0.3)	-	1 (0.2)	0

AE = adverse event; SAE = serious adverse event; ULN = upper limit of normal, WDAE = withdrawal due to adverse event.
Source: Clinical Study Report for FOURIER;[7] Clinical Study Report for GLAGOV.[8]

Discussion

Summary of Available Evidence

Evidence Reviewed Previously

Four double-blind RCTs were included in the original CDR review. Three of the studies were 12 weeks in duration, and the fourth study (DESCARTES) was 52 weeks. Approximately one-third of the patients in these studies had established CV disease at baseline, and the studies were not powered to assess clinical outcomes such as mortality and morbidity. As a result, CDEC's recommendation was "do not list" for patients with ASCVD.

New Evidence Identified in the Current Review

For this resubmission, the manufacturer submitted a new clinical trial, GLAGOV. In addition, although it was not part of their resubmission, results from FOURIER also became available at the time of this resubmission and were therefore included in the systematic review. FOURIER randomized 27,564 patients with clinically evident ASCVD in a 1:1 manner either to evolocumab or to placebo, while in GLAGOV, 970 patients with ASCVD were randomized 1:1 either to evolocumab or to placebo over a course of 78 weeks. In FOURIER, patients were only enrolled if they had a prior MI, stroke, or symptomatic PAD; the majority (81%) of patients had had a prior MI. The primary outcome of FOURIER was a composite clinical end point of major CV events (CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization), while GLAGOV featured vascular imaging (change from baseline in PAV) as its primary end point. Therefore, of the two studies, FOURIER best addresses the limitations CDEC cited in the original review of evolocumab.

Interpretation of Results

Efficacy

For this resubmission, the manufacturer presented a range of different information in an effort to establish the efficacy of evolocumab in a population with ASCVD. The new clinical trial in their resubmission was GLAGOV, which featured vascular imaging as its primary end point. In GLAGOV, evolocumab was superior to placebo for reducing the PAV and the TAV, meeting both its primary and key secondary end points. Although not included as part of their resubmission, results from the FOURIER trial became available at the same time as the resubmission, and FOURIER is the best source of evidence for the use of evolocumab in ASCVD.

In their input to CDR, patients identified the risk of clinical events such as MI as a key source of concern. In FOURIER, evolocumab demonstrated superiority over placebo for the primary composite outcome and a number of secondary outcomes related to CV events, but it did not reduce the risk of all-cause mortality or CV deaths. This may be considered a somewhat surprising finding, given that PCSK9 inhibitors lower LDL-C to a greater extent than statins, to levels not seen in previous trials of any lipid-lowering therapy. However, there are potential explanations for the lack of benefit with respect to mortality. First, the number of deaths in FOURIER was notably lower than in previous statin trials. Patients in FOURIER were already benefiting from statin therapy as background, and thus one might expect these patients may already have had a reduced risk of death versus patients who were not receiving a statin. Similarly, the management of events such as acute MI continues to evolve and improve; thus, one would expect lower rates of death in studies conducted now versus even a decade ago. These improvements in management, which would include patient education and preventive interventions that might reduce the risk of mortality from a subsequent event, would be expected to be even more impactful in a clinical trial setting where care is optimized. Additionally, the follow-up in FOURIER may simply not have been long enough for enough deaths to occur, as the trial ended with a much shorter duration of follow-up than originally expected by the manufacturer, at 26 months instead of 5 years. Finally, most importantly, although the difference between evolocumab and placebo for the primary and key secondary outcomes was statistically significant, the treatment effect was small (with an absolute difference of 1.5% between groups for each outcome); therefore, the clinical significance of such a difference is not clear. Since the publication of results from FOURIER, much has been made of the fact that the 15% reduction in risk of primary outcome events was lower than expected. These expectations appear to be based on an extrapolation of the LDL-C lowering effects of evolocumab. Therefore, although results from FOURIER suggest that additional LDL-C lowering to levels not previously seen in clinical trials appears to be safe and does confer additional benefits regarding clinical outcomes, there may be diminishing returns with further LDL-C lowering. The interpretation of these results is again complicated by the shorter-than-expected trial duration. In other words, although there was a large reduction in LDL-C with evolocumab, the follow-up might not have been long enough to derive the full benefit on clinical outcomes. It is also noteworthy that, in FOURIER, the treatment effect for both the primary and key secondary composite outcomes appears to have been largely driven by a reduction in the risk of MI. Thus, for example, hospitalizations for unstable angina were not reduced with evolocumab therapy. Therefore, given the large number of patients that would need to be treated to prevent one major CV event, and the high cost of

therapy, there is a need to focus use of evolocumab on the population that might benefit most.

PCSK9 inhibitors have been on the market for over a year now in Canada, and researchers continue to search for a way to identify a population, or a few populations, for which this class of drugs is best suited. Of the subgroups of interest in FOURIER, there was no difference in response based on the type of ASCVD (MI, stroke, PAD, or polyvascular disease), baseline statin intensity (high/not high), ezetimibe use (yes/no), or baseline LDL. It is somewhat surprising that baseline LDL-C levels ranging from below 2.1 to above 2.8 mmol/L have similar results for the primary outcome. This finding suggests that decisions about how to restrict the use of these drugs should be made by policy-makers rather than using data from trials like FOURIER in order to identify a population that would be best suited for the drug. For example, in non-familial hypercholesterolemia or mixed dyslipidemia, the National Institute for Clinical Excellence only recommends evolocumab for use in patients with CVD, in high-risk patients on maximally tolerated statin therapy with an LDL of ≥ 4.0 mmol/L, and in very high-risk patients with an LDL of ≥ 3.5 mmol/L.[12] High-risk patients are defined as those who have experienced acute coronary syndrome, coronary or other revascularization procedures, chronic heart disease, ischemic stroke, or PAD; very high-risk patients are defined as those who have experienced recurrent CV events or polyvascular disease. None of the subgroup analyses in FOURIER focused on LDL-C levels this high; therefore, it is not known what the results would be in these patients. Another potential approach to identifying patients who might benefit most from evolocumab is to use risk stratification. Multiple scoring systems are used to quantify CV risk, but there is no consensus favouring one over the other. Therefore, according to the clinical expert, using a risk score to determine eligibility for evolocumab therapy would be very challenging. The Canadian Cardiovascular Society included the PCSK9 inhibitors in its most recent guidelines, recommending that they be used in patients who were not at their LDL-C goal despite maximally tolerated statin therapy.[3]

There are currently two PCSK9 inhibitors marketed in Canada, evolocumab and alirocumab, which both received notices of compliance at around the same time and share the same indication. What is not known about these two drugs is how they compare with each other. The manufacturer submitted a Bayesian NMA published by Toth et al. in 2016, which included comparisons of evolocumab with alirocumab, ezetimibe, or placebo in patients with familial or non-familial hypercholesterolemia who were candidates for evolocumab or other lipid-lowering therapies as an add-on to statins (see Appendix 7 for the review).[6] The NMA focused on LDL-C reduction, rather than clinical events, and included 15 trials. Evolocumab reduced LDL-C to a greater extent than alirocumab, and these results were consistent across the various doses that were compared. At its maximum, there was a 20% absolute difference in per cent reduction in LDL-C between the twice-monthly dosage regimens of evolocumab at 140 mg and alirocumab at 75 mg at the mean of weeks 10 and 12 (evolocumab) and week 12 (alirocumab). There are some important limitations of such an analysis, the most notable being that the NMA does not focus on populations with ASCVD; however, this analysis does raise the possibility that evolocumab may have greater lipid-lowering capabilities than alirocumab. However, clinical events were not part of the analysis; therefore, the true impact of such a difference in LDL-C lowering capability is unknown. Additionally, harms were not included in the analysis; therefore, it is not known whether this potential for enhanced lipid lowering with evolocumab comes at the expense of an increased risk of adverse effects. Not enough is known about the mechanisms of these drugs to speculate as to why evolocumab might have greater lipid-lowering efficacy; therefore, these two drugs need to be compared

directly in order to determine whether there is an advantage to one versus the other, balancing both efficacy and harms.

As in the earlier trials of evolocumab, quality of life (QoL) was not assessed in FOURIER. From the patient input to CDR, the major issues related to QoL appear to include AEs from statin therapy as well as concern and frustration over the inability to reach LDL-C targets. Data from FOURIER and from previous trials leave little doubt that evolocumab will allow more patients to reach their LDL-C targets; however, the impact of evolocumab on statin-related adverse effects, and most notably myalgia, is more in question. Evolocumab is currently indicated as an adjunct to statin therapy, rather than as a substitute for it. Therefore, if the drug reduces the risk of myalgia, it is likely because of a "statin-sparing" effect that allows patients to reduce their dose of statin below the threshold for developing myalgia while still achieving their LDL-C target. FOURIER was not designed to assess the effects of evolocumab on statin dosing, and as noted in the next section, there was no evidence that evolocumab reduced the risk of myalgia with statins. Therefore, the potential for this to occur, which is clearly of critical importance to patients, will only be seen with real-world use. The subjective nature of statin-related myalgia will further complicate the issue of eligibility for evolocumab, as this AE limits the dose of statin that can be used, which contributes to the number of patients who are not able to reach their targets and who are thus candidates for evolocumab.

Harms

Neurocognitive events were a notable harm with the first review of evolocumab, and in FOURIER and GLAGOV, there was no indication of an increased risk of neurocognitive events with evolocumab therapy. In the original review, there was a numerical increase in the risk of neurocognitive events with evolocumab over placebo across studies, and there was also a mechanistic rationale suggested by the reduction in cholesterol to levels that might impair neurological function. However, results from FOURIER suggest that evolocumab is unlikely to cause neurocognitive impairment. Results from FOURIER also appeared to suggest that reducing LDL-C to previously unseen levels is safe, at least over a median follow-up of 26 months. Given the important role of cholesterol in various physiological processes, there has been a concern that lowering LDL-C too far may cause harm. So far, results from FOURIER suggest that this might not be the case, and this finding may someday result in a further lowering of targets for LDL-C, according to the clinical expert. Koren at al. recently published data from the phase II OSLER-1 trial, which has 543 patients with more than four years of exposure to evolocumab. No significant safety signals were noted as yet; however, the open-label design does not provide the same opportunity to assess harms as FOURIER.[13]

Less than 1% of patients developed antibodies to evolocumab in the FOURIER and GLAGOV trials, and none developed neutralizing antibodies. Bococizumab was withdrawn by its manufacturer after neutralizing antibodies developed in 29% of patients across the clinical trials.[14] Bococizumab has a murine component, while alirocumab and evolocumab are fully human monoclonal antibodies, which likely accounts for the difference in antibody development. Injection site reactions occurred in 2.1% of evolocumab-treated patients and 1.6% of placebo-treated ones. Allergic reactions occurred in 3.1% and 2.9% of evolocumab and placebo-treated patients in FOURIER, respectively. These types of reactions are not uncommon with monoclonal antibodies.

Evolocumab is indicated for use in patients on maximally tolerated statin therapy; therefore, it is important to know the impact of using evolocumab while running the risk of statin-

associated adverse effects. Statins are well known for their muscle-related AEs, and this is by far the most common reason for statin intolerance. From the trials included in this review, there is no indication that adding evolocumab to maximally tolerated statin therapy leads to an increase in muscle-related AEs. In FOURIER, the proportion of patients with a muscle-related AE was 5.0% in the evolocumab group and 4.8% in the placebo one. The proportion of patients with elevated CK was 0.7% in each of the evolocumab and placebo groups, and rhabdomyolysis occurred in 0.1% of patients in each group. The issue of statin intolerance will continue to be an important one, as those muscle-related AEs are often dose-limiting (i.e., they prevent patients from achieving the maximum dose, and therefore the maximum benefit, from their statin).

Potential Place in Therapy[a]

Evolocumab is indicated in patients with ASCVD in whom the LDL-C remains above the current target (LDL-C > 2.0 mmol/L on maximally tolerated statin therapy ± ezetimibe).[3,10] Uncertainty remains around three key issues regarding the use of evolocumab in clinical practice. These include using ezetimibe before the use of a PCSK9 inhibitor; prioritizing high-risk patients in secondary prevention of ASCVD to receive PSCK9 inhibitors; and defining an LDL-C threshold to initiate a PCSK9 inhibitor. This last point is not supported by the current available evidence.

[a] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Conclusions

FOURIER addressed two key limitations of the original CDR submission, enrolling patients with established ASCVD and focusing on clinical end points. FOURIER demonstrated the superiority of evolocumab over placebo for the primary composite end point, as well as the key secondary composite of CV death, MI, or stroke, which was considered to be a meaningful outcome from a Health Technology Assessment perspective. The treatment effect was small for each of these end points, with an absolute difference between evolocumab and placebo of 1.5% for the primary and key secondary end points, and a hazard ratios of 0.85 (95% CI, 0.79 to 0.92; $P < 0.001$) for the primary end point and 0.80 (95% CI, 0.73, to 0.88, $P < 0.001$) for the key secondary end point. The clinical significance of such a difference is not clear.

The treatment effect appears to have been largely driven by an improvement in the risk of MI and stroke, and there was no difference in mortality (all-cause or CV) or hospitalizations for unstable angina between groups. The reduction in clinical events was less than what was anticipated based on the LDL reduction provided by evolocumab; however, this finding might have been due to the unexpectedly short follow-up in this trial (a median of 26 months versus the planned five years). GLAGOV was a much smaller study, and although it met its primary outcome, demonstrating the superiority of evolocumab over placebo for reduction in PAV, the clinical significance of this finding is less clear. An NMA provided by the manufacturer offers minimal value in assessing efficacy versus the other available PCSK9 inhibitor or ezetimibe, as it did not evaluate clinical outcomes or include the results of FOURIER. There was no clear difference between evolocumab and placebo with respect to SAEs or AEs in either study. Notable harms, such as neurocognitive, muscle-related, and hepatic events, were also similar between evolocumab and placebo. There was a slight numerical increase in the risk of injection site reactions with evolocumab over placebo, which is not uncommon with monoclonal antibodies. The duration of follow-up (FOURIER: median of 26 months; GLAGOV: 78 weeks) is likely inadequate for assessing the long-term safety of PCSK9 inhibition. The relative efficacy and harms of evolocumab versus other available therapies such as alirocumab or ezetimibe are currently unknown.

Appendix 1: Patient Input Summary

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

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

Input was received from one patient group.

The Cardiac Health Foundation of Canada (CHFC) is an organization that raises funds for cardiovascular (CV) rehabilitation programs, funds and promotes applied research on CV rehabilitation and management of cardiovascular disease (CVD) in Canada, and provides public education and resources aimed at prevention and management of CVD in Canada. CHFC did not declare any conflict of interest with anyone playing a significant role in compiling this submission. CHFC declared receiving funding in the form of corporate sponsorships from the following members of the pharmaceutical industry: Bayer, Amgen, Boehringer Ingelheim, and Lily Canada.

2. Condition Related Information

The information CHFC provided was gathered through an online survey and a telephone interview targeted to patients living with atherosclerosis and their caregivers. Fifty-five patients completed the online survey. Among them, two had experience with evolocumab. One patient who had experience with evolocumab participated in a one-on-one telephone interview.

Patients and their caregivers noted a number of physical issues related to living with atherosclerosis. Of the 40 patients who described the impact of their condition, 78% indicated that they experience fatigue and tiredness, 40% said shortness of breath is a common aspect of living with their illness, and 38% said they experience dizziness or light-headedness. Also, chest pain or pressure, pins and needles in the arms and legs, numbness or weakness in the arms or legs, and pain in the leg or arm, or any area affected by a blocked artery, were among the common symptoms reported. Controlling the progression of the disease was a major concern for most patients, as was fatigue. One patient noted, “My fatigue is disproportionate to the amount of limited activity I can do.” Thirty-four patients indicated that their quality of life was affected because they were anxious about having a heart attack or stroke, or a recurrence of either, for those who had had one. Thirty patients indicated that they were fearful and worried about their deteriorating health. Almost half of patients expressed concern about the impact of their illness on their family, spouse, or partner. Depression was also noted by around a third of patients.

Some of the patients indicated that their spouse had had to take on more physically demanding daily tasks that the patient could no longer do as a result of fatigue. Patients and caregivers commented that they had to adjust to a new lifestyle of diet and exercise. One patient said, “I am the patient. My husband goes with me to every doctor appointment, and listens to the cardiologist. His worry never stops.” Another said that taking daily medications is a constant worry, as are the side effects of high doses, which sometimes do not control the progression of the disease.

3. Current Therapy Related Information

The methods of the information collection in this section were the same as those used in section 2.

Of the patients who answered the survey, 60% had been prescribed rosuvastatin and 40% had been prescribed atorvastatin. Fifty-four per cent had had bypass surgery. Five patients had received ezetimibe. Of the 30 patients who shared their experience with rosuvastatin, 18 patients found it very effective, nine somewhat effective, one not very effective, and two not effective at all. Of the 20 patients who shared their experience with atorvastatin, 10 found it very effective, seven somewhat effective, one not very effective, and two not effective at all. Of the 24 patients who shared their experience with bypass surgery, 54% found the surgery to be very effective in controlling their symptoms.

The most common side effects noted by 16 out of 25 patients were sore muscles, cramping, or weakness. Twenty-three out of 25 patients experienced digestive symptoms with current treatments, such as gas, constipation, or upset stomach. The symptoms from current medications that were most difficult to tolerate included muscle pain, discomfort, and weakness. One patient said, “I had to stop the medication as the pain had spread from my chest to my shoulders and legs. This got so bad it was interfering with walking, which at the time was the only exercise I could do.” Another patient said, “I still get severe foot cramping at night.”

Seven patients noted that they had unmet needs with current treatments because they could not take statins, and three said they experience too many side effects on current treatments. Other comments related to not being able to achieve optimum cholesterol targets on statins.

4. Expectations About the Drug Being Reviewed

The methods of the information collection in this section were the same as those used in section 2.

Most of the 53 patients who completed the survey did not have experience with evolocumab. Patient’s expectation of this drug would be to lower cholesterol levels with minimal side effects, predominantly not to experience the loss of muscle function or muscle weakness experienced with statins. The loss of muscle function is a side effect that most patients are not willing to tolerate. With respect to evolocumab, one patient commented, “I know that other patients need this drug and clinical trials have shown incredible results.” Another patient was concerned about not having private insurance to cover the cost of the new medication, and what other medications would need to be taken with evolocumab.

Of the patients included in the online survey and telephone interview, only three had had experience with evolocumab. Of these, two found evolocumab to be very effective in lowering their cholesterol, and noted that they had more energy, with limited to no side effects. The third patient found evolocumab not very effective, mentioning that while their cholesterol had decreased, they experienced sore arms as a side effect. None of the patients commented about any issues with an injection versus another pill. One patient indicated that being on a fixed income made it difficult to pay for evolocumab; however, this patient was managing to find the funds to pay for the drug and would continue to do so because of the benefits it was providing.

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:	March 20, 2017
Alerts:	Weekly search updates until July 19, 2017
Study Types:	No search filters were applied
Limits:	No date or language limits were used

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
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.rn	CAS registry number
.nm	Name of substance word
ppez	**Ovid database code: MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present**
oemezd	Ovid database code: Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY
1. (Repatha* or evolocumab* or AMG 145 or AMG145 or LKC0U3A8NJ or UNIILKC0U3A8NJ).ti,ot,ab,sh,hw,rn,nm,kf.
2. (1256937-27-5 or "1256937275" or "125693727 5" or 1256937 275).rn,nm.
3. 1 or 2
4. 3 use ppez
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. remove duplicates from 9

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. 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:	March 2017
Keywords:	Repatha (evolocumab)
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a Practical tool for searching health-related grey literature* (https://www.cadth.ca/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

Table 12: Excluded Studies

Reference	Reason for Exclusion
Cho L, Rocco M, Colquhoun D, Sullivan D, Rosenson RS, Dent R, et al. Clinical Profile of Statin Intolerance in the Phase 3 GAUSS-2 Study. Cardiovasc Drugs Ther. 2016 Jun;30(3):297-304.	Trial from original submission
Blom DJ, Djedjos CS, Monsalvo ML, Bridges I, Wasserman SM, Scott R, et al. Effects of Evolocumab on Vitamin E and Steroid Hormone Levels: Results From the 52-Week, Phase 3, Double-Blind, Randomized, Placebo-Controlled DESCARTES Study. Circ Res [Internet]. 2015 Sep 25 [cited 2017 Apr 6];117(8):731-41. Available from: http://circres.ahajournals.org/content/117/8/731.long	
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.	
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 [Internet]. 2014 May 14 [cited 2017 Apr 6];311(18):1870-82. Available from: http://jamanetwork.com/journals/jama/fullarticle/1869210	
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 [cited 2017 Apr 6];63(23):2541-8.	
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 [Internet]. 2014 May 8 [cited 2017 Apr 6];370(19):1809-19. Available from: http://www.nejm.org/doi/pdf/10.1056/NEJMoa1316222	
Cheng C, Sun S, Zhou Y, Yang X. Efficacy and safety of different doses of evolocumab in reducing low-density lipoprotein cholesterol levels: A meta-analysis. Biomed Rep [Internet]. 2016 Nov [cited 2017 Apr 6];5(5):541-7. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5103663/pdf/br-05-05-0541.pdf	Wrong design
Koren MJ, Sabatine MS, Giugliano RP, Langslet G, Wiviott SD, Kassahun H, et al. Long-term Low-Density Lipoprotein Cholesterol-Lowering Efficacy, Persistence, and Safety of Evolocumab in Treatment of Hypercholesterolemia: Results Up to 4 Years From the Open-Label OSLER-1 Extension Study. JAMA Cardiol [Internet]. 2017 Mar 14 [cited 2017 Apr 7]. Available from: http://jamanetwork.com/journals/jamacardiology/fullarticle/2611950	
Shah P, Glueck CJ, Goldenberg N, Min S, Mahida C, Schlam I, et al. Efficacy, safety, Low density lipoprotein cholesterol lowering, and calculated 10-year cardiovascular risk reduction of alirocumab and evolocumab in addition to maximal tolerated cholesterol lowering therapy: a post-commercialization study. Lipids health dis [Internet]. 2017 Jan 23 [cited 2017 Apr 7];16(1). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5259842/pdf/12944_2017_Article_416.pdf	
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.	Wrong population
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.	

Reference	Reason for Exclusion
Kiyosue A, Honarpour N, Kurtz C, Xue A, Wasserman SM, Hirayama A. A Phase 3 Study of Evolocumab (AMG 145) in Statin-Treated Japanese Patients at High Cardiovascular Risk. Am J Cardiol. 2016 Jan 1;117(1):40-7.	
Giugliano RP, Mach F, Zavitz K, Kurtz C, Schneider J, Wang H, et al. Design and rationale of the EBBINGHAUS trial: A phase 3, double-blind, placebo-controlled, multicenter study to assess the effect of evolocumab on cognitive function in patients with clinically evident cardiovascular disease and receiving statin background lipid-lowering therapy-A cognitive study of patients enrolled in the FOURIER trial. Clin Cardiol [Internet]. 2017 Feb [cited 2017 Apr 7];40(2):59-65. Available from: http://onlinelibrary.wiley.com/doi/10.1002/clc.22678/epdf	Results not available
Nissen SE, Stroes E, nt-Acosta RE, Rosenson RS, Lehman SJ, Sattar N, et al. Efficacy and Tolerability of Evolocumab vs Ezetimibe in Patients With Muscle-Related Statin Intolerance: The GAUSS-3 Randomized Clinical Trial. JAMA [Internet]. 2016 Apr 19 [cited 2017 Apr 7];315(15):1580-90. Available from: http://jamanetwork.com/journals/jama/fullarticle/2511043	Wrong intervention

Appendix 4: Detailed Outcome Data

Table 13: Other Efficacy Outcomes

	FOURIER		GLAGOV	
	Evolocumab N = 13,784	Placebo N = 13,780	Evolocumab N = 484	Placebo N = 484
% Atheroma volume (primary outcome)	NR	NR		
PAV, mean baseline (95% CI])	NR	NR	36.4 (35.6 to 37.2)	37.2 (36.4 to 38.0)
LSM[a] (95% CI) change from baseline to week 78 (IVUS population-primary analysis)	NR	NR	−0.95 (−1.33 to −0.58) N = 423	0.05 (−0.32 to 0.42) N = 423
Between-group differences, LSM (95% CI)	NR	NR	−1.01 (−1.4 to −0.64)	
P value	NR	NR	*P* < 0.0001	
Total Atheroma Volume (TAV)				
Mean (SD) nominal change from baseline to week 78 in TAV, mm^3	[redacted]	[redacted]	[redacted]	[redacted]
LSM[a] (95% CI) change from baseline to week 78	NR	NR	−5.80 (−8.19 to −3.41)	−0.91 (−3.29 to 1.47)
Between-group differences, LSMs (95% CI)	NR	NR	−4.89 (−7.25 to −2.53) *P* < 0.0001	
Patients with regression in PAV at week 78, n (%)(95% CI)	NR	NR	[redacted]	[redacted]
Between-group differences (95% CI)	NR	NR	[redacted]	
Patients with regression in TAV at week 78, n (%)(95% CI)	NR	NR	[redacted]	[redacted]
Between-group differences (95% CI)	NR	NR	[redacted]	
Non–HDL-C				
Baseline, mean (SD) mmol/L	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline to weeks 48 and 78	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) % change from baseline to weeks 48 and 78	[redacted]	[redacted]	[redacted]	[redacted]
MD (95% CI) in % change between groups [c]	[redacted]			
Apolipoprotein-B				
Baseline, mean (SD) g/L	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline to week 78	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) % change from baseline to week 78	[redacted]	[redacted]	[redacted]	[redacted]
MD (95% CI) in % change between groups [c]	[redacted]			
VLDL-C				
Baseline, mean (SD) mmol/L	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline to week 78	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) % change from baseline to week 78	[redacted]	[redacted]	[redacted]	[redacted]
MD (95% CI) in % change between groups [c]	[redacted]			

	FOURIER		GLAGOV	
	Evolocumab N = 13,784	Placebo N = 13,780	Evolocumab N = 484	Placebo N = 484
Triglycerides				
Baseline, mean (SD) mmol/L	1.698 (0.796) N = 13,784	1.683 (0.797) N = 13,779	[redacted]	[redacted]
Mean (SD) change from baseline to week 78	−0.211 (0.772) N = 12,564	0.065 (0.904) N = 12,601	[redacted]	[redacted]
Mean (SD) % change from baseline to week 78	−9.28 (39.38)	6.79 (44.15)	[redacted]	[redacted]
MD (95% CI) in % change between groups [c]	−15.88 (−16.90 to −14.86), *P* < 0.0001			
Lipoprotein-a				
Baseline, mean (SD) nmol/L	94.9 (114.2) N = 12,557	93.3 (111.3) N = 12,539	[redacted]	[redacted]
Mean (SD) change from baseline to week 78	−22.4 (40.4) N = 11,863	−1.8 (36.2) N = 11,817	[redacted]	[redacted]
Mean (SD) % change from baseline to week 78	−23.69 (88.75)	3.93 (73.20)	[redacted]	[redacted]
MD (95% CI) in % change between groups [c]	−35.48 (−35.96 to −35.01), *P* < 0.0001			

ANCOVA = analysis of covariance; CI = confidence interval; IVUS = intravascular ultrasound; LS = least squares; LSM = least squares mean; MD = mean difference; PAV = per cent atheroma volume; SD = standard deviation; TAV = total atheroma volume; VLDL-C = very low-density lipoprotein cholesterol.

[a] LSM is from the general linear ANCOVA model, which includes terms for the treatment group, the geographic region stratification factor, and baseline PAV (or TAV for change in TAV from baseline).

[b] Based on CMH test stratified by geographic region.

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

Source: Clinical Study Report for FOURIER;[7] Clinical Study Report for GLAGOV.[8]

Table 14: Subgroup Analyses

	FOURIER					
	Evolocumab N = 13,784	Placebo N = 13,780	HR (95% CI)	Evolocumab N = 13,784	Placebo N = 13,780	HR (95% CI)
Subgroups Based on:	**Primary Outcome**			**Key Secondary Outcome (CV Death, Stroke, MI)**		
Types of disease						
MI alone	**N = 19,113**			**N = 19,113**		
Proportion of patients (%)	9.6%	10.8%	0.88 (0.80 to 0.96)	5.2%	6.4%	0.80 (0.71 to 0.90)
Stroke alone	**N = 3,366**			**N = 3,366**		
Proportion of patients (%)	6.0%	8.5%	0.70 (0.54 to 0.90)	5.0%	6.5%	0.77 (0.58 to 1.02)
PAD alone	**N = 1,505**			**N = 1,505**		
Proportion of patients (%)	6.7%	9.9%	0.67 (0.47 to 0.96)	4.5%	7.8%	0.57 (0.38 to 0.88)
Polyvascular disease	**N = 3,563**			**N = 3,563**		
Proportion of patients (%)	15.5%	17.4%	0.88 (0.75 to 1.03)	11.1%	12.9%	0.86 (0.71 to 1.04)
Test for interaction	*P* = 0.19			*P* = 0.38		
Baseline statin intensity						
Statin intensity – high	**N = 19,103**			**N = 19,103**		
Proportion of patients (%)	10.2%	11.6%	0.87 (0.80 to 0.95)	6.1%	7.4%	0.82 (0.74 to 0.92)
Statin intensity – not high	**N = 8,461**			**N = 8,461**		
Proportion of patients (%)	8.8%	10.7%	0.80 (0.70 to 0.92)	5.5%	7.2%	0.74 (0.63 to 0.88)
Test for interaction	*P* = 0.37			*P* = 0.33		
Ezetimibe						
Yes	**N = 1,440**			**N = 1,440**		
Proportion of patients (%)	13.4%	13.6%	0.98 (0.74 to1.31)	7.4%	9.8%	0.74 (0.52 to 1.06)
No	**N = 26,124**			**N = 26,124**		
Proportion of patients (%)	9.5%	11.2%	0.84 (0.78 to 0.91)	5.8%	7.2%	0.80 (0.73 to 0.88)
Test for interaction	*P* = 0.26			*P* = 0.76		

	FOURIER					
	Evolocumab N = 13,784	Placebo N = 13,780	HR (95% CI)	Evolocumab N = 13,784	Placebo N = 13,780	HR (95% CI)
Baseline LDL-C						
LDL-C below 2.07 mmol/L	**N = 6,961**			**N = 6,961**		
Proportion of patients (%)	8.3%	10.4%	0.80 (0.69 to 0.93)	5.1%	6.6%	0.78 (0.64 to 0.95)
LDL-C 2.07 to < 2.38 mmol/L	**N = 6,886**			**N = 6,886**		
Proportion of patients (%)	9.3%	11.2%	0.82 (0.71 to 0.96)	5.4%	6.8%	0.79 (0.65 to 0.96)
LDL-C 2.38 to 2.82 mmol/L	**N = 6,887**			**N = 6,887**		
Proportion of patients (%)	10.2%	11.3%	0.89 (0.77 to 1.03)	6.3%	7.9%	0.79 (0.66 to 0.94)
LDL-C > 2.82 mmol/L	**N = 6,829**			**N = 6,829**		
Proportion of patients (%)	11.2%	12.5%	0.89 (0.77 to 1.02)	6.9%	8.2%	0.83 (0.70 to 0.99)
Test for interaction	*P* = 0.69			*P* = 0.96		
	GLAGOV					
Subgroups*[a] *(Change From Baseline to Week 78 in PAV)	**Evolocumab N = 484**	**Placebo N = 484**	**MD vs. Placebo (95% CI)**			
Prior MI – yes	[redacted]	[redacted]				
LSM [95% CI] change from baseline	[redacted]	[redacted]	[redacted]			
Prior MI – no	[redacted]	[redacted]				
LSM [95% CI] change from baseline	[redacted]	[redacted]	[redacted]			
Test for interaction	[redacted]					
Statin intensity – high	[redacted]	[redacted]				
LSM [95% CI] change from baseline	[redacted]	[redacted]	[redacted]			
Statin intensity – other	[redacted]	[redacted]				
LSM [95% CI] change from baseline	[redacted]	[redacted]	[redacted]			
Test for interaction	[redacted]					
Prior statin use – yes	[redacted]	[redacted]				
LSM [95% CI] change from baseline	[redacted]	[redacted]	[redacted]			
Prior statin use – no	[redacted]	[redacted]				

	FOURIER					
	Evolocumab N = 13,784	Placebo N = 13,780	HR (95% CI)	Evolocumab N = 13,784	Placebo N = 13,780	HR (95% CI)
LSM [95% CI] change from baseline	[redacted]	[redacted]	[redacted]			
Test for interaction	[redacted]					
LDL-C below median (2.28 mmol/L)	[redacted]	[redacted]				
LSM [95% CI] change from baseline	[redacted]	[redacted]	[redacted]			
LDL-C above median	[redacted]	[redacted]				
LSM [95% CI] change from baseline	[redacted]	[redacted]	[redacted]			
Test for interaction	[redacted]					

ANCOVA = analysis of covariance; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; LDL-C = low-density lipoprotein cholesterol; LS = least squares; LSM = least squares mean; MD = mean difference; MI = myocardial infarction; PAD = peripheral artery disease; PAV = per cent atheroma volume; vs. = versus.

[a] Subgroups: Results are obtained from the general linear ANCOVA model within each subgroup. The general linear ANCOVA model includes terms for the treatment group, the geographic region stratification factor, and the baseline PAV as a covariate.

Source: Clinical Study Report for FOURIER;[7] Clinical Study Report for GLAGOV.[8]

Appendix 5: Summary of Indirect Comparisons

Background

The aim of this section is to review and critically appraise any indirect treatment comparisons (ITCs) that compared evolocumab with other therapies for the management of lipid levels in hyperlipidemia.

Evolocumab has been previously compared with placebo or ezetimibe in six clinical trials. However, no head-to-head evidence of evolocumab compared with alirocumab exists. Therefore, an ITC that includes evolocumab can provide information on the effectiveness and safety of this drug compared with existing therapies and would be relevant to this CADTH Common Drug Review (CDR).

Methods

One ITC submitted by the manufacturer was reviewed and critically appraised. In addition, an information specialist performed a comprehensive literature search to identify published ITCs. ITCs identified from the literature were summarized and contrasted against the manufacturer's ITC.

Description of ITCs Identified

The manufacturer-submitted ITC,[6] Toth et al. (2016), was a systematic review and a Bayesian-based ITC of LDL-C reduction with all available lipid-lowering therapies (including alirocumab) in adult patients with primary familial or non-familial hypercholesterolemia (HC) who were candidates for evolocumab or other pharmacological lipid-lowering therapies added to statins.

Review and Appraisal of ITCs

Review of Toth et al. (2016)

Objectives and Rationale for Toth et al. (2016)

The objective of the manufacturer's ITC was to perform an analysis to compare low-density lipoprotein cholesterol (LDL-C) reduction with evolocumab versus other lipid-lowering therapies (including alirocumab) in patients receiving statin background therapy.[6]

The lack of head-to-head comparison, the absence of any formal ITCs, and the absence of meta-analyses specifically focused on patients whose HC was not controlled with statin therapy alone (the primary populations for which evolocumab and alirocumab are indicated) were used as rationales for conducting this ITC. The authors also reported that no other ITC comparing these interventions existed in the literature.

Methods for Toth et al. (2016)

Study Eligibility and Selection Process

Studies included in the Toth et al. (2016) ITC were phase III randomized controlled trials (RCTs) of adult patients (≥ 18 years) with primary familial or non-familial HC who were candidates for evolocumab or other pharmacological lipid-lowering therapies added to

statins. The therapies (i.e., interventions) assessed were evolocumab and other pharmacologic agents for the management of HC. The efficacy outcomes of interest were per cent change from baseline in LDL-C, high-density lipoprotein cholesterol (HDL-C), non–HDL-C, apolipoprotein-B (ApoB), and lipoprotein-a (LP-a). Only studies with at least 12 weeks of follow-up and at least 10 patients per group were included. The exclusion criteria eliminated patients with organ transplantations, infectious diseases such as HIV/AIDS, New York Heart Association class III or IV heart failure, or stage 4 or 5 renal dysfunction. Studies were also excluded if patients were only receiving a low-intensity statin as background therapy.

In terms of the literature search, MEDLINE, Embase, the Cochrane Database of Systematic Reviews and Controlled Trials CENTRAL, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment Database were searched from inception to August 2016. Where possible, the search strategy was limited to randomized studies and those in humans, but was not restricted by date or language. Clinical trial registries and conference abstracts, presentations, and posters were also searched in order to identify unpublished studies. For studies sponsored by Amgen, both publications and clinical study reports were used.

Two independent reviewers screened titles and abstracts to exclude records that did not meet inclusion criteria; two reviewers then obtained and independently screened full texts for inclusion in the systematic review. Throughout the screening, discrepancies between reviewers were resolved through discussion or by consulting a third reviewer.

Data Extraction

Data were extracted by one reviewer and independently checked for errors by another reviewer. Throughout the data extraction process, discrepancies between reviewers were resolved through discussion or by consulting a third reviewer.

Fifteen trials in which patients predominantly received moderate- to high-intensity statin background therapy were included in the primary networks. There were four studies of evolocumab (LAPLACE-TIMI-57, LAPLACE-2, YUKAWA-1, and YUKAWA-2) that were 12 weeks in duration and one study of evolocumab (DESCARTES) that was 52 weeks in duration. All studies compared evolocumab with placebo, and one (LAPLACE-2) also included a comparison with ezetimibe. In total, there were nine studies of alirocumab (McKenney 2012, ODYSSEY COMBO I and II, OPTIONS I and II, CHOICE I, JAPAN, HIGH FH, and LONGTERM). The alirocumab studies were 12 to 104 weeks in duration. All studies reported 12-week and 24-week data except for one that reported 24-week data only (in the network meta-analyses [NMAs], the 12-week data were used, except for the study in which they were not available). Six studies compared alirocumab with placebo, and three studies (ODYSSEY COMBO II and ODYSSEY OPTIONS I and II) compared alirocumab at 75 mg every two weeks (Q2W) with ezetimibe. Finally, there was one eligible study comparing ezetimibe with placebo (Masana 2005). Follow-up ranged from 12 weeks to 104 weeks. Studies differed in the types of HC observed, which included primary or secondary HC (eight studies); primary HC alone (four studies); mixed dyslipidemia (one study); and homozygous familial hypercholesterolemia (HeFH) only (one study). In one study, the type of HC was not reported or unclear.

Comparators

All relevant comparators were included in Toth et al. (2016), including evolocumab 140 mg every two weeks or evolocumab 420 mg once monthly, alirocumab 75 mg and 150 mg every two weeks , alirocumab 300 mg once monthly, and ezetimibe.

Outcomes

Toth et al. (2016) focused on reporting on the per cent change from baseline in LDL-C, HDL-C, non–HDL-C, ApoB, and LP-a.

Quality Assessment of Included Studies

The methodological quality of all included studies was assessed by one reviewer and independently checked for errors by another reviewer using the Cochrane Collaboration Risk of Bias Assessment Tool.

Table 15: Details About Studies Included in Main Networks

Study Name	Follow-Up, Weeks	Age, Years[a]	Investigational Drug and Dose	Control	Type HC	CVD Risk Status	FH Status	Type 2 Diabetes Status	Obesity Status	Background Therapy
DESCARTES	52	55.9 (10.8)[b]	EvoMab 420 mg QM	Placebo	Primary or secondary HC	With or without CVD or equivalent	NR/unclear	With and without	All	Diet through 80 mg atorvastatin + ezetimibe
LAPLACE-TIMI 57	12	62.0 (55.0 to 67.0)	EvoMab 70 mg, 105 mg, or 140 mg Q2W; 280 mg, 350 mg, or 420 mg QM	Placebo	Primary HC	Without prior CVD	NR/unclear	With and without	Overweight	Statin ± ezetimibe at physician discretion
LAPLACE-2	12	59.6 (9.9)[b]	EvoMab 140 mg Q2W; 420 mg QM	Placebo	Mixed dyslipidemia	NR/unclear	NR/unclear	With and without	Overweight	Moderate to high dose atorvastatin or rosuvastatin, moderate dose simvastatin
YUKAWA-1	12	61.5 (9.7)	EvoMab 70 or 140 mg Q2W; 280 mg or 420 mgQM	Placebo	Primary or secondary HC	With or without CVD or equivalent	NR/unclear	With and without	Overweight	Statin as prescribed by physician
YUKAWA-2	12	62 (11)	EvoMab 140mg Q2W; 420 mg QM	Placebo	Primary or secondary HC	With or without CVD or equivalent	HoFH- and HeFH-eligible	With and without	NR/unclear	20 mg atorvastatin (intensive dose for Japanese population)
McKenney 2012	12	56.7 (10.0)	AliMab 50, 100, 150, or 200 mg Q2W; 300 mg QM	Placebo	Primary HC	NR/unclear	NR/unclear	With and without	Overweight	10, 20, 40 mg atorvastatin
ODYSSEY CHOICE I	56	60.7 (9.1)[c]	AliMab 75 mg Q2W or 300 mg QM	Placebo	Primary HC	Moderate to very high risk, no CVD	HoFH excluded	With and without	Normal, overweight, and obese	Maximally tolerated atorvastatin, rosuvastatin, or simvastatin
ODYSSEY COMBO I	52	63.0 (9.5)	AliMab 75 mg Q2W	Placebo	Primary or secondary HC	With or without CVD or equivalent	No FH patients	With and without	NR/unclear	Maximally tolerated statin with/without other lipid-lowering therapy
ODYSSEY COMBO II	104	61.7 (9.4)[d]	AliMab 75 mg Q2W	Ezetimibe	Primary or secondary HC	With or without CVD or equivalent	NR/unclear	NR/unclear	NR/unclear	Stable maximally tolerated statin therapy
ODYSSEY HIGH FH	78	49.8 (14.2)[d]	AliMab 150 mg Q2W	Placebo	HeFH only	NR/unclear	HeFH only	NR/unclear	NR/unclear	Maximally tolerated statin with/without

Study Name	Follow-Up, Weeks	Age, Years[a]	Investigational Drug and Dose	Control	Type HC	CVD Risk Status	FH Status	Type 2 Diabetes Status	Obesity Status	Background Therapy
										other lipid-lowering therapy
ODYSSEY-JAPAN	24	60.3 (9.7)	AliMab 75 mg Q2W	Placebo	NR/unclear	With or without CVD	NR/unclear	NR/unclear	NR/unclear	Stable lipid-lowering therapy
ODYSSEY LONG TERM	78	60.4 (10.4)	AliMab 150 mg Q2W	Placebo	Primary HC	With or without CVD or equivalent	HeFH included	NR/unclear	NR/unclear	Maximally tolerated statin with/without other lipid-lowering therapy
ODYSSEY OPTIONS I	24	64.2 (10.4)[e]	AliMab 75 mg Q2W	Placebo, ezetimibe	Primary or secondary HC	CVD or equivalent	Non-FH or HeFH	With and without	NR/unclear	Statins according to study group assignment
ODYSSEY OPTIONS II	24	57.9 (8.9)[f]	AliMab 75 mg Q2W	Placebo, ezetimibe	Primary or secondary HC	CVD or equivalent	Non-FH or HeFH	NR/unclear	NR/unclear	Statins according to study group assignment
Masana 2005	48	61 (28 to83)[g]	Ezetimibe	Placebo	Primary or secondary HC	With or without CVD or equivalent	NR/unclear	With and without	Overweight	Up to 80 mg simvastatin

AliMab = alirocumab; CVD = cardiovascular disease; EvoMab = evolocumab; FH = familial hypercholesterolemia; HC = hypercholesterolemia; HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; Q2W = every 2 weeks; QM = once monthly; NR = not reported.

[a] Values are mean (standard deviation) or median (interquartile range). The mean age for all patients is given unless unavailable, in which case the intervention group was used (marked with a footnote). There was no indication in the references that ages were statistically different between groups.

[b] All evolocumab patients.

[c] Alirocumab 75 mg Q2W taking statins.

[d] All alirocumab patients.

[e] Alirocumab 75 mg /150 mg Q2W + atorvastatin 40 mg.

[f] Alirocumab 75 mg/150 mg Q2W + rosuvastatin 20 mg.

[g] All ezetimibe patients. Values in parentheses represent the range of ages observed.

Source: Reproduced from Toth et al. (2016).[6]

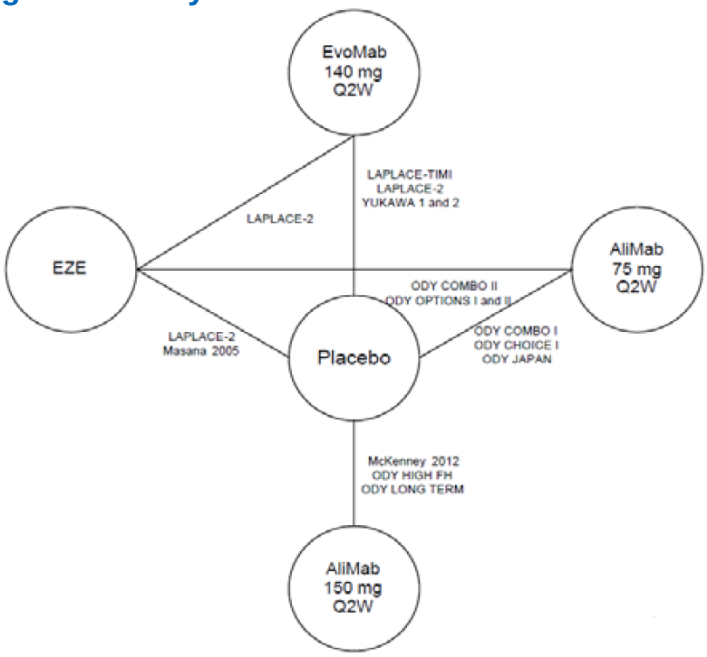
Evidence Network

Two separate networks for comparing evolocumab with other lipid-lowering therapies by dosage regimen (evolocumab at 140 mg once every two weeks or evolocumab at 420 mg once monthly) were used. Both networks included placebo and ezetimibe (10 mg daily). The network with evolocumab at 140 mg once every two weeks also included alirocumab at 75 mg and 150 mg once every two weeks; the network with evolocumab at 420 mg once monthly included alirocumab at 300 mg once monthly.

There were four studies of evolocumab (LAPLACE-TIMI-57, LAPLACE-2, YUKAWA-1, and YUKAWA-2) in both networks, all of which were 12 weeks in duration. There was one additional study of evolocumab (DESCARTES) in the 420 mg once-monthly network that was 52 weeks in duration.

In total, there were nine studies of alirocumab in the once-every-two-weeks network (McKenney 2012 and ODYSSEY COMBO I and II, OPTIONS I and II, CHOICE I, JAPAN, HIGH FH, and LONGTERM), of which two (McKenney 2012 and CHOICE I) were included in the once-monthly network. Alirocumab studies were 12-104 weeks in duration. All studies reported 12-week and 24-week data, except for one that reported 24-week data only (in the NMAs, the 12-week data were used except for the study in which it was not available). The alirocumab 75 mg and 150 mg once-every-two-weeks doses were included as separate therapies in the once-every-two-weeks network, and the 300 mg once-monthly dose was included in the once-monthly network. Six studies compared alirocumab with placebo, and three studies (ODYSSEY COMBO II and ODYSSEY OPTIONS I and II) compared alirocumab 75 mg once every two weeks with ezetimibe. Figure 2 and Figure 3 present the network of available connections for comparing change in LDL-C for evolocumab at 140 mg once every two weeks and evolocumab at 420 mg once monthly, respectively.

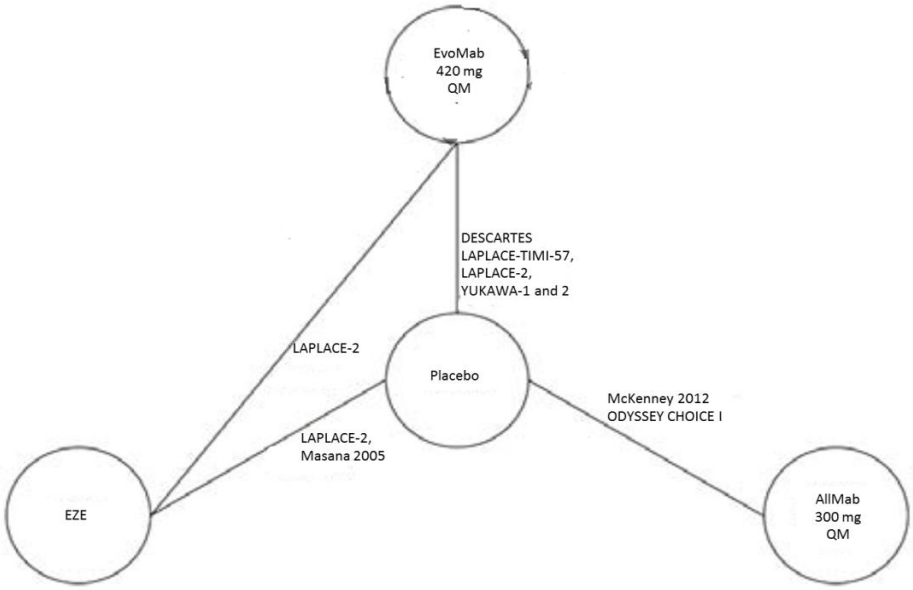
Figure 2: Network of Available Connections for Comparing Change in LDL-C for Evolocumab at 140 mg Once Every Two Weeks



AliMab = alirocumab; EvoMab = evolocumab; FH = familial hypercholesterolemia; EZE = ezetimibe; LDL-C = low-density lipoprotein cholesterol; ODY = ODYSSEY; Q2W = every 2 weeks.

Source: Reproduced from Toth et al. (2016).[6]

Figure 3: Network of Available Connections for Comparing Change in LDL-C for Evolocumab at 420 mg Once Monthly



AliMab = alirocumab; EvoMab = evolocumab; EZE = ezetimibe; LDL-C = low-density lipoprotein cholesterol; QM = once monthly.

Source: Reproduced from Toth et al. (2016).[6]

Indirect Treatment Comparison Methods

The NMA was conducted using Bayesian models in WinBUGS. The authors used a random-effects model. The mean treatment difference or risk ratio for each comparison was estimated after an initial burn-in of 40,000 Markov chain Monte Carlo simulations, followed by a further 40,000 simulations. Two chains were used. Non-informative normal priors (mean 0, variance 10,000) for treatment effects and a non-informative uniform prior (interval 0 to 5) to estimate the between-study standard deviation were used. Convergence and auto-correlation were assessed by monitoring the trace and auto-correlation plots in WinBUGS. Model fit was assessed using residual deviance and the deviance information criterion. All analyses used the treatment effect from each study (i.e., mean difference, rather than the mean and standard error for each group). Assumptions of homogeneity based on the I^2 statistic from the direct meta-analyses, similarity using the baseline characteristics and designs of the included studies, and consistency using the IFPLOT command in Stata in comparisons with both direct comparisons and ITCs were reviewed within the NMA. Sensitivity analyses combining both evolocumab dosage groups and including studies with all background therapies were also conducted.

The co-primary end points for most evolocumab studies were the per cent change in LDL-C from baseline to the mean of 10 weeks and 12 weeks and to week 12. Since data from some comparator studies were only available for a follow-up of longer than 12 weeks (e.g., up to 78 weeks), for the analysis, values of evolocumab at the mean of 10 weeks and 12 weeks or at week 12 versus comparators at ≥ 12 weeks were used. If the outcome was not available at week 12, the nearest time point after week 12 was used. For alirocumab studies, in which dose titration is often employed, only patients who were taking 75 mg once every two weeks, 150 mg once every two weeks, or 300 mg once a month were analyzed.

Results

LDL-C Reduction

Treatment differences between lipid-lowering therapies for the per cent reduction in LDL-C from baseline are presented in Table 16 for evolocumab at 140 mg once every two weeks at the mean of weeks 10 weeks and 12 weeks versus comparators at ≥ 12 weeks and for evolocumab at week 12 versus comparators at ≥ 12 weeks; and in Table 17 for evolocumab 420 mg once monthly at the mean of weeks 10 and 12 versus comparators at ≥ 12 weeks and for evolocumab at week 12 versus comparators at ≥ 12 weeks. All treatment differences between evolocumab at 140 mg, alirocumab at 75 mg, alirocumab at 150 mg, or ezetimibe versus placebo, were statistically significant.

Evolocumab had a greater LDL-C reduction than alirocumab. For evolocumab at 140 mg once every two weeks at the mean of weeks 10 and 12 versus comparators at ≥ 12 weeks, the treatment difference versus alirocumab 75 mg was −20.03% (95% credible interval [CrI], −27.32% to −12.96%) and −13.63% (95% CrI, −22.43% to −5.33%) compared with alirocumab 150 mg. The treatment difference between evolocumab 420 mg once monthly and alirocumab 300 mg once monthly was −19.21% (95% CrI, −28.52% to −10.35%) for evolocumab at the mean of weeks 10 and 12 and comparators at ≥ 12 weeks. Treatment differences were similar for evolocumab at week 12 versus comparators at ≥ 12 weeks.

Table 16: Treatment Difference in Per Cent LDL-C Change (95% CrI), Evolocumab 140 mg Q2W Network

Per Cent LDL-C Change (95% CrI)	Alirocumab 75 mg Q2W	Alirocumab 150 mg Q2W	Ezetimibe	Placebo
Evolocumab at the mean of weeks 10 and 12 vs. comparator at ≥ 12 weeks				
Evolocumab 140 mg Q2W	−20.03 (−27.32 to −12.96)	−13.63 (−22.43 to −5.33)	−46.10 (−53.28 to −39.06)	−74.10 (−79.81 to −68.58)
Evolocumab at week 12 vs. comparator at ≥ 12 weeks				
Evolocumab 140 mg Q2W	−19.65 (−26.62 to −12.94)	−13.08 (−21.44 to −5.13)	−45.97 (−52.88 to −39.21)	−73.56 (−78.67 to −65.87)

CrI = credible interval; LDL-C = low-density lipoprotein cholesterol; Q2W = every 2 weeks; vs. = versus.

Source: Reproduced from Toth et al. (2016).[6]

Table 17: Treatment Difference in Per Cent LDL-C Change (95% CrI), Evolocumab 420 mg QM Network

Per cent LDL-C Change (95% CrI)	Alirocumab 300 mg QM	Ezetimibe	Placebo
Evolocumab at the Mean of Weeks 10 and 12 Versus Comparator at ≥ 12 Weeks			
Evolocumab 420 mg QM	−19.21 (−28.52 to −10.35)	−47,52 (−55.22 to −39.89)	−71.54 (−76.75 to −66.39)
Evolocumab at Week 12 Versus Comparator at ≥ 12 Weeks			
Evolocumab 420 mg QM	−10.79 (−19.71 to −2.15)	−43.14 (−52.83 to −33.43)	−63.00 (−67.34 to −58.68)

CrI = credible interval; LDL-C = low-density lipoprotein cholesterol; QM = once monthly.

Reproduced from Toth et al. (2016).[6]

A sensitivity analysis was conducted where evolocumab 140 mg once every two weeks and 420 mg once monthly were combined as one treatment arm at the mean of weeks 10 and 12, and LDL-C reduction of evolocumab versus alirocumab 75 mg was −18.32% (95% CrI, −24.30% to −12.40%) and alirocumab 150 mg was −11.06% (95% CrI, −18.72% to −3.73%) once every two weeks at ≥ 12 weeks.

Another analysis included all studies that met the inclusion criteria, regardless of the background therapy (e.g., ezetimibe, other lipid-lowering therapies, or low-intensity/no statin). In this analysis, evolocumab 140 mg once every two weeks at the mean of weeks 10 and 12 had a greater LDL-C reduction than alirocumab at ≥ 12 weeks; the treatment difference versus alirocumab 75 mg was −16.76 (95% CrI, −22.54 to −11.02); versus alirocumab 150 mg once every two weeks, the difference was −9.88 (95% CrI, −17.60 to −2.29).

Direct meta-analyses suggested that high statistical heterogeneity (I^2 ≥ 70%) was observed for some comparisons. This was investigated using sensitivity analyses (excluding studies conducted in Japan [YUKAWA-1, YUKAWA-2, and ODYSSEY-JAPAN], as well as ODYSSEY HIGH FH). Several sensitivity analyses were conducted in the NMA, where studies conducted in Japan or in ODYSSEY HIGH FH, all of which drove heterogeneity, were excluded. In general, the conclusions of these sensitivity analyses with regard to per cent LDL-C reduction were consistent in direction and statistical significance with respect to the main analyses, although the magnitudes changed slightly.

High-Density Lipoprotein Cholesterol, Non–High-Density Lipoprotein Cholesterol, Apolipoprotein-B, and Lipoprotein-A

NMA of HDL-C results demonstrated a moderate increase from baseline associated with evolocumab and alirocumab compared with placebo or ezetimibe. NMA results for non–HDL-C were similar in direction and magnitude to LDL-C results, and the same was true of

the results for ApoB and LP-a, although the networks were smaller for these comparisons (Table 18).

Table 18: Treatment Difference in Per Cent (95% CrI) Change From Baseline, Evolocumab 140 mg Q2W at the Mean of Weeks of 10 and 12 Vs. Comparator at ≥ 12 Weeks: for HDL-C, Non–HDL-C, ApoB, and LP-a

Evolocumab 140 mg Q2W	Alirocumab 75 mg Q2W	Alirocumab 150 mg Q2W	Ezetimibe	Placebo
HDL-C	2.26 (−2.67 to 7.86)	5.02 (−0.33 to 11 80)	8.19 (3.54 to 13.50)	10.01 (6.30 to 14.46)
Non–HDL-C	−14.56 (−21.76 to −7.57)	−11.19 (−19.37 to −3.43)	−38.10 (−44.92 to −31.42)	−63.18 (−68.38 to −58.02)
ApoB	−13.93 (−21.31 to −6.52)	−8.79 (−17.09 to −0.70)	−37.00 (−44.41 to −29.61)	−59.12 (−64.51 to −53.72)
LP-a	−9.35 (−18.52 to −0.26)	−13.71 (−24.89 to −2.65)	−32.41 (−41.41 to −23.49)	−37.81 (−45.60 to −30.12)

ApoB = apolipoprotein-B; CrI = credible interval; HDL-C = high-density lipoprotein cholesterol; LP-a = lipoprotein-a; Q2W = every 2 weeks; vs. = versus.

Source: Reproduced from Toth et al. (2016).[6]

Critical Appraisal

Toth et al. (2016)[6] provided a research question that incorporated a clear population, interventions, comparators, and outcomes. The inclusion of patients with primary familial or non-familial HC who were candidates for evolocumab or other pharmacological lipid-lowering therapies added to statins and the specific assessment of evolocumab 140 mg once every two weeks and evolocumab 420 mg once monthly make this ITC for this review irrelevant, given that the patient population is not exactly the same as the one identified in the requested listing indication under review for reimbursement. In addition, the outcomes synthesized per cent change from baseline in LDL-C, HDL-C, non–HDL-C, ApoB, and LP-a in a manner that was identical to the efficacy assessment used in this CDR; however, clinical events were not part of the analysis. The authors conducted a wide search strategy that is likely to have captured all relevant studies over two major bibliographic databases. However, the study lacks reporting on essential items that would allow us to assess the credibility and quality of the results and the conduct of the studies. These items include the following:

- In the method section, it was indicated that consistency in comparing both direct comparisons and ITCs was to be evaluated using the IFPLOT command in Stata; however, no results were reported on that comparison. Consistency testing is useful for validating the ITC results by allowing comparison to the available direct evidence. Direct comparative evidence was available in some of the treatments.
- Not enough information was provided regarding the population in each of included studies. Such information is important in assessing potential methodological and clinical heterogeneity in the included studies.
- It was not clear whether the statistical model achieved convergence. In the method section, the authors indicated that convergence would be assessed, but no results were provided for that assessment.
- It was not clear that there was a good statistical fit for the model. Diagnostics for statistical fit of the model indicate the extent to which the model is appropriate for accommodating the data at hand. The authors indicated in the method section that model fit was assessed using residual deviance and the deviance information criterion, but the authors did not report the results of that assessment.

All analyses used the treatment effect from each study (i.e., mean difference, rather than the mean and standard error for each group). Using this approach assumes that the treatment effects of the individual studies were exchangeable. However, this assumption might not be valid; therefore, there is uncertainty about the results from this NMA. Given that no ITC was conducted where the mean and standard error for each group were used rather than mean difference, it is not possible to judge if the results are accurate or biased (or, if biased, the direction of the bias).

There have been no such head-to-head studies on evolocumab comparing the LDL-C lowering capacity of pro-protein convertase subtilisin/kexin type 9 (PCSK9) inhibitors with each other. Thus, this review is limited by the quantity and quality of the data available from the included clinical trials.

Evolocumab 75 mg once every two weeks and evolocumab 150 mg once every two weeks were not studied in a parallel-group trial; therefore, there is lack of availability of a well-characterized estimate of the treatment effect for each dose.

There was a difference in the time point used for the comparison between treatments. In the main analysis, the time point used for evolocumab was the mean of weeks 10 and 12, while the time point for the comparators was at ≥ 12 weeks. Several sensitivity analyses were conducted trying to align the time period between difference comparators, and the results were in line with the base-case analysis.

The GLAGOV and FOURIER trials of evolocumab that were included in this CDR review, as well as the RUTHERFORD-2, DESCARTES, and GAUSS-2 trials of evolocumab from the previous submission for evolocumab, were not included in this NMA because of its inclusion criteria.

Clinical events were not part of the analysis; therefore, the true impact of differences in LDL-C lowering capability is unknown.

Finally, the NMA did not include any safety or harm outcomes, nor did it include health-related quality of life data.

Discussion and Conclusion

The manufacturer submitted a systematic review and a Bayesian NMA published by Toth et al. in 2016 that included comparisons of evolocumab with alirocumab, ezetimibe, or placebo in patients with familial or non-familial HC who were candidates for evolocumab or other lipid-lowering therapies as an add-on to statins.[6] The NMA focused on LDL-C reduction, rather than clinical events, and included 15 trials. Evolocumab reduced LDL-C to a greater extent than did alirocumab; these results were consistent across the various doses that were compared. At its maximum, there was a 20% absolute difference in per cent reduction in LDL-C between the twice-monthly dosage regimens of evolocumab 140 mg and alirocumab 75 mg at the mean of weeks 10 and 12 (evolocumab) and week 12 (alirocumab). There are some important limitations of such an analysis, the most notable being that the population observed in Toth et al. (2016) differs from that identified in the requested listing indication under this review for reimbursement. This limitation resulted in the exclusion of trials included in this review and in the previous submission for evolocumab. However, the findings in Toth et al. do raise the possibility that evolocumab may have a greater lipid-lowering capability than alirocumab. However, clinical events were not part of the analysis; therefore, the true impact of such a difference in LDL-C-lowering

capability is unknown. Additionally, harms were not included in the analysis; therefore, it is not known whether this potential for enhanced lipid-lowering with evolocumab comes at the expense of an increased risk of adverse effects. Finally, all analyses used the treatment effect from each study rather than the mean and standard error for each group. Using this approach means that there was an assumption that the treatment effects of the individual studies were exchangeable; however, this assumption might not be valid. Therefore, there is uncertainty about the results from this NMA.

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